UNIVERSITY OF THESSALY

SCHOOL OF HEALTH SCIENCES

FACULTY OF VETERINARY SCIENCE

CLINIC OF MEDICINE

METAGENOMIC AND METABOLOMIC ANALYSIS OF THE SHORT-TERM AND LONG-TERM EFFECTS OF ANTIBIOTIC THERAPY ON THE INTESTINAL MICROBIOTA IN GROWING KITTENS AND THEIR RELATION TO THE OVERALL HEALTH STATUS OF THESE KITTENS

EVANGELIA M. STAVROULAKI, DVM

DOCTORAL THESIS

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STUDY

METAGENOMIC AND METABOLOMIC ANALYSIS OF THE SHORT-TERM AND LONG-TERM EFFECTS OF ANTIBIOTIC THERAPY ON THE INTESTINAL MICROBIOTA IN GROWING KITTENS AND THEIR RELATION TO THE OVERALL HEALTH STATUS OF THESE KITTENS

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DOCTORAL THESIS CONDUCTED AT THE CLINIC OF MEDICINE, FACULTY OF VETERINARY SCIENCE, SCHOOL OF HEALTH SCIENCES, UNIVERSITY OF THESSALY

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To those who believed in me and to my beloved dog, Rozita.

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ABBREVIATIONS

AMC group: cats treated with amoxicillin/clavulanic acid for 20 days

ARE: antibiotic responsive enteropathy

ASD: autism spectrum disorder

AT: antibiotic treatment

BA: bile acids

BCFAs: branched chain fatty acids

BSH: bile salt hydrolase

CAZ-enzymes: carbohydrate active enzymes

CE: chronic enteropathies

CD11b: cluster of differentiation 11b

CD36: cluster of differentiation 36

CIBDAI: canine inflammatory bowel disease activity index

CRP: C-reactive protein

CI: confidence interval

cfu: colony forming units

CKK: cholecystokinin

CON group: cats not treated with antibiotics

DNA: deoxyribonucleic acid

Dgat-1: diglyceride acyltransferase-1

DGGE: denaturing gradient gel electrophoresis

DOX group: cats treated with doxycycline for 28 days

EPI: exocrine pancreatic insufficiency

FCEAI: feline chronic enteropathy activity index

FCoV: feline coronavirus

FIP: feline infectious peritonitis

FISH: fluorescence in situ hybridization

FIV: feline immunodeficiency virus

FMT: fecal microbiota transplantation

FS: fecal scoring

FXR: farnesoid-X-receptor

GABA: gamma-aminobutyric acid

GF: germ free

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GI: gastrointestinal

GI LSA: small cell gastrointestinal lymphoma

GOS: galactooligosaccharide

HMP: human microbiome project

HP: high protein

HPLC: high protein low carbohydrate

IBD: inflammatory bowel disease

IgA: immunoglobulin A

IF: intrinsic factor

IL: interleukin

ILC: innate lymphoid cells

LPS: lipopolysaccharide

MPMC: moderate protein moderate carbohydrate

NEC: necrotizing enterocolitis

NF-κB: nuclear factor kappa B

NGS: next generation sequencing

NLRs: NOD-like receptors

NR1-C1: Peroxisome proliferator-activated receptor alpha

OR: odds ratio

OTUs: operational taxonomic units

PCFT: proton-coupled folate carrier

PCR: polymerase chain reaction

PD1: programmed cell death protein 1

Ppar-α: peroxisome proliferator-activated receptor alpha

RR: relative risk

PRRs: pattern recognition receptors

PYY: Peptide-tyrosine tyrosine

qPCR: quantitative polymerase chain reaction

RFC: folate carrier

RNA: ribonucleic acid

rRNA: ribosomal ribonucleic acid

RT-PCR: real time PCR

SCFAs: short chain fatty acids

SCT: secretin

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SD: standard deviation

SIBO: small intestinal bacterial overgrowth

TGR-5: G protein-coupled receptor 5

Th17: T helper 17 cells

TLRs: toll-like receptors

TNF: tumor necrosis factor

T1D: type 1 diabetes

T2D: type 2 diabetes

URTI: upper respiratory tract infection

16S rRNA: RNA component of the 30S subunit of a prokaryotic ribosome

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ACKNOWLEDGMENTS

This PhD thesis was carried out at the Clinic of Medicine, Faculty of Veterinary Science, University of Thessaly, Greece. This research was funded by the Winn Feline Foundation, Miller Trust Award, MT18-003 and the Operational Program "Human Resources Development, Education and Life Lifelong Learning”, MIS 5048925. The thesis aimed at investigating the effects of antibiotics on the gastrointestinal microbiota and serum and fecal metabolites of growing cats.

Completing my doctoral thesis, I would like to thank the following people:

First of all, I would like to thank my supervisor, Dr Panagiotis Xenoulis, for the assignment of the subject of the thesis, the confidence he showed to me from the beginning of my project, and his dedicated support at every stage of my PhD project. I would also like to thank him for his kindness, his guidance, his advice, all the things he taught me and the profound impact he had on my career and life choices. The most important, I am grateful because he taught me the hardest thing to learn, love and particularly how to love research, and internal medicine.

I would also like to thank my two co-supervisors. More specifically, I would like to warmly thank the member of the advisory and examination committee Dr Jan Suchodolski for his interest, observations, ideas, state of the art knowledge and assistance at all the steps of the project, as well as his immediate response to all my queries. I would also like to particularly thank the other member of the advisory and examination committee, Dr Manolis Saridomichelakis for the help and the valuable knowledge I gained from him, his academic and moral support, throughout my project,

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and his contagious strength in fighting for the things that we believe and the importance of teamwork.

Moreover, I would like to acknowledge the valuable impact of Dr Manolis Chatzis, academic fellow at the UTH, who was a role model for me during my internship and my project. I would like to thank him for his encouragement, support and help throughout those years. A big thank for him because he taught me that educators should be approachable, and that knowledge should be simple to get. In addition, I would like to thank all the staff of the clinic of Medicine, Dr Labrini Athanasiou, associate professor of Small Animal Internal Medicine at UTH and Dr Athanasia Tzivara, member of the specialized laboratory teaching staff at UTH, for their help and encouragement during the project.

I am also gratefully indebted to the Gastrointestinal Laboratory of Texas A&M University and particularly Dr Joerg Steiner, Professor in the Department of Veterinary Small Animal Clinical Sciences, TAMU, Dr Jonathan Lidbury, Associate Professor in the Department of Veterinary Small Animal Clinical Sciences, Dr Rachel Pilla Research Assistant Professor, College of Veterinary Medicine and Biomedical Sciences, TAMU, and Dr Chi-Hsuan Young, PhD student, College of Veterinary Medicine and Biomedical Sciences, TAMU for their advices, their assistance, their invaluable help in this project, their state of the art knowledge and facilities provided for the next generation sequencing, PCR, and metabolomic methods.

From my colleagues and friends, I owe a big thank to Dr Evi Sofou, PhD student, Small Animal Medicine, for her kindness, her help and moral support, and the precious time we spent together in all stages of my PhD project. In addition, I would like to thank Dr Eirini Chrysovergi, resident in Small Animal Medicine, UCD, Dr Kassiopi

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Kokkinaki, PhD, Small Animal Medicine, UTH, and Dr Dimitra Karra, PhD Student, Small Animal Medicine, UTH for their help and support during all these years.

Finally, I owe I big thank to my family for their support during my project and in their belief in me and my abilities. In particular, I would like to thank Magda, Christina, and Stefanos for their emotional support not only throughout my project but also in every step of my life.

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PART ONE-REVIEW OF THE LITERATURE

1. Definitions

1.1. Bacterial flora, microflora

Living microorganisms in the human feces were observed for the first time in 1672 and belonged to *Giardia* spp. During the 18th century, *Escherichia coli* was the first bacterium isolated with culture.[1] At the end of 19th century, with the wide acceptance of germ theory for disease, which states that certain microbes may be pathogenic and can lead to diseases, cultivation became a widely applicable diagnostic tool and subsequently led to the discovery of several bacteria.[2]

The terms bacterial flora and microflora have been used for more than a century for describing the bacterial inhabitants of various environmental and body sites. Bacteria during this period were categorized in the plant kingdom and, therefore, were termed microflora or bacterial flora.[3] According to the literature, the first documented scientific report that describes the GI bacterial flora of dogs and cats (among other animal species) was published in 1906.[4] In the mid-70s, new molecular techniques were incorporated in microbiology. This allowed the creation of a new classification system which categorized hierarchically living organisms based on the similarity of their gene sequence and re-categorized bacteria as a separate domain. This new classification also led to the construction of the phylogenetic tree which includes and relates the three domains of life, bacteria, archaea and eukaryota with the latter including plants. As a result, the term microflora should not be used anymore because bacteria do not belong in the plant kingdom.[5]

1.2. Microbiota

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The term microbiota appeared in the 1960s and for several years the terms 'microbiota' and 'bacterial flora' or 'microflora' were used interchangeably. A more accurate definition is that 'microbiota' represents the community of microorganisms, which includes not only bacteria, but also archaea, fungi, protists, and viruses. Due to the fact that the number of bacterial cells is usually by far the largest, and because bacteria play the most important role in host's health, the term commonly refers only to bacterial members.[6]

1.3. Microbiome

In mid-1990s the term 'microbiome' appeared in the literature and was firstly defined as 'a convenient ecological framework in which to examine biocontrol systems'.[7] Microbiome encompasses microorganisms plus their activity. Another definition of microbiome is the collective genome of microbial inhabitants in a certain environment.[8] or the collective genomes of microorganisms, as well as their metabolites.[9] Therefore, the term microbiome describes the whole microbial genome while the term microbiota refers to the actual microorganisms.

1.4. Dysbiosis

Dysbiosis is a vague term describing an imbalance in microbiota composition and function. With culture-based techniques, the only form of dysbiosis described in the GI tract of dogs and cats was small intestinal bacterial overgrowth (SIBO), which was characterized by increased numbers of total bacteria in the small intestine.[10] With the application of molecular techniques, other forms of dysbiosis have also been identified. In particular, four different types of dysbiosis have been defined and include increases in the numbers of potentially pathogenic bacteria (pathobionts), decreases in the

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numbers of "key-stone bacterial taxa", loss of diversity, and shifts in the metabolic capacity of the microbiome.[11,12]

1.5. Metagenomics

Metagenomics is a research tool that was applied to microbiology to answer the questions "who are there and what they are doing". The term genome was defined in 1920 by a botany professor to describe the hereditary material contained in all organisms, even before it was widely accepted that this is the DNA. Genomics only answers "who is there". The suffix –omics is used for the collective characterization of biological molecules and the prefix meta- for the development of superior methods than the ones used previously.[13]

The first studies in human microbiome research using metagenomics were published in 2005.[14,15] The human microbiome project (HMP) was launched in 2007 and by 2012 the microbiome of 5 body sites (oral cavity, skin, nares, GI tract, and urogenital tract) in healthy individuals had been described. The HMP then launched a second phase (from 2013 to 2016) to describe the functional aspects of the microbiome as well as the microbial and functional shifts during disease states. During the second phase, new molecular techniques were added including metabolomics, transcriptomics and proteomics.[16] The first studies applying metagenomics for describing the canine and feline GI microbiome were published in 2010.[17-19]

1.6. Metabolomics

Metabolomics appeared later in biology compared to genomics and proteomics.[20] Metabolomics elucidates 'the metabolic products of gene expression in a biological system in order to understand the metabolic engineering of bacteria'.[21] Metabolome is a

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complete set of small molecules (<1.5 kDa) or metabolites found in a biological sample. The word is a combination of the words metabolite and chromosome and appeared in the literature for the first time in 1998.[22]

In the past, only predetermined compounds could be investigated because investigation of new ones was considered unapproachable.[21] Mass-spectrometry allowed the simultaneous quantification of all metabolites present in samples and subsequently led to the discovery of new molecules useful in different aspects; from filling gaps in cellular processes to new biomarkers for diseases[23] and as a result the field of untargeted metabolomics started to emerge. In 2007 the Human Metabolome project was launched and by 2018 more than 100,000 metabolites have been included in the Human Metabolome Database.[24] One of the first studies applying untargeted metabolomics in dogs searched for the dietary effect in the urinary metabolites of different canine breeds.[25] In cats, one of the first studies searched for differences in their plasma metabolites compared to the plasma metabolites of dogs.[26]

2. Methods to investigate the microbiome

2.1. Pre molecular techniques era

Microbiology has relied on culture for investigating microbial inhabitants for research purposes, identifying pathogens, performing susceptibility testing and genotyping the culture-isolated bacteria for treating diseases.[27] Through culture, it was recognized that total bacterial counts increase from the stomach to rectum, and that factors such as aging, antibiotics and host diseases affect the bacterial numbers present along the GI tract and feces.[28-30] Cats harbour higher numbers of bacteria in their proximal small intestine compared to humans[31] and dogs,[32] with higher numbers of

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anaerobic bacteria present compared to dogs.[33] It was believed that these differences in the numbers of bacteria could explain the differences in the prevalence of gastrointestinal immunological diseases between dogs and cats.[32] Dysbiosis was manifested as SIBO in dogs, and diagnosis was based on bacterial quantification of small intestinal fluid through culture.[34,35]

Culture based studies have found that bacteria in cats vary from 10^4 to 10^5 colony forming units (cfu)/g of content in the stomach,[35] 10^5 to 10^8 cfu/g in the duodenum and jejunum,[32] 10^7 to 10^9 cfu/g in the ileum,[33,35] 10^9 to 10^{10} cfu/g in the cecum and colon[33,35] and 10.7 log counts/g in the feces.[6] The numbers of aerobic and anaerobic bacteria are relatively similar in the proximal parts of the intestine, whereas anaerobic bacteria predominate in the distal intestine (mainly in the large intestine).[6] The most commonly isolated bacteria from the feline GI tract based in culture were *Bacteroides* spp., *Clostridium* spp., *Enterococcus* spp., *Streptococcus* spp., *Fusobacteria* spp., and *Eubacteria* spp.[6] Knowledge of the most prevalent culture-isolated bacteria have been the cornerstone for the production of probiotics.[36]

Traditional techniques based on agar plates have proven to be inaccurate in terms of whole microbiota description due to the fact that different substrates promote the multiplication of different bacteria, and 80%[37] to 90%[27] of microorganisms cannot be cultured.[38] Culturomics is an emerging field that utilizes mass spectrometry techniques to identify bacterial taxa and increases the potential of culture-based methods.[37]

2.2. Post culture techniques era

With the first studies using culture-independent approaches it became apparent that a vast number of previously unknown microorganisms inhabit different body

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regions and play a significant and multivariable role in the host's health and disease. Several methods have been used for microbiome assessment over the last years.

For DNA-based methods, the first step is DNA extraction from the samples. Care should be given in choosing the appropriate DNA extraction protocol as every method might not be equally effective for all bacteria present,[39] and in avoiding DNA environmental and reagent contamination during the extraction procedure.[39,40]

Denaturing gradient gel electrophoresis (DGGE) is a molecular fingerprinting technique with the ability to separate equal length 16S rRNA amplicons (DNA/RNA products after PCR amplification) with different sequences.[37] A polyacrylamide gel containing a chemical gradient (urea and/or formamide) is used for electrophoretic separation of the amplicons.[37] DNA amplicons are melting at a certain level based on their sequence, forming bands across the gel. This method is useful for evaluating the species diversity within a sample and the bands formed can be amplified with PCR.[27] Limitations of this method include the lack of precision in the quantitative numbers of the taxa present,[37] and that some bands may be overlapped.[27]

Quantitative PCR (qPCR) or reverse transcription quantitative PCR (RT-PCR) allow detection of DNA amplicons and quantification with continuous fluorescence detection. Quantitative PCR assays have been widely used, from investigating and quantifying potentially pathogenic bacteria to constructing the so called dysbiosis index (an algorithm the combines the numbers of the 8 most commonly upregulated bacteria for describing the degree of dysbiosis in canine IBD).[41] The most important limitation of this method is that it does not allow discovery of new bacteria.[42]

Fluorescence in situ hybridization (FISH) is a cytogenetic technique that uses fluorescent probes that bind to complementary parts of a chromosome. For bacteria, the probes used bind to regions of the 16S rRNA gene.[37] This method allows objective

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bacterial quantification, visualization of the bacterial distribution, and demonstration of bacteria that are in close contact with the host's intestinal mucosa, but a major limitation is that it cannot be used for the investigation of new bacteria.[37]

Scientific progress led to the application of Next Generation Sequencing (NGS) technologies. Sequencing means "reading the DNA" i.e. determining the order of nucleotides in a DNA chain.[43] Marker gene analysis is based on targeting an amplicon of one gene instead of sequencing all or most genes in a sample. The marker gene that is most commonly used for bacteria is the 16S ribosomal RNA (rRNA) gene, which is located in the 30S subunit of a prokaryotic ribosome and consists of 9 highly conserved regions and 9 hypervariable regions (V1-V9). The conserved regions are used as binding sites for PCR primers, and the variable regions are used for microbial identification and taxonomic categorization because they are highly diverse in terms of length and sequence among the taxa.[40] Sequencing amplicons for one or more of the variable regions of the 16SrRNA gene answers "who is there" with phylogenetic categorization of bacteria, estimation of alpha diversity [species richness (how many species are present in a sample), species evenness (how similar are the numbers of species present)] and beta diversity (between sample diversity, the diversity between different samples). Pipelines are a useful series of tools or scripts developed with predefined parameters in order to automatically execute the steps by applying appropriate softwares (from data quality filtering to data visualization) required for genomic data analysis.[44] Pre-processing of the samples is required to check the quality of sequence reads and to filter the data from low-quality reads. Following filtering, raw sequence reads undergo a process called "binning" in which DNA sequences with the highest similarity are grouped together. During this process, barcode sequences, which are short sections of DNA from a specific gene (in this case the 16SrRNA) and unique for each

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microorganism, are attached to the primers prior to amplification. Read binning is the clustering into operational taxonomic units (OTUs) based on at least 97% sequence similarity. Grouping is performed either de novo or based on reference databases. Removal of chimeric sequences (DNA sequences originating from multiple transcripts or parent sequences that can be mistakenly recognized as microorganisms) is achieved either with using optimized PCR protocols or with appropriate softwares.[40] Then, further computational approaches are applied for statistical analysis and result visualization.

Limitations of marker gene analysis include biases in PCR primers against particular 16SrRNA gene sequences, some bacteria with very low abundance may be overlooked due to the presence of thousands of OTUs in a single sample, and taxonomic distribution is feasible only at genus and not at species level.[40] The lack of standardization for region selection, primers and amplification parameters used are other major limitations of 16S rRNA analysis.[44]

Roche 454-pyrosequencing was the first NGS platform released[45] with the (V1-V3)[46] or the (V4-V6) regions[47] of the 16S rRNA genes used for amplification in canine and feline microbiome studies. This platformed method is off the market since 2016. The Illumina platform is currently the most widely available and it is considered highly accurate and provides very high outputs.[39]

Metagenomic analysis allows capturing of all or most DNA present in a sample (both microbial and eukaryotic) and provides high-depth genomic information. Profiling the microbiota present at a species or strain level and the functional genetic capacity of the whole microbial community are determined thus answering “what can the microbiota do?”, which is far beyond the abilities of marker-gene sequencing.[48] According to Quince et al., a study based on shotgun metagenomics typically follows 5 steps: (a) sample collection, processing, and sequencing, (b) pre-processing of the sequence reads,

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(c) sequence analysis to profile taxonomic, functional and genomic features of the microbiome, (iv) statistical and biological post-processing analysis, and (v) validation.[39] Care should be taken for confounding factors influencing the microbiome during the control group selection.[44] It is suggested to compare samples from the same host over time, when this is feasible, or to exclude samples from individuals that might be confounding the results (outliers). Illumina MiSeq has the ability to read long read lengths (300-400 bp) covering several variable regions of the 16SrRNA gene and providing higher phylogenetic assignment. Illumina HiSeq reads even longer lengths (700 bp) covering higher genomic regions and satisfying the criteria for shotgun sequencing.[44] In companion animal studies, the V4-V6 region of the 16S rRNA gene has been used for sequencing with Illumina MiSeq platform.[49] Complex bioinformatic analysis of the data follows with computational approaches. The first step is the quality check of the reads, which should be performed before further analysis of the data with removement of low-quality reads as they can inhibit contigs assembly (DNA short-reads assembly and merge to form longer DNA fragments) and annotation (taxonomic or functional assignment of genes). Softwares assessing the quality of every sequence run and filtering and processing the sequence reads are applied.[44] Contigs assembly is performed either *de novo* (with algorithms) or it is based on reference genomes (on previously identified species) or both.[50] The next step is the sequence binning, which is the process of grouping contigs based on distinguishable characteristics, either their genetic similarity, or a specific length of the read.[44] All millions of bins then are classified either taxonomically (to microbial taxa) or functionally (genes) the latter through gene prediction followed by gene annotation with the help of computational methods.[51,52] Pipelines combining computational analysis required for metagenomics have been developed and are commonly used.[50]

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The most important limitation of metagenomic analysis is that it sequences the host's genome along with the microbial genome and for samples containing high levels of host's tissue e.g. biopsy samples is difficult to find the microbial genome.[42] Other limitations include that no consensus exists for the methodology of data analysis and interpretation, and therefore, comparisons among studies are difficult. In addition, computational analysis of the data is rather complicated.[39] Another limitation of all PCR based techniques is that they are unable to differentiate living from dead microorganisms.[53]

A more comprehensive picture of the microbial functions and the host-microbial interactions can be obtained with the application of metabolomics. Metabolomics allows profiling of the small biochemical products of metabolism. Identification of these new molecules has led to the discovery of new disease biomarkers, has allowed understanding of impaired signalment pathways in diseases states, and contributed to the concept of personalized medicine.[54] Targeted metabolomics is the type of analysis in which predefined metabolites are investigated based on a reference database. Untargeted metabolomics is used for identification of every small microbial molecule present in a sample. Targeted metabolomics is more precise in quantification of the metabolites under investigation, whereas untargeted metabolomics is superior in terms of discovery of new metabolites. Interpretation of these new metabolites however may be difficult.[42] The first step is choosing the most suitable extraction solvent depending on the metabolic class under investigation.[55] Gas or liquid chromatographic methods, infrared spectrometry, nuclear magnetic resonance can all be applied for metabolite separation,[56] followed by mass spectrometry tools for analysis of metabolites as charged ions.[42] Fecal metabolites are more representative of the direct microbial metabolic products of the GI microbiome. When metabolomic analysis was performed in both fecal samples and

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tissue samples obtained from the GI tract of patients with IBD similar results were obtained.[57] Blood metabolites represent those that eventually entered the systemic circulation and may have greater impact on the host.[42] Nuclear magnetic resonance imaging is more commonly used for untargeted metabolomics because it identifies metabolites hard to be ionized, whereas the other methods can precisely quantify many groups of known metabolites.[55] Care should be given in choosing the right platform (e.g., liquid chromatography/mass spectrometry cannot identify short chain fatty acids).[42]

2.3 Samples used for microbiome analysis

The samples used in microbiome research depend on the scientific question under investigation and there in no gold standard for what constitutes the perfect sample. For studies investigating the GI microbiome, fecal samples, rectal swabs or GI biopsies have been used.[58] Fecal samples obtained either with natural defecation or during rectal examination are the most common samples used for GI microbiome research[59,60] and represent bacteria present mainly in the intestinal lumen.[61] Feces are useful for diagnosing dysbiosis, identifying dysbiotic patterns and monitoring treatment response because individuals can be easily and repeatedly sampled.[58] In humans, it has been demonstrated that rectal swabbing obtains sufficient amounts but lower quality of DNA.[60] Some studies support that rectal swabs produce comparable results in terms of microbiota composition compared to feces[59] whereas others have found distinct differences between the two methods.[61,62] Studies using naturally passed feces outnumber those using rectal swabs in dogs and cats.[63-66] In a single feline study, rectal swabbing produced better quality of DNA compared to feces, yet distinct differences in the microbiota at a phylum level were found.[63]

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In humans, fecal samples may not be representative of the microbes present in the upper parts of the GI tract, or microbes adherent to the GI mucosa thus may not add specific information about which microbes play a significant role especially in upper GI diseases.[42] In contrast to humans, feces are considered a reliable source for microbiome research in dogs, due to their unique intestinal anatomy and because key bacterial taxa are always present in feces.[67] Canine and feline microbial community composition and diversity is only minorly affected by storage temperature. Four days storage of fecal samples at room temperature does not seem to affect the feline microbial composition,[68] and 7 to 14 days storage at 4ºC results in differences in the abundancies of a few genera in canine and feline fecal samples but richness and diversity remain unaffected.[69]

GI biopsies allow assessment of the mucosal microbiome, thus demonstrating which bacteria are in closer contact with the host's immune system and potentially play a more important role in GI diseases.[58] A few studies have examined the mucosal microbiome in biopsies obtained from various parts of the GI tract from dogs[46,70-78] and cats[79-82] and have found significant associations between mucosa adherent and invasive bacteria with GI health and disease. Monitoring GI mucosal microbiota changes over time or in response to treatment is usually not feasible due to the invasive methods required for obtaining the biopsies.[58]

3. Feline gastrointestinal microbiota

3.1 Healthy gastrointestinal microbiota of young cats

It is currently assumed that bacterial colonization of the feline GI tract starts immediately after birth. Acquisition of bacteria starts during labour and delivery, whereas environmental exposure is also involved thereafter.[27] Bacterial density and

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richness increase with aging until the microbiota reaches an adult state plateau.[83,84] It is still unknown at what age the microbial composition and function reaches maturity in cats, although suggested ages include 2 to 4 months[85] or around 7 months.[86] The human and canine microbiota reaches an adult state at the end of the weaning period i.e., around 2-3 years and 8 weeks, respectively.[67]

From a molecular perspective, the microbiota of kittens has been described by studies investigating the effect of diet,[66,85,87-92] aging,[30,88] and neutering/castration status.[86] In all these studies, kittens were laboratory born and bred for the purposes of each study and fecal material was used for assessing microbial composition.[30,66,85-87,89-93] Caution should be taken when comparing the results of these studies. First, nutritional composition of each diet administered was unique for each study. Other biases due to the differences in sampling techniques and storage conditions, DNA extraction procedures, and molecular methods used might also affect the results. The fecal samples of kittens fed either a high protein and low carbohydrate (HPLC) or a moderate protein, moderate carbohydrate (MPMC) diet were analysed by 2 different studies.[85,89] The only difference in the methodology between these studies was in the molecular method used for assessing microbiota composition; Hooda et al. used 454 pyrosequencing,[89] whereas Deusch *et al*. applied Illumina metagenomic sequencing.[85] In both studies, the phylum Firmicutes was the most abundant. Interestingly, Deusch *et al.* reported that the phylum Bacteroidetes was the second most abundant[85] which is in contrast to Hooda et al. where no sequences belonging to this phylum were identified.[89]

In most studies, the queen's diet was also taken into consideration.[85,87-92] Maternal diet may influence the offspring's microbiota. *Streptococcus* spp. levels were higher in 17-week old kittens born from cats fed kibbled diet compared to cats fed canned diet. *Escherichia* spp. and *Shigella* spp. were also reported to be affected by the queen's and

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the offspring's diet.[92] However, in another study, maternal diet did not have an effect in the offspring's microbiota.[87] Kittens relatedness to each other has been reported as a major factor driving microbiota composition until 8 weeks of age in kittens fed either canned or dry diet. In contrast, at 12 weeks and 16 weeks of age the microbiota of kittens clustered according to diet.[91]

Two studies have used molecular methods for assessing fecal microbial composition or quantification of specific bacterial taxa during the pre-weaning period (i.e., until 4 weeks of age).[30,90] Masuoka *et al.* has investigated the levels of *Bifidobacterium* spp. and *Lactobacillus* spp. with qPCR in 5 different age groups of cats: 12 to 13 days old, 7 to 8 weeks old, 2-3 years old and 10-14 years old. *Lactobacillus* spp. were at similar levels across all age groups, whereas *Bifidobacterium* spp. levels decreased with age.[30] The second study compared the effect of 2 different commercial dry diets in kittens from 4 weeks until 9 months of age using FISH and DGGE. In this study, species diversity decreased with age as less bands were found over time in both groups and kittens fed a higher protein diet had a more similar microbiota to each other.[90] It has been shown that dysbiotic individuals have a more variable microbial composition compared to healthy individuals[94] and thus lower protein diets might induce dysbiosis in kittens. At an order level, within the phylum Firmicutes, the lactic acid bacteria were considered one of the most prevalent bacteria in kitten feces at all time points. *Enterococcus* spp. and *Clostridium* spp. increase after 4 and 6 weeks of age respectively, with Clostridium Cluster XIV being the most prevalent in kitten feces until 9 months of age. Within the phylum Actinobacteria, *Bifidobacterium* spp. and *Atopobium* spp. were highly prevalent in all age groups. Within the phylum Proteobacteria and within the phylum Bacteroidetes, *Desulfovibrio* spp. and *Bacteroides* spp. respectively decreased after 4 weeks of age in kittens.[90]

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In another study the fecal microbiota of kittens from 8 until 17 weeks of age fed either kibbled or canned diet was investigated with 454 Pyrosequencing as well as the expression of genes related to insulin and glycose pathways in the adipose tissue with RT-PCR.[87] No significant changes were identified over time in the microbiota of kittens that could be attributed to aging. The most prevalent phyla in both groups were Firmicutes (66%), followed by Bacteroidetes (22%). In kittens fed the canned diet, the 3rd most abundant phylum was Fusobacteria (19%), whereas in kittens fed the kibbled diet the 3rd most abundant phylum was Proteobacteria (1.6%). Expression levels of genes encoding leptin, insulin receptors and plasminogen activator inhibitor-1 were increased in blood of the offsprings born from queens fed canned diet.[87]

Bermingham *et al.* published a study investigating the fecal microbial shifts with 454 Pyrosequencing, as well as body composition and insulin sensitivity in kittens fed either dry or canned diets. Samples in this study were collected at 8, 17, 104 and 260 weeks of age. At a family level, Veillonellaceae, Prevotellaceae, Ruminococcaceae, Porphyromonadaceae, and Peptostreptococcaceae decreased from 8 to 17 weeks of age. A trend was observed for insulin sensitivity to be higher in kibble fed cats. The levels of butyrate, valerate, isobutyrate, isovalerate, hexanoate, and succinate decreased from 17 weeks of age until adult life in cats.[88]

In another study, rectal swabs were obtained from kittens 15 to 25 weeks of age until they became 25 to 35 weeks of age.[66] Samples were analyzed by using an Illumina platform. The most predominant phylum in this study was Bacteroidetes (33.3%) followed by Firmicutes (31.6%). No significant changes were observed in species richness or diversity over time in these age groups.[66]

Finally, the effect of early neutering in the fecal microbiota of male and female kittens has been investigated.[86] Kittens at enrollment were between 14 to 18 weeks of

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age and they were categorized by gender and by the time of neutering i.e., early (19 weeks of age), or conventionally (31 weeks of age). All kittens received amoxicillin subcutaneously during the operation and collection of samples took place 1 to 3 weeks later. Microbial composition and function did not seem to be affected by gender or by the age of neutering. Species richness and diversity significantly increased from 18 to 30 weeks of age in kittens, and minor differences were observed at 42 weeks of age, thus it was suggested that the feline microbiota stabilizes around 30 weeks. Samples within the same age groups represented high interindividual variability. The most prevalent phylum in all ages was Firmicutes (43.2%). At 18 weeks of age, the 2nd most prevalent phylum was Actinobacteria followed by Bacteroidetes, Proteobacteria and Spirochaetes. At 30 and 42 weeks of age the 2nd most prevalent was Bacteroidetes, followed by Actinobacteria, Proteobacteria and Spirochaetes. Out of the 605 genera identified, 585 increased over time and only 4 decreased.

The functional genetic composition of the immature feline microbiota has also been investigated in some of the above-mentioned studies.[85,86,92] These results demonstrate only the functional potential of the microbiota and cannot be translated into actual functional activity. The most activated biochemical pathways identified in the feces of kittens at 8, 12, and 16 weeks of age were related to; replication and repair (12.5%), amino acid metabolism (12.4%), carbohydrate metabolism (11.4%), translation (8.4%), nucleotide metabolism (7%), membrane transport (6.9%), energy metabolism (6.1%), folding, sorting, degradation (3.3%), and metabolism of cofactors and vitamins (3.3%). Some differences were observed in the functional aspects of the microbiota depending on the kitten’s diet. MPMP kittens had higher levels of genes related to amino acid biosynthesis and metabolism, vitamin, fatty acids and peptidoglycan biosynthesis, genes associated with oxidative phosphorylation, purines, pyrimidines, and sugars

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metabolism as well as urease subunits-α, β, and γ. On the other hand, feces of HPLC kittens had higher levels of genes related to mucin degradation.[85] At 17 weeks of age, kibbled-fed kittens had more genes related to bacterial proliferation, carbohydrate transport and metabolism compared to canned-fed kittens.[92] On the contrary, canned-fed kittens had more genes related vitamin biosynthesis, metabolism and transport, energy production and conversion, and taurine degradation.[92]

Between the of ages of 18 and to 42 weeks of age, genes encoding metabolic pathways related to oxidative phosphorylation increased. This finding was attributed to the concurrent increase of facultative anaerobes. Also, an increase was observed in genes related to enzymes for carbon metabolism and was accompanied by an increase in the diversity of bacteria that can utilize more carbon sources. In contrast, genes encoding pathways related to cell motility i.e., chemotactic signaling pathways and flagella, decreased with age.[86]

Similar to humans, a fecal immature microbiota that has been disrupted by antibiotics shows decreased colonization resistance. Watson *et al.* reported that AT treated kittens were susceptible to experimentally induced infection with enteropathogenic *E.coli.* In contrast, kittens not having been exposed to antibiotics were resistant to infection and enrichment of *Enterococcus hirae* decreased clinical signs in diseased kittens.[95] This study highlights that the protective role of the microbiota is conditional to exogenous factors and the health status of the cat.

3.2. Healthy gastrointestinal microbiota of adult cats

The microbiota of healthy adult cats has been extensively described in studies investigating the microbiota *per se*[18,96] and in comparative studies investigating the effect of different factors on the microbiota including age,[88,97,98] dietary

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macronutrients,[93,99,100] several diseases such as diabetes[97], and in response to medications such as omeprazole.[101] Different segments of the GI tract have distinct microbial populations; however, it has been shown that the microbiota is more similar within each cat compared to the microbiota of each intestinal compartment among cats.[79] Ten to 30 different bacterial phyla have been identified[102-104] and although there are important differences in study design and methods used for microbiota assessment, most studies agree that Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Fusobacteria are the predominant phyla present in adult cat feces. Less commonly identified bacterial phyla include Tenericutes,[105] Synergistetes, Thermotogae,[106] Spirochaetes, Verrucomicrobia, Cyanobacteria, Chloroflexi, Planctomycetes,[102] and TM7, OD1 and Acidobacteria.[104] The microbiota of senior cats is mainly comprised of Firmicutes and Actinobacteria,[98] and differences compared to adult cats have been identified at a family level with Peptostreptococcaceae,[88] and at a genus level with *Faecalibacterium* spp., *Enterococcus* spp., and *Lactobacillus* spp. affected by ageing.[30,88,97]

Firmicutes is commonly the most abundant phylum present in feline feces varying from 13% to 93.5% (mean 59.3%)[19,64,79,93,97,101,103-115] and its most prevalent classes are Clostridia, Bacilli, Erysipelotrichia,[112] and Negativicutes,[64] while the most prevalent orders are Clostridiales and Lactobacillales.[97] The order Clostridiales is comprised by Clostridium clusters (e.g. *Lachnospiraceae* spp., *Faecalibacterium* spp., *Ruminococcus* spp., *Dorea* spp., *Blautia* spp.), which are present in different abundancies across the GI tract with Clostridium Clusters XIVa and IV being the most prevalent clusters of Clostridiales.[102]

The abundance of Actinobacteria commonly varies in feline studies from 1.2% to 68% (mean 16.5%).[19,64,79,93,97,101,103,105-108,110-115] Few studies support that Actinobacteria

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is the most prevalent phylum of fecal microbiota, as demonstrated mainly in healthy laboratory bred adult cats,[99,112,113] and in a single study in indoor and outdoor cats.[116] Actinobacteria levels have been underestimated in studies using 16S rRNA gene sequencing when using universal primers.[102,111] Within this phylum, the class Actinobacteria[64] and the orders Coriobacteriales and Bifidobacteriales have been reported as the most prevalent in feline feces.[97] In a FISH study, Atopobium clusters and *Bifidobacterium* spp. were the most prevalent bacteria present in cats.[99]

The abundance of the phylum Bacteroidetes varies from 0.5% to 35% (mean 13.4%)[64,79,93,97,101,103,105-115] and within this phylum, Bacteroidia,[64,112] and Bacteroidales,[106] have been reported as the most abundant class, and order, respectively, present in feline feces. Interestingly, Prevotella and Bacteroides were the most prevalent genera among all genera present in a study using Illumina.[96]

Proteobacteria levels vary from 0.2% to 37.5% (mean 9.1%).[64,79,93,97,101,103,105-108,111-115] Within this phylum, Gammaproteobacteria and Epsilonproteobacteria have been reported as the most abundant classes.[64,112] Although members of this phylum including *E.coli*, *Campylobacter* spp., and *Salmonella* spp., are considered pathogenic, they have been isolated from fecal samples of healthy cats.[117]

Fusobacteria phylum is commonly a minor constituent of the feline fecal microbiota with an abundance varying from 0% to 11.7% (mean 2.1%).[64,79,93,97,101,103,105-108,110-115] Within this phylum, Fusobacteriia is the most prevalent class[112] and Fusobacteriales the most prevalent order.[97] In a single study, the genus Fusobacteria was one of the most abundant genera present.[96] A bias in the abundance of this phylum might exist since it has been found at higher levels in cats fed high protein diets such as canned or raw,[118] whereas in most studies cats consume dry diets.

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In addition to bacteria, fungi, archaea, and viruses also inhabit the GI tract of cats.[102] The feline fungal microbiota represents 0.02%[106] to 0.31%[107] of the phylogenetic sequences. Most fungal sequences have been reported to belong to the kingdom Dikarya,[106] the phyla Ascomycota,[107,119] Neocallimastigomycota,[119] or Ascomycota and Chordata[107] and the genera Aspergillus and Saccharomyces represent the predominant communities present.[18] Archaea represent 0.9% to 1% of phylogenetic sequences[106,107] with the phyla Crenarchaeota, Euryarchaeota and Korarcheota being the most predominant communities.[106,119] The virome ranges from 0.09%[106] to 0.24%[107] with Rotavirus, Astrovirus and Bocavirus constituting the main feline viral communities.[120]

Besides the taxonomic profiling of the feline genome, the functional gene content has also been described. The most abundant functional gene sequences of the feline metagenome are related to carbohydrate, protein and amino acid metabolism, cell wall and capsule synthesis and transport, DNA and RNA metabolism, virulence factors, biosynthesis of vitamins, co-factors, prosthetic groups, and pigments.[106,107] Genes encoding resistance to antibiotics can also be present at small percentages (<1%).[106]

3.3. Role of the gastrointestinal microbiota in health

With the advances of research and molecular techniques over the last years it has been widely recognized that the GI microbiota plays an irreplaceable role in macronutrient metabolism, local and systemic immune development and response, and production of bioactive molecules important in health maintenance and disease development.

3.3.1. Carbohydrate metabolism

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Carbohydrates are a more preferable energy source for the human GI microbiota compared to proteins.[121] Dietary carbohydrates that escape primary digestion in the small intestine reach the large intestine. Mammals are able to metabolize disaccharides but not polysaccharides and rely on their microbiota on harvesting energy from polysaccharides. Polysaccharides include cellulose, xylan and pectin. The undigested carbohydrates are metabolized by members of the large intestinal microbial communities with a process called saccharolytic fermentation.[122] Despite the carnivorous nature of cats, the feline microbiota not only has the ability to ferment carbohydrates at a similar magnitude with omnivorous animals[123,124] but also the end-bacterial products have beneficial effects for this species.[125] Some bacteria (e.g. members of the genera Bacteroides and Bifidobacterium), are also enriched with the ability to breakdown host carbohydrates, which enables them to thrive during periods of decreased dietary carbohydrate consumption. Host carbohydrates include mostly mucus components and mucus consumption compromises the intestinal epithelium integrity.[126]

The microbial genome includes genes encoding carbohydrate-active enzymes (CAZ-enzymes) and specific transporters, both of which are necessary for carbohydrate break-down.[127] These enzymes include glycoside, hydrolases, carbohydrate esterases, glycosyl transferases, and polysaccharide lyases.[128] Each bacterium possesses different metabolic pathways for degrading carbohydrates. After carbohydrate fermentation, pyruvate is produced, which is the starting material for short chained fatty acid (SCFA) formation. In more detail, pyruvate is initially catabolized into succinate, acetyl-Coa, and lactate and these metabolic products are further metabolized to produce SCFAs, and mainly acetate, byturate and propionate.[121] The beneficial and multifactorial role of SCFAs in the host regardless of its feeding behaviour is incontrovertible.[129] SCFAs provide 10% of the human daily caloric requirements and 60-70% of the colonic cells'

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energy requirements. Their importance has also been highlighted during their absence, especially butyrate absence, in which intestinal epithelial cells of germ-free mice present autophagy.[121] Moreover, SCFAs have antidiarrheic effects,[130] decrease the luminal pH, and increase intestinal absorption of sodium.[131] After intestinal absorption, they enter the blood stream and they act systemically affecting many organs.[132] SCFAs seem to participate in the communication of the gut-brain axis through mediating the release of serotonin by the intestinal enterochromaffin cells, protecting the blood-brain barrier and affecting the process of neuro-inflammation.[133] Insulin secretion by the pancreatic beta cells, lipid and glycose metabolism in the liver, adipose and muscle tissue are also mediated by SCFAs. In more detail, they act as a substrate for de novo glycose and lipid formation in the liver (see lipid metabolism), they increase fatty acid oxidation in the adipose tissue, and affect glycogen storage in the muscle tissue.[131] Finally, they influence innate and adaptive immunity, satiety,[134] they have anti-inflammatory properties[135] and are decreased in humans and dogs with IBD.[130]

3.3.2. Protein metabolism

Small and large intestinal microbiota utilize both dietary and host proteins as an energy substrate. Bacteria have acquired the ability to synthesize amino acids as well as fermenting them. Amino acids are grouped into families; glytamate, serine, aspartate, pyruvate and aromatic amino acids families and can all be synthesized by members of the GI microbiota.[136] Proteins reaching the small intestine are broken down by pancreatic enzymes into amino acids, which can then be absorbed by the small intestinal epithelium and/or be fermented by small intestinal bacteria.[137] Approximately 90% of proteins are efficiently digested in mammals. Undigested proteins reach the large intestine where they can only be broken down by bacterial proteases into amino acids. Because the

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bacterial-produced amino acids cannot be absorbed by the large intestinal epithelium, these amino acids are further fermented by large intestinal bacteria.[136] The main site of bacterial protein fermentation is the distal large intestine.[138] The degree of protein and amino acid bacterial fermentation in the large intestine depends on many factors. Increased colonic pH and transit time as well as decreased consumption of carbohydrates are associated with increased protein and amino acid fermentation by large intestinal bacteria.[138]

Amino acid catabolism results in microbial synthesis of a wide variety of substances including important neurotransmitters, sulphide-containing metabolites, aromatic compounds, and polyamines. Representative examples include GABA synthesis from glytamine catabolism, serotonin and indole synthesis by tryptophan, phenol, and p-cresol synthesis by tyrosine, and histamine synthesis by histidine. In some cases, microbial amino acid fermentation can result in SCFAs and branched chain amino acids (BCFAs); isobutyrate, 2-methylbutyrate and isovalerate formation.[138] Ammonia is also released during amino acid fermentation and is an integral component for further microbial synthesis of various amino acids.[137] High concentrations of ammonia negatively affect energy consumption by the colonocytes in humans.[138]

High protein (HP) diets increase satiety through an increase of Peptide-tyrosine tyrosine (PYY) levels in humans. It is speculated that bacterial-amino acid utilizers indirectly participate in PYY release from intestinal cells through their metabolic products including indoles and SCFAs.[134,138] On the other hand, differences in dietary protein quantity and quality have been associated with an increased risk of IBD-relapse, colorectal cancer and impaired kidney function in humans and concerns have been raised regarding a possible role of microbial fermentative end products of amino acids.[138] Cats are obligate carnivores and the deleterious effects of HP diets in omnivorous species,

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such as humans, most likely do not apply to cats. Cats are able to rapidly catabolize high levels of proteins without having increased levels of ammonia in contrast to humans and can use rapidly proteins for glyconeogenesis.[139] High dietary protein levels are compulsory for producing essential amino acids i.e., amino acids that the cat cannot synthesize by its own, as well as nitrogen for synthesizing necessary compounds such as non-essential amino acids, and hormones. Cats cannot synthesize taurine from methionine and cysteine,[140] and require daily arginine supplementation and higher levels of methionine and/or cysteine in their diet.[139]

3.3.3. Lipid metabolism

It appears that there is a crosstalk between members of the GI microbiota and lipid metabolism. Small intestinal microbiota and especially bacteria that inhabit the jejunum have an impact on lipid absorption and transport.[141] During feeding, the I and S endocrine cells of the proximal small intestine release cholecystokinin (CKK) and secretin (SCT) and these hormones facilitate lipid digestion. CCK stimulates bile secretion from the gallbladder and lipase secretion from the pancreas. SCT stimulates pancreatic digestive enzyme secretion, pancreatic and bile secretion of bicarbonate and water secretion.

Germ free (GF) mice have higher concentrations of fecal lipids and do not develop obesity when fed high fat diets because of decreased lipid absorption. An impairment in CCK signaling to the pancreas was observed as a result of decreased expression of genes encoding pancreatic CCK receptors. Transplantation of bacteria in these mice increased the expression of this gene and eventually increased lipid absorption. Another reason for decreased lipid absorption was an upregulation of genes expressing lipid transporters, and mediators of liponeogenesis and of fatty acid oxidation. The expression of

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translocase Cd36, which facilitates fatty acid uptake in the heart and muscle, diglyceride acyltransferase-1 (Dgat-1), which is responsible for triglyceride formation in order to be absorbed by the intestine and the adipose tissue, and the peroxisome proliferator-activated receptor alpha (Ppar-α or NR1-C1), which is involved in intracellular fatty acid uptake and utilization were all decreased in GF mice.[141]

Other important mechanisms through which bacteria affect lipid metabolism include bile acid and SCFAs homeostasis.[142] A unique finding in cats is that they conjugate bile acids in the liver only with the amino acid taurine and not with glycine like humans.[140] Primary bile acids are released into the intestine and interact with the intestinal bacteria, which convert them to secondary bile acids. The bile salt hydrolase (BSH), which is of bacterial origin, is responsible for bile acid deconjugation.[143] An important role of bile acids is lipid emulsification into smaller particles, which are broken down by lipases into absorbable fatty acids.[144] Uptake of fat-soluble vitamins A, D, E, K by the intestine is also facilitated by bile acids.[145] The GI microbiota interferes with bile acid receptor signaling and especially with the nuclear receptors farnesoid-X-receptor (FXR) and G protein-coupled receptor 5 (TGR-5).[142] FXR and TGR-5 activation results in an improvement in lipid profile levels and metabolic homeostasis.[142,146] Interestingly altered expression of these receptors has been observed in dysbiotic subjects and is one the main hypotheses that can explain the hypothesis in which dysbiosis is a cause or trigger and not an effect of IBD.[143]

After entering the bloodstream, SCFAs can promote lipid oxidation in the liver, muscle and adipose tissue, and inhibit lipolysis in adipose tissue.[132] In the liver, acetate and butyrate are used as substrates for lipogenesis and cholesterogenesis, whereas propionate inhibits these processes as it is glyconeogenic.[122,142] Contradicting results exist regarding the role of SCFAs in obesity development and satiety regulation. Some

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studies suggest that increased SCFA levels can promote obesity through increasing total calory intake. However, other studies have shown that SCFAs increase the release of gut derived satiety hormones glycagon like peptide (GLP-1), and PYY, thus inducing short-term satiety[142] and indirectly protecting humans from weight gain.[122]

3.3.4. Immune system

The microbiota and its end metabolic products are known for orchestrating immune system development and response. The host and the immune system are co-evolving. This starts during development as through this period the microbiota, especially the GI microbiota, 'educates' the immune system about which bacteria can be considered harmful.[147]

Until recently, placenta was considered sterile. However, with the advances of molecular methods some evidence supports microorganism interactions with the infant during pregnancy, but results are conflicting.[148] In case of eventually rejecting this hypothesis, the mode of delivery and breastfeeding are believed to be the main factors that shape the microbiota at its earlier stages.[149,150] The colostrum provides IgA to the infant, which covers food and microbial antigens and protects from an excessive immune response, as well as carbohydrates, which act as a substrate for the growth of health-associated bacteria.[151] The immaturity of the immune system during early developmental stages allows microbial establishment without excessive inflammation. Microbial compartmentalization aids in the intestinal barrier and lymphoid tissue construction. The host daily interacts with a wide variety of microbial metabolites and the immune system should be taught to be stimulated in cases of pathogen invasions or production of deleterious microbial metabolites. The GI microbiota education of the human immune

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system lasts until 2 to 3 years of age, at which time the microbiota stabilizes. However, it is still unknown at which age the canine and feline microbiota become mature.[147]

After microbiota maturation, a healthy and balanced GI microbiota protects the host from pathogen colonization and/or proliferation and maintains what is called 'colonization resistance'. Colonization resistance is achieved through competition for essential nutrients, maintaining a low pH, changing oxygen levels, mucus, producing of IgA and antimicrobial peptides and regulating the balance between proinflammatory Th17 cells and anti-inflammatory Treg cells.[152]

Under stable conditions, the balance between the GI microbiota and the host is achieved through avoiding contact of microorganisms with the host's epithelial cells. The first barrier for avoiding this interaction is the mucus secreted by goblet cells.[152] The innate and adaptive immunity are further orchestrating microbial homeostasis. The innate immunity regulates balance through pattern recognition receptors (PRRs), mostly Toll-like (TLRs) and NOD-like (NLRs) receptors, as well as α-defensin secretion by Paneth cells, and by innate lymphoid cells (ILC) that secrete interferons and tumor necrosis factor (TNF). The adaptive immunity responds to microbial perturbations mainly through the expression of the inhibitor receptor programmed cell death protein 1 (PD1) by the T follicular helper cells which also regulates the production of IgA by beta cells. IgA is used by the immune system to "watch" colitogenic bacteria. Other mechanisms of adaptive immunity include invariant natural killer cells that sense microbial metabolites and mainly lipids as well as γδ intraepithelial lymphocytes that express receptors related to mucosal health maintenance.[11]

On the other hand, the dysbiotic microbiota and the secondary dysregulated metabolites produced may manipulate the immune system in triggering and maintaining a long-term inflammation. Especially in cases of dysbiosis during early developmental

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stages, the immune system receives different signals that can affect long term future inflammatory processes. For example, early interactions with lipopolysaccharide (LPS), an endotoxin which is part of the outer membrane of gram-negative bacteria may result in decreased immune responses against this substance in the future.[152] Inflammasome production, manipulation of TLRs and degradation of IgA are all reactions orchestrated by the GI microbiota and can lead to intestinal inflammation.[11]

3.3.5. Micronutrients

The GI microbiota harbors members with the ability to synthesize micronutrients. Mammals cannot synthesize vitamins and as a result vitamin sources come from either the diet or the GI microbiota. The GI microbiota provides the host with a variety of vitamins essential for health, including vitamin groups C, K, and B. Based on human evidence, it is believed that microbially derived vitamins are primarily absorbed in the colon, in contrast to vitamins derived from the diet, which are absorbed in the small intestine.[153]

Bacteria having the ability to synthesize B group vitamins also aid in maintenance of colonic immunity and intestinal barrier. Molecules produced during B vitamin microbial synthesis activate specific immune cells, called mucosa-associated invariant T-cells. Two vitamins of particular interest in dogs and cats are cobalamin (vitamin B12) and folate (vitamin B9). Abnormalities in their serum concentrations may reflect small intestinal dysbiosis, disease processes in their corresponding intestinal sites of absorption, and/or exocrine pancreatic insufficiency (EPI) in cats.[154] In cats, cobalamin deficiency results in serious metabolic and clinical outcomes including methylmalonic acidemia,[155] and abnormalities in serum amino acid concentrations,[156] and is associated with negative prognosis in chronic enteropathies.[157]

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Cobalamin is provided through the diet or is produced by bacteria and archaea inhabiting the GI tract either aerobically, anaerobically or following the salvage pathway. Absorption of cobalamin in feline species is a complex process. Dietary cobalamin is released into the stomach and binds to the R-protein. After transportation to the small intestine, the R-protein is degraded by pancreatic proteases, and free cobalamin binds to the intrinsic factor (IF). Cats are unique in that IF is produced exclusively by the exocrine pancreas. After binding to IF, cobalamin travels through the GI tract and binds to IF receptors located in the ileum, through which is absorbed, enters portal circulation and binds to trans-cobalamins that carry cobalamin to the target cells.[155] Microbial members of the large intestine have the ability to produce cobalamin;[27] however due to the lack of receptors in the large intestine, it cannot be absorbed. In humans, about 80% of non-absorbed cobalamin is converted to corrinoids.[158] Cobalamin is important for DNA, fatty acid[159] and methionine synthesis,[160] and plays a role in normal hematopoiesis and neurologic function.[159]

Folate is both dietary- and microbially-derived. Folate is mainly absorbed by the proximal small intestine in dogs and cats.[161] Recent evidence from human studies suggests that colon may be an additional site of folate absorption.[153,162] Microbial members may be folate producers, consumers or both. The phyla Firmicutes and Proteobacteria possess the highest genetic capacity of *de novo* folate synthesis, whereas other phyla mainly have genes related to folate intermediate metabolite production.[153] Dietary folate is found in a polyglutamate form and should be converted to a monoglutamate with the help of the enzyme folate deconjugase.[161] On the contrary, microbes produce folate in a monoglutamate form.[162] Folate transport takes place only after deconjugation by the help of 2 carriers: the proton-coupled folate carrier (PCFT), which is the most important, and the reduced folate carrier (RFC). Transportation takes

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place in the proximal small intestine. After intestinal absorption folate enters systemic circulation and affects cells of many tissues.[163] Folate is essential for one-carbon transfer, methylation metabolism, amino acid, purines and pyrimidine synthesis. After its absorption is essential for nucleotide biosynthesis, and DNA replication, methylation, and repair.[153]

Biotin (vitamin B7) is a vitamin mostly used as a cofactor for enzymes involved in carboxylation and this renders it necessary for fatty acid synthesis, for metabolism of odd chain fatty acids and glyconeogenesis.[163,164]

Other vitamins of the B group that are produced by the microbiota and can be useful for the host after colonic absorption include thiamin (B1), riboflavin (B2) and vitamin B6.[165]

In mammals, the vitamin menaquinone (K2) may be received with the diet after having undergone bacterial fermentation. Alternatively, K2 may be formed by members of the GI microbiota that have genes for K2 production or by conversion of phylloquinone (K1) derived from vegetables to K2. K2 absorption is believed to depend on BAs; absorbed by the ileum and transferred through the portal vein to the liver. Bacteria that produce vitamin K2 are located in the ileum and colon. Vitamin K2 is known for its importance in blood coagulation,[163] myelin integrity in the brain[166] and for affecting bone quality.[167]

Key mineral absorption seems to be affected by the GI microbiota. The microbiota has developed mechanisms for intracellular iron absorption and GF mice develop iron deficiency anemia when fed a low iron diet compared to conventional mice.[158]

4. Antibiotics

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Antibiotics have transformed the way of living. Since their discovery in the early 19th century, previously fatal bacterial infections are successfully treated saving millions of lives. Scientific evidence suggests that the history of antibiotics starts before the widely available knowledge of their mode of action meaning that some people were exposed to antibiotics without knowing it. The dawn of antibiotic era starts with the discovery of three antibiotics (Salvarsan, Prontosil, and penicillin) and new classes of antibiotics had been discovered by the 1970s.[168] Most newly synthesized antibiotics come from natural substances and in fact these natural substances are microbial metabolites. Thousands of metabolites with antibacterial action are produced by bacteria and fungi.[169]

4.1 Antibiotics and the human and gnotobiotic animal microbiota

Antibiotic treatment (AT) affects the microbiota of humans and animals in several ways. A reduction in the overall microbial diversity is the most observed effect. Microbial shifts might persist for years after antibiotic withdrawal,[170] whereas the abundances of some bacterial taxa may never return to their initial state. Antibiotics with anaerobic spectrum of activity are reported to affect the microbiota for longer periods of time, given that 95% of the GI bacteria are anaerobic.[171] AT affects not only bacterial communities but also the virome and mycobiome.[169]

AT in women during the perinatal period reduces normal vaginal transmission of *Lactobacillus* spp. to newborns.[172] In healthy infants, bacterial diversity rapidly increases during the first month of life and the human microbiota reaches an adult-like state at 2 to 3 years of age. A delayed increase in diversity and an unpredictable bacterial colonization is observed in children treated with antibiotics during this period.[173] Antibiotic treatment before stabilization of the microbiota seems to delay its

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developmental progression and maturation. Increases in *Enterococcus* spp. and Enterobacteriaceae and decreases in *Bifidobacterium* spp. have been observed in infants treated with antibiotics during the first months of life compared to untreated infants.[173,174]

Profound shifts as a result of AT have also been found in adults. Beta lactams and macrolides, including azithromycin and clarithromycin, are reported to decrease Firmicutes, and Actinobacteria and increase Bacteroidetes and Proteobacteria.[175,176] Fluoroquinolones decrease Firmicutes and Actinobacteria and increase Bacteroidetes.[176] The most common family that is increased after AT is Enterobacteriaceae.[177] Bacterial genera whose abundance is more commonly affected after AT are *Bifidobacterium* spp., *Bacteroides* spp., *Faecalibacterium* spp., *Enterococcus* spp., *Clostridium* spp., *Prevotella* spp., *Blautia* spp., *Escherichia* spp., *Lactobacillus* spp., *Ruminococcus* spp., *Streptococcus* spp., and *Eubacterium* spp.[169]

The function of the microbiota often recovers earlier than community composition and diversity following antibiotic exposure in humans.[178] The main metabolic functions normally performed by bacteria eradicated by antibiotic treatment are disrupted or are carried out by the remaining bacteria by creating an 'alternative equilibrium state',[179] which highlights the existence of a core microbiota.[172] However, some genes encoding functions of the microbiota may be over- or under-presented resulting in differences in the end metabolic products. Beta lactams and fluoroquinolones resulted in an increase, and lincosamides in a decrease of genes encoding endospore formation.[178,179] In addition, lincosamides increased the number of genes encoding lipopolysaccharide formation and genes involved in fatty acid and phospholipid catabolism.[179]

The percentage of the known fecal end metabolic products that are altered after AT in humans ranges between 4.4% to 87%.[169] The most commonly altered metabolic

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products are BAs, amino acids, SCFAs, vitamins and neurotransmitters.[169,179-182] Gentamycin and ceftriaxone resulted in decreased levels of monosaccharides and SCFAs, disturbances in the levels of amino acids and in the composition of BA.[180] Ampicillin/sulbactam and cefazolin administration led to increases of long chain fatty acids, BAs, sterol lipids, cholesterol derivatives, vitamin D precursors and prostaglandin.[179] In another study of adult humans in a prediabetic state, seven days of vancomycin administration, but not of amoxicillin, decreased fecal BA and SCFA concentrations.[183] Administration of antibiotics in neonates resulted in differences in abundances of SCFAs.[169]

4.2. Association of antibiotic induced dysbiosis with human diseases

4.2.1. AT and susceptibility to GI diseases

Clostridioides difficile-associated diarrhea – C. difficile is a spore-forming, toxin-producing bacillus. Although it has become one of the most significant nosocomial infection in humans, some people are asymptomatic carriers of this bacterium. A healthy GI microbiota is considered the only barrier that can inhibit the growth of *C. difficile* that is resistant to heat, acid, and some antibiotics.[184] Disruption of the GI microbiota with antibiotics results in an increased risk of *C. difficile*-associated diarrhea,[185] and an 87-90% of the recurrent form of this condition is successfully treated with FMT, highlighting the role of a healthy microbiota in maintaining colonization resistance.[186]

Necrotizing enterocolitis (NEC) – NEC is an intestinal disease of unknown etiology that mainly affect premature neonates.[187] Infants that have been exposed to antibiotics either prenatally or postnatally are at 1.3 to 2.7 higher risk to develop NEC

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[188-190] and a prolonged antibiotic course, (>10 days in one study), has been associated with a higher risk for NEC.[191,192]

Inflammatory bowel disease - Although its etiology is multifactorial and still poorly understood, IBD in humans has been associated with previous AT. These associations appear to be dose dependent, (i.e., the risk increases with the number of antibiotic courses) and is stronger for particular antibiotics, including cephalosporins,[193] metronidazole, and quinolones.[194] Children that have been exposed to antibiotics either prenatally or postnatally were 2- and 3-times, respectively, more likely, to be diagnosed with IBD during childhood.[194,195] In a recent large case-control study, adults exposed to antibiotics had an odds ratio (OR) of 1.88 for developing IBD.[193]

4.2.2. AT and susceptibility to other diseases

Obesity – Obesity has also been linked to previous antibiotic use in people. A meta-analysis and a population-based cohort study showed that the relative risk (RR) for obesity in children having received antibiotics ranged between 1.21 to 1.45 compared to controls.[196,197] The risk increases for each additional antibiotic course.[197] The microbiota influences energy homeostasis,[198] and facilitation of weight gain has been observed in severely malnourished children after receiving antibiotics.[199] The composition of an ‘obese microbiota’ appears to have a distinct signature and can induce or contribute to an obese phenotype.[200] AT in GF mice did not facilitate weight gain indicating a role of antibiotic induced-dysbiosis in obesity.[176] The ‘obese microbiota’ extracts more calories from the diet [201] and is characterized by increased abundance of gram-negative bacteria, which contain an endotoxin that has been repeatedly associated with low-grade chronic inflammation as the one seen in obesity.[202]

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Allergies – The "hygiene hypothesis" suggests that the increased incidence of allergic and autoimmune diseases during the last decades may be attributed to a reduced exposure to microbes early in life.[203] Microbes provide essential signals for a healthy immune system maturation and AT early in life results in limited exposure to microbes or to a dysbiotic microbiota. Mounting evidence exists supporting associations between asthma, atopy, allergen sensitization, allergic asthma, and allergic rhinitis with pre- or postnatal AT. Among antibiotics, macrolides, cephalosporins and penicillins have been mostly associated with allergies.[197,204-206] A dose-response relationship seems to exist for atopy and asthma with an increasing risk for developing these conditions as the number of antibiotic courses increases.[205,207]

Diabetes - The incidence of type 1 diabetes (T1D) has increased more than fivefold during the last 50 years. It is still unclear whether dysbiosis can trigger or exacerbate T1D.[208] In humans genetically predisposed to T1D, early probiotic treatment decreased the incidence of the disease by 60%, suggesting a protective role of the microbiota on islet autoimmunity.[209] Although some studies have found no associations between early life exposure to antibiotics and subsequent T1D development,[210] other studies have found that treatment with broad spectrum antibiotics before the age of 2 years,[211] or >2 courses of commonly used antibiotics, such as penicillins, cephalosporins, and quinolones, [212,213] increased T1D incidence in humans.

Type 2 diabetes (T2D) is characterized by impaired β-cell function, insulin resistance, high blood glucose concentrations and has also been associated with antibiotic use and GI dysbiosis. The role of microbiota in energy metabolism has been acknowledged and, in many cases, modulation or ablation of the T2D microbiota leads to alleviation of insulin resistance and inflammation, and to inhibition of β-cell apoptosis.[214-217] Amoxicillin, vancomycin, gentamycin and meropenem had no effects

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on metabolic variables in obese or in lean non-diabetic humans.[183,218] Fluoroquinolones,[219] narrow-spectrum and bactericidal antibiotics,[218] have been mostly associated with an increased risk of T2D development.

Neuropsychiatric disorders - The crosstalk between the GI tract and the brain is influenced by the GI microbiota and patients with neuropsychiatric disorders commonly have altered GI microbiota.[220] Germ-free mice have impaired social behavior and differences in the abundances of brain microglia cells.[221] The severity of GI symptoms that humans with Autism Spectrum Disorder (ASD) commonly experience, is associated with ASD severity.[222] Short term improvement in clinical manifestations of autism have been found in children receiving vancomycin [223], or vancomycin followed by FMT.[222] Some studies have found significantly increased risks (11% to 29%) for autism during early life after previous AT [224,225] whereas other studies do not support these associations.[197,226]

4.3 Antibiotics and the canine GI microbiota

Antimicrobials are commonly used in dogs and an increasing number of studies show a profound effect of antibiotics on the canine GI microbiota. The effect of AT on the GI microbiota has been investigated in healthy dogs, dogs with IBD, and dogs with acute or chronic diarrhea (Table 1). The majority of studies investigated the efficacy of metronidazole or tylosin in dogs with GI diseases as well as the effect of these antibiotics on the GI microbiota.

4.3.1. Metronidazole

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Metronidazole is commonly administered to canine patients with acute or chronic GI diseases. In one study, the duration of acute diarrheic episodes of unspecified etiology was significantly reduced by 1.5 day in dogs treated with metronidazole for 7 days compared to dogs receiving placebo (Table 2). However, in the same study, diarrhea resolved in about 90% of dogs within 7 days in the placebo group as well.[227] Other studies failed to identify significant or additional benefits of metronidazole for the treatment of acute diarrhea compared to probiotics[228] or other antibiotics.[229] The use of probiotics in addition to metronidazole led to resolution of diarrhea in 66% of dogs compared to 38% of dogs receiving metronidazole alone.[230] (Table 2)

In dogs with IBD, metronidazole combined with prednisolone did not have a significant impact on disease remission rates compared to prednisolone alone.[231] In another study, 80% of dogs with IBD experienced disease remission right after a 3-week course of metronidazole, and a similar percentage was noted in dogs treated with rifaximin.[232] It has been traditionally thought that, in dogs with GI signs, antibiotics primarily work by rectifying dysbiosis. However, studies applying -omic techniques have shown that metronidazole alone or in combination with enrofloxacin cause a decrease in species richness and diversity, an increase in the dysbiosis index, and a long-term disruption in bacterial abundances after their withdrawal.[233-235] The fecal microbiota of diarrheic dogs treated with FMT and the fecal microbiota of IBD dogs treated solely with corticosteroids resembled more the healthy canine fecal microbiota compared to the diarrheic and IBD dogs treated with metronidazole.[47,236] Decreases in the phyla Firmicutes, Bacteroidetes, and Fusobacteria, and increases in Actinobacteria have been reported.[233] In IBD dogs, a reduction in health-associated bacteria, such as *Blautia* spp. and *Faecalibacterium* spp., which are known for their ability to produce SCFAs, and an increase in potentially pathogenic bacteria, such as *Escherichia* spp. has

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been reported after metronidazole treatment.[47] The fecal metabolome is also altered in response to metronidazole. Increases in fecal primary BAs, cholic acid and chenodeoxycholic acid, and decreases in fecal secondary BAs, deoxycholic acid and lithocholic acid have been found in healthy dogs and dogs with acute diarrhea.[234,236] As mentioned above, the decrease in secondary BAs impairs colonization resistance. In addition, decreases in fecal vitamin and antioxidant concentrations, and increases in oxidative stress molecules (such as isothreonic acid and ribonic acid) have been found in healthy dogs treated with metronidazole.[234] The serum metabolome of IBD dogs remained unaffected after metronidazole treatment.[47]

4.3.2. Tylosin

Four decades ago, tylosin was reported to be effective in cases of chronic intermittent diarrhea in dogs. For that reason, this condition was named tylosin-responsive diarrhea.[237,238] In one study, 85% of dogs had resolution of diarrhea by the end of a 7-day course with tylosin, compared to 29% of dogs receiving placebo.[239] However, after the initial response to treatment, relapse of clinical signs was common, reported in 55% of dogs within 20 days, and in 85% of dogs within 30 or 60 days; subsequently these dogs commonly required multiple tylosin courses.[238-240] In other studies, tylosin led to complete resolution of diarrhea in all dogs or resulted in firmer feces when combined with a GI diet compared to when administered alone.[237,238]

The effects of tylosin on the fecal microbiota have only been investigated in healthy dogs. Similar to metronidazole, tylosin decreased fecal species richness and diversity, and increased the dysbiosis index as well as the levels of primary bile acids in feces.[241] Immediate decreases were observed in the abundance of Bacteroidaceae, and discordant results were found for Clostridiaceae. At a genus level, some health-

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associated bacteria increased, such as and *Enterococcus* spp.[242] while others decreased, such as *Blautia* spp., *Faecalibacterium* spp., and *Turicibacter* spp. after tylosin treatment.[241]

Based on the above studies, treatment with metronidazole or tylosin commonly leads to resolution of clinical signs in dogs with chronic diarrhea, but in most cases this resolution is short-term and clinical signs relapse. In addition, AT failed to correct GI dysbiosis in studies applying -omic techniques. Therefore, despite the initial response in dogs with chronic diarrhea treated with metronidazole or tylosin, if one considers that relapses requiring additional AT are common, that disruption of the normal microbiota after AT is also common, and the fact that antibiotic resistance is a problem of global importance, the real value of the routine use of these antibiotics in dogs with acute or chronic diarrhea might need to be reconsidered. As a result, alternative methods that modulate the GI microbiota could be used, such as FMT or next generation probiotics.

4.3.3. Fecal microbiota transplantation (FMT)

FMT is a procedure in which processed fecal material is transfused from a healthy donor to a recipient and it provides a healthy microbiota to a diseased patient. FMT has been proven more effective in controlling dysbiosis compared to all other microbiota-modulating therapeutic options in humans with acute and chronic GI diseases, [243] and has been tested in dogs with promising results. In one study, all diarrheic dogs positive for *C. perfingens* toxin a, were refractory to antibiotics but had resolution of diarrhea after FMT.[244] Puppies with parvoviral enteritis that received fecal enemas, required fewer hospitalization days, and had faster resolution of diarrhea compared to puppies that received standard treatment.[245] In another study, 9 dogs diagnosed with IBD were treated with a single fecal enema and a significant decrease of the canine IBD activity

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index (CIBDAI) scoring was demonstrated 2 weeks after the procedure.[246] Therefore, MFT has shown promising results in treating GI dysbiosis in dogs. However, their clinical efficacy for certain conditions needs to be tested in clinical trials.

Table 1. Studies investigating the effects of antibiotics on the GI microbiota of dogs.

Refs	Animals	AT	Samples and collecting days after AT	Methods
242	5 healthy Beagles	Tylosin 20-22mg/kg/24h x 14d	Jejunal brush D0, 14, 28	16S rRNA
241	16 healthy	Tylosin 20mg/kg/12h x 7d	Feces D0, 7, 21, 63	16S rRNA, qPCR
233	5 healthy Beagles	Metronidazole 12.5mg/kg/12h x 14d	Feces D0, 14, 28, 42	Illumina
247	20 IBD 10: AT + prednisolone, 10: probiotic, 10: healthy	Metronidazole 20mg/kg/12h x 60d	Feces D0, 60	qPCR
248	24 healthy adults 8: control 8: AT + hydrolyzed diet 8: hydrolyzed diet	Metronidazole 15mg/kg/12h x 14d	Feces D0, 14, 28, 42	qPCR
47	12 IBD Pre IBD Post IBD (5/12 received AT) 10 healthy	Metronidazole 10mg/kg/12h x 18d	Feces serum D0, 18	454 pyrosequencing Untargeted metabolomics in serum
249	24 healthy 8: control 8: AT + hydrolyzed diet 8: AT + standard diet	Metronidazole 15mg/kg/12h x 14d	Feces, serum D0, 14, 28, 42	Illumina Untargeted metabolomics in feces and serum
234	24 healthy 8: fed various diets (1) 8: hydrolyzed diet x 6w and then AT (2) 8: various diets + AT (3)	Metronidazole 15mg/kg/12h x 14d	Feces (1): D0, 7, 21, 42 (2): D0, 21, 42, 49, 56 (3): D0, 7, 14, 28, 42	Illumina, qPCR, Untargeted metabolomics in feces and serum
236	18 dogs with acute diarrhea 11: FMT 7: AT	Metronidazole 15 mg/kg/12h x	Feces D0, 7, 28	Illumina, qPCR, Targeted metabolomics for BAs
250	20 healthy Beagles 5: AT 15: AT + 3 different formulations of ribaxamase	Amoxicillin 40mg/kg/8h x 6d	Feces serum D0, 6	Illumina
251	20 healthy Beagles 5: AT 15: AT + 3 different dosages of ribaxamase	Amoxicillin 40mg/kg/8h x 6d	Feces, serum D0, 6	Illumina

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252	7 healthy relatives	Amoxicillin 10mg/kg/12h x 7d	Feces D0, 2-5, 7, 14, 21	PCR, DGGE, culture for resistant bacteria
253	42 healthy dogs 21: AT 21: AT + clavulanate	Amoxicillin 10 to 20 mg/kg/12h x 7d	Feces D0, 5, 12-14	16S rRNA, culture for resistant bacteria
254	16 dogs with acute diarrhea 8: AT 8: placebo	Amoxclav 12.5 to 25 mg/kg/12h x 7d	Feces D0,6,30	qPCR, culture for resistant *E.coli*
235	22 healthy research dogs 11: AT 11: AT + probiotic	Enrofloxacin 10 mg/kg q24h x 21d and Metronidazole 12.5 mg/kg q12h x 21d	Feces D0, 5–7, 26–28, and 82–84	Illumina, qPCR Untargeted metabolomics

Table 2. Studies investigating the effects of antibiotics in acute and chronic GI diseases in dogs.

Ref	Study design	Antibiotics administered	Parameters evaluated	Results
237	Beagles with CD (*n* = 7) Part one: AT 1 + diet 1 (*n* = 7); Part two: AT 2 + diet 2 + PRED 2 mg/kg q24h (*n* = 6)	AT 1: TYL 20 mg/kg q24h (*n* = 7) AT 2: MET 30 mg/kg q12h (*n* = 3), TRIM-SUL 30 mg/kg q12h (*n* = 2), DOX 6 mg/kg q12h (*n* = 3)	FS	Sign diff in 1. ↓FS within 2-3d with TYL; 2. Diarrhea re-appeared within 2w in all TYL dogs. No sign diff in FS in dogs receiving AT 2 + PRED
238	Dogs with CD (*n* = 14) Part one: AT (*n* = 14); Part two: dogs that relapsed AT; Part three: dogs that relapsed AT + PRED	TYL 6-16 mg/kg q24h x 2w	Resolution of diarrhea	In 14/14 dogs diarrhea resolved and in 12/14 dogs diarrhea relapsed within a month
231	Dogs with IBD (*n* = 54) PRED (*n* = 25) PRED + AT (*n* = 29)	MET 10 mg/kg q12h x 21d	Complete or partial remission [a]	No sign diff in remission rates: 83% PRED + AT vs 88% PRED
239	Dogs with CD (*n* = 71) Part one: AT (*n* = 47) or placebo (*n* = 24); Part two: dogs that relapsed received again AT or placebo (*n* =	TYL 25 mg/kg q24h x 7d	Resolution of diarrhea	Part one: 61 dogs – 43.3% diarrhea re-appeared within 2m; Part two: 85% TYL dogs diarrhea resolved vs 29% placebo dogs diarrhea resolved; Part three: 6 dogs total (2-TYL, 4-placebo) - 50% dogs diarrhea resolved

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	61); Part three: all dogs that relapsed AT			
240	Dogs with TYL-responsive diarrhea received different AT doses (*n* = 15)	TYL 5 mg/kg or 15 mg/kg or 25 mg/kg q24h x 7d	Efficacy of different TYL doses	No sign diff in diarrhea resolution between dogs receiving different TYL doses
232	Dogs with CE (*n* = 25) AT 1 (*n* = 10) or AT 2 (*n* = 15)	AT 1: MET 15 mg/kg q12h x 21d, AT 2: RIF 25 mg/kg q12h x 21d	Complete or partial remission, CRP	Sign diff after 21d in 1. remission rates with both ATs; 2. CRP reduction. No sign diff in the efficacy between the ATs and CRP reduction.
230	Dogs with unspecified diarrhea AT + probiotic or AT + placebo	MET 25 mg/kg q 12h x 7d	Resolution of diarrhea	Sign diff in 1. Resolution of diarrhea on d7: 65.6% AT + probiotic vs 46.9% AT; 2. FS<4: 2.5d MET + probiotic vs 3d MET + placebo
229	Dogs with AHD (*n* = 34) AT 1 (*n* = 14) or AT 2 (*n* = 20)	AT1: AMC 8.75 mg/kg q8h AT2: AMC + MET 10 mg/kg q12h	Duration of hospitalization	No sign diff in duration of hospitalization: 26.3h with AMC vs 29.6h with both ATs
228	Dogs with AD (*n* = 60) Probiotic (*n* = 20), AT (*n* = 20), placebo (*n* = 20)	MET 125 mg in dogs 4-10 kg q12h 250 mg in dogs 10.1-20 kg q12h 400 mg in dogs 20.1-40 kg q12h	Resolution of diarrhea	No sign diff in 1. Mean duration of diarrhea: 3.5d probiotic, 4.6d MET, 4.8d placebo; 2. Relapse of diarrhea: 4/20: probiotic, 1/20: MET, 3/20: placebo
227	Dogs with AD (*n* = 31) AT (*n* = 14), placebo (*n* = 17)	MET 10-15 mg/kg q12h x 7d	Resolution of diarrhea	Sign diff in duration of diarrhea: 2.1d MET vs 3.6d placebo

AD, acute diarrhea; AHD, acute hemorrhagic diarrhea; AMC, amoxicillin-clavulanic acid; AT, antibiotic treatment; CD, chronic diarrhea; CE, chronic enteropathies; CRP, C-reactive protein; d, days; DOX, doxycycline; FS, fecal scoring; h, hours; IBD, inflammatory bowel disease; MET, metronidazole; PRED, prednisolone; RIF, rifaximin; sign diff, significant difference; TRIM-SUL, trimethoprim-sulfadiazine; TYL, tylosin.
a Complete remission: >75% reduction in the Canine Inflammatory Bowel Disease Activity Index Score (CIBDAI) and partial remission: 25%-75% reduction in the CIBDAI.

4.3.4. Effect of other antibiotics on the canine GI microbiota

Microbial compositional alterations have also been observed with amoxicillin treatment leading to a reduction is species richness and diversity.[250] In one study, amoxicillin-clavulanate induced broader changes in the fecal microbiota compared to

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amoxicillin alone, with decreases in SCFA-producing bacteria, such as *Roseburia* spp. and *Lactococcus* spp.[253] Ribaxamase, a beta lactamase, has been experimentally used for beta lactam degradation in the small intestine distal to the site of oral beta lactam absorption in order to reduce the microbiota disruption with promising results.[250,251] Increases in Firmicutes, Fusobacteria and Proteobacteria and decreases in Bacteroidetes and Actinobacteria were observed in dogs receiving amoxicillin compared to dogs receiving amoxicillin plus ribaxamase.[251] In another study, Enterobacteriaceae, *Enterococcus* spp., *Campylobacter* spp. increased while *Bacteroides* spp. decreased after amoxicillin treatment compared to the pre-treatment period.[252] Finally, resistant enterococci and *E.coli* strains have been isolated from dogs treated with amoxicillin 1- and 3-weeks post treatment.[253,254]

4.4 Antibiotics and the feline GI microbiota

A disruption of the GI microbiota has also been observed in cats receiving AT (Table 3). The effects of amoxicillin/clavulanic and clindamycin have been described in healthy adult cats (Table 3).[112,113,255]

Table 3. Studies investigating the effects of antibiotics on the GI microbiota of cats.

Refs	Animals	AT	Samples and collecting days after AT	Methods
255	34 research healthy 17: AT + probiotics 17: AT + placebo	Amoxclav 62.5mg/cat/12h x 7d	Feces D0, 7, 14	Illumina
113	16 research healthy 8: AT + probiotics 8: AT + placebo	Clindamycin 150mg/cat/24h x 21d	Feces D0, 1-7, 26-28, 631	Illumina, qPCR Untargeted metabolomics
112	16 research healthy 8: AT + probiotic 8: AT + placebo	Clindamycin 75mg/cat/24h x 21d	Feces D0, 21, 63	Illumina, qPCR Untargeted metabolomics

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Antibiotic responsive enteropathy is a poorly described condition in cats. Although altered GI microbiota and metabolome have been described in cats with acute or chronic GI diseases,[256,257] there is currently little evidence that antibiotic use helps in the management of these conditions.[258] The effects of metronidazole and tylosin on the GI microbiota and secondary metabolites have not been described in cats.

Clindamycin effects on the fecal GI microbiota and metabolome persisted for at least 2 years after its discontinuation. A decrease in the number of different species and microbial diversity has been reported at the end of clindamycin treatment, while decreases in the families Prevotellaceae, Veillonelaceae, Enterobacteriaceae, and Porphyromonadaceae were still found after 2 years of clindamycin withdrawal.[113] The fecal metabolome was also profoundly affected in response to clindamycin. Decreases in cholic acid, a primary BA, and deoxycholic acid, a secondary BA, were observed one month and two years after treatment, respectively. In addition, clindamycin caused a disruption in the abundances of metabolites related to SCFAs, amino acid metabolites, such as tryptophan and indole-3-lactate, sphingolipids, and antioxidant functions.[112,113]

Amoxicillin/clavulanic acid in adult cats increased fecal concentrations of *Enterobacteriaceae*, and *Enterococcus* spp., and decreased *Bifidobacterium* spp., and *Collinsella* spp.[255] In another study, all kittens treated with a combination of amoxicillin/clavulanic acid and pradofloxacin developed clinical signs after experimental infection with enteropathogenic *E.coli* whereas the administration of a probiotic containing *Enterococcus hirae* ameliorated the severity of clinical signs. In contrast, kittens not having been exposed to antibiotics were resistant to infection.[95]

5. Feline gastrointestinal microbiota in diseases

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Alterations of the feline GI microbiota have been identified in both intestinal and extra-intestinal disorders. GI disorders include acute and chronic diarrhea,[259,260] viral and parasitic infections,[64,114,115,261,262] and IBD and alimentary lymphoma.[80-82,257,263,264] Extra-intestinal disorders include type 2 diabetes,[97,265] obesity,[63,108,266,267] and chronic kidney disease.[268-270].

5.1. Acute and chronic diarrhea

The fecal microbiota of laboratory adult cats with naturally occurring chronic large bowel diarrhea, was evaluated in response to 2 dietary treatments for one month in a crossover manner. Fecal samples were analysed by using 454 pyrosequencing. Bacteria that were found to be strongly associated with fecal scoring were *Slackia* spp., *Raoultella* spp., and *Collinsella* spp., *Campylobacter upsaliensis* as well as unclassified bacteria belonging to the orders Clostridiales and Aeromonadales and the families Lachnospiraceae and Succinivibrionaceae.[259]

In another study, the fecal microbiota, and the microbial functional gene content of cats with acute or chronic diarrhea compared to healthy cats was described by using 16S rRNA sequencing and qPCR for specific bacteria. Diarrheic cats had increased levels of Beta- and Gamma-Proteobacteria, Bacilli and *Clostridium* spp. compared to healthy cats. *Faecalibacterium* spp. levels were lower in cats with chronic diarrhea compared to healthy cats. *C. perfingens* was found increased in a sub-group of cats with haemorrhagic diarrhea.[260] Other evidence suggests that *C. perfingens* is the most prevalent bacterium detected in fecal samples from diarrheic cats (81.3%) followed by *Campylobacter* spp. (47.6%), and *Salmonella* spp. (1.7%).[261] Bacteroidaceae was overrepresented in acute diarrheic cats compared to chronic diarrheic cats, whereas Erysipelotrichia and *Lactobacillus* spp. were underrepresented. The levels of genes

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related to the functional characteristics of the microbiota also showed differences between diarrheic and healthy cats. Carbohydrate and amino acid metabolism, as well as vitamin and other substance synthesis were altered in diarrheic cats.[260]

5.2. Chronic constipation and megacolon

In a single study, cats with chronic constipation and megacolon did not have a significantly different fecal microbial community composition compared to healthy cats as determined by qPCR. However, a probiotic mixture of lactic acid bacteria for 90 days resulted in amelioration of clinical signs (i.e., improvement of fecal scoring, reduction in FCEAI scoring), increase in the numbers of health associated bacteria and cells related to GI motility and a reduction in mucosal inflammation.[271]

5.3. Viral and parasitic infections

Two studies exist that report GI microbiota alterations in privately owned cats with viral infections including coronavirus (FCoV) and feline immunodeficiency virus (FIV) both using Illumina metagenomic sequencing. Cats with coronavirus were either asymptomatic or were diagnosed with feline infectious peritonitis (FIP) and their fecal microbiota was compared with FCoV negative healthy cats. There was a tendency for significant differences at a phylum level and this can be depicted by the differences in the Firmicutes/Bacteroidetes ratios in each group (0.9 in the control group, 0.5 in the FIP group and 0.1 in the FCoV-positive group). The fecal microbiota of the FCoV group demonstrated more differences compared to the FIP and the control group, and that was probably due to the higher enteric tropism of FCoV compared to its mutated form. The highest interindividual variability was observed within the cats with FIP. However, a very small number of animals was used in each group (n=5) possibly masking additional

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differences.[115] Weese *et al.* searched for differences in the microbiota of FIV positive compared to healthy FIV negative cats by obtaining rectal swabs. Differences were observed at an order level, with FIV positive cats having higher counts of Bifidobacteriales, Aeromonadales, and Lactobacillales.[64]

The fecal microbiota during GI parasitoses, Giardia spp., coccidia,[262] and nematodes[114] has also been evaluated. The fecal microbiota of 16 Giardia-negative cats and 8 Giardia-positive cats; 6 clinically healthy cats and 2 cats with diarrhea was investigated with 16S rRNA sequencing. One out of the 2 diarrheic cats tested positive for *Tritrichomonas foetus*. Giardia positive cats had decreased levels of *Subdoligranulum* spp. and increased levels of *Roseburia* spp., both genera belonging to Firmicutes phylum. Eight out of 22 cats were Cystoisospora positive, and those cats showed more differences in their fecal microbial members at a genus level compared to Giardia infected cats. These differences were increases in genera belonging mostly to Firmicutes (*Olsenella* spp., *Megamonas* spp., *Geobacillus* spp.), Proteobacteria (*Thermomonas* spp., *Schlegelella* spp.) and the genus Bifidobacterium. Finally, the *Toxocara cati*-induced fecal bacterial shifts have been investigated compared to negative cats, all being on the same diet, with Illumina metagenomic sequencing. Increases in the members of the phylum Actinobacteria (Coriobacteriia, Coriobacteriales, Coriobacteriaceae, *Collinsella* spp.), and Firmicutes (Lactobacillales, Enterococcaceae, *Dorea* spp., *Ruminococcus* spp. and decreases of Gamma proteobacteria were observed in positive cats.[114]

5.4 Inflammatory bowel disease and alimentary lymphoma

Few studies in cats have described the GI microbiota in IBD either in comparison to healthy animals,[263] or to cats with alimentary lymphoma,[81,82,257] or before and after

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therapeutic interventions.[99] Some studies have used fecal samples[99,263,264] whereas others have used duodenal,[80,81] ileal and colonic biopsies.[82] Dysbiosis observed and the innate dysregulated immune responses in feline IBD share many similarities with human IBD.[33]

Inness *et al.* compared the fecal microbiota of cats with small and large bowel IBD with the microbiota of healthy cats using FISH. Same diets were administered to the cats of each group but not between groups with the IBD group receiving a diet higher in protein and fiber. Total bacteria, *Bifidobacterium* spp., and *Bacteroides* spp. were decreased and *Desulfovibrio* spp. was increased in IBD cats compared to healthy cats. *Bifidobacterium* spp. is reported to act antagonistically with *Desulfovibrio* spp., which is associated with GI-related human diseases.[263] FISH was also used in another study to compare the microbiota in duodenal biopsies from cats with IBD and healthy colony cats and the same time RT-PCR was used to evaluate cytokine expression. A different distribution of bacteria in mucus, epithelium and within the mucosa was observed between healthy and cats with IBD. Higher levels of bacteria were observed in the free and adherent mucus of healthy cats with Enterobacteriaceae, *Clostridium* spp. and *Streptococcus* spp. located more frequently within the free mucus. Enterobacteriaceae was the most abundant bacterial group observed in IBD cats and some members were located within the adherent mucus. Invasive *Clostridium* spp. was also identified in IBD cats. Total bacteria counts were higher in IBD cats and total bacteria were associated with mucosal structure rearrangements and abnormal accumulation of inflammatory cells (T cells and macrophages). Adherent Enterobacteriaceae, free and invasive *Clostridium* spp. and free *E. coli* were correlated with clinical severity, with abnormalities in mucosal architecture and with differences in proinflammatory cytokines (IL-1, -8, -12) expression.[80]

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In an attempt to investigate the effect of the administration of a novel galactooligosaccharide (GOS) on the fecal microbiota, cats with IBD and healthy cats were initially fed a diet that contained GOS, followed by a control diet in a crossover manner, and fecal samples were analyzed using FISH. In contrast to the Inness et al. study,[263] no differences in total bacteria and *Bifidobacterium* spp. were found between IBD and healthy cats. However, the high interindividual variability in the fecal microbiota of these cats may explain the lack of differences between cats of IBD and healthy cats in response to prebiotic administration.[99]

Another study used FISH to compare mucosal ileal and colonic samples of cats with IBD and cats with small cell alimentary lymphoma. Increased *Fusobacterium* spp. levels were observed in free mucus and the epithelial surface in the colon, as well as in the adherent mucus in the colon and ileum of cats with lymphoma compared to cats with IBD. Also, increased *Bacteroides* spp. levels were observed in the free, adherent mucus and the epithelial surface of the ileum in the cats with lymphoma. The main distribution of bacteria was observed within the adherent mucus compared to the other compartments.[82]

CD11b is expressed on bone marrow derived-myeloid cells and acts as a chemoattractant to initiating leucocyte accumulation and a cascade of immune responses. These cells are present at high amounts in cancer microenvironments and influence cancer development and progression. In humans colorectal cancer, CD11b deficiency has been associated with decreased the tumor growth.[272] Nuclear factor kappa B (NF- κ B), a complex of transcription factors, has the ability to trigger the expression of pro-metastatic genes and high expression of this factor is associated with tumor genesis and metastasis in humans and dogs. *Fusobacterium* spp. were associated with

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increased CD11b and NF- κB levels in cats with GI lymphoma compared to cats with IBD.[82] In people, *Helibobacter pylori* has been associated with GI carcinogenesis.[81]

Marsilio *et al.* compared the fecal microbiota and metabolome of healthy cats and cats with chronic enteropathies (CE) including cats with IBD and lymphoma, using Illumina metagenomic sequencing and untargeted metabolomics, respectively.[256,257] Species richness was decreased in cats with CE compared to healthy cats. A trend was observed for decreased Ruminococcace, *Turicibacter* spp., *Bifidobacterium* spp., members of the phylum Bacteroidetes and increased Enterobacteriaceae and Streptococcaceae in CE cats compared to healthy cats.[257] Regarding the fecal metabolome, increased concentrations of several amino acids, arachidonate and simple sphingolipids, and reduced indole derivatives were found in the feces from CE cats compared to healthy cats.[256]

Finally, the mucosal microbiota of cats with small intestinal alimentary lymphoma, either small- or large-cell, and small intestinal IBD was compared to healthy cats with FISH. The amount and distribution of bacteria were visualized in luminal, mucus, adherent, invasive, intravascular, or serosal biopsy compartments. More bacteria were found in the lumen of cats having both lymphoma types compared to controls and more bacteria were found in cats with large cell lymphoma compared to cats with small cell lymphoma. In cats with large cell lymphoma, mucosal invasive or serosal surface colonizing bacteria and exclusively intravascular bacteria were found more frequently compared to the other groups rendering them susceptible to bacterial infections and septicemia.[81]

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PART TWO – OUR STUDY

1. Aims of the study

Antibiotic treatment has repeatedly been in the spotlight as a determinant factor for the creation of a disrupted gastrointestinal microbiota that may persist for an extended period. In humans, antibiotic-induced dysbiosis during childhood has been implicated in the pathogenesis of a wide range of diseases, including obesity, gastrointestinal and allergic conditions. Currently, there are no studies investigating the impact of antibiotic treatment on the composition of the gastrointestinal microbiota or the microbial function in kittens. The aim of this study was a) to describe and compare the fecal microbiota between kittens receiving antibiotics and kittens not receiving antibiotics over a time period of 10 months; b) to describe the normal fecal microbiota of healthy kittens and how the microbiota composition changes over time; c) to describe the fecal and serum metabolome, and how both of these are affected by antibiotics as well as their changes during development (from 2 months to one year of age).

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2. Article No 1

E.M. Stavroulaki, J.S. Suchodolski, R. Pilla, G.T. Fosgate, C. Sung, J.A. Lidbury, J.M. Steiner, P.G. Xenoulis

Short- and long-term effects of amoxicillin/clavulanic acid or doxycycline on the gastrointestinal microbiome of growing cats. PLoS One, 2021;16(12):e0253031

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PLOS ONE

RESEARCH ARTICLE

Short- and long-term effects of amoxicillin/clavulanic acid or doxycycline on the gastrointestinal microbiome of growing cats

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Abstract

Antibiotic treatment in early life influences gastrointestinal (GI) microbial composition and function. In humans, the resultant intestinal dysbiosis is associated with an increased risk for certain diseases later in life. The objective of this study was to determine the temporal effects of antibiotic treatment on the GI microbiome of young cats. Fecal samples were collected from cats randomly allocated to receive either amoxicillin/clavulanic acid (20 mg/kg q12h) for 20 days (AMC group; 15 cats) or doxycycline (10 mg/kg q24h) for 28 days (DOX group;15 cats) as part of the standard treatment of upper respiratory tract infection. In addition, feces were collected from healthy control cats (CON group;15 cats). All cats were approximately two months of age at enrolment. Samples were collected on days 0 (baseline), 20 or 28 (AMC and DOX, respectively; last day of treatment), 60, 120, and 300. DNA was extracted and sequencing of the 16S rRNA gene and qPCR assays were performed. Fecal microbial composition was different on the last day of treatment for AMC cats, and 1 month after the end of antibiotic treatment for DOX cats, compared to CON cats. Species richness was significantly greater in DOX cats compared to CON cats on the last day of treatment. Abundance of Enterobacteriales was increased, and that of Erysipelotrichi was decreased in cats of the AMC group on the last day of treatment compared to CON cats. The abundance of the phylum Proteobacteria was increased in cats of the DOX group on days 60 and 120 compared to cats of the CON group. Only minor differences in abundances between the treatment groups and the control group were present on day 300. Both antibiotics appear to delay the developmental progression of the microbiome, and this effect is more profound during treatment with amoxicillin/clavulanic acid and one month after treatment with doxycycline. Future studies are required to determine if these changes influence microbiome function and whether they have possible effects on disease susceptibility in cats.

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Citation: Stavroulaki EM, Suchodolski JS, Pilla R, Fosgate GT, Sung C-H, Lidbury JA, et al. (2021) Short- and long-term effects of amoxicillin/clavulanic acid or doxycycline on the gastrointestinal microbiome of growing cats. PLoS ONE 16(12): e0253031. https://doi.org/10.1371/journal.pone.0253031

Editor: Brenda A. Wilson, University of Illinois Urbana-Champaign, UNITED STATES

Received: May 23, 2021

Accepted: October 18, 2021

Published: December 15, 2021

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Data Availability Statement: The raw sequences files are uploaded to NCBI Sequence Read Archive (project number SRP16253). The remaining relevant data are within the manuscript and its Supporting Information files.

Funding: The study was funded by the Miller Trust Award of the Winn Feline Foundation (MT18-003; JSS, PGX, JMS, EMS). The URL of the funder's website is https://everycat.org/. The funders had no role in the study design, data collection and

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analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Antibiotic discovery represents one of the most important achievements in the history of medicine [1]. However, overuse of antibiotics compromises their health benefits because of the development and dissemination of antibiotic resistant genes and their impact on the gastrointestinal microbiome [2,3]. The extent that the microbiome is affected by antibiotics has become apparent after the application of "omics" approaches in research that allow the assessment of whole microbial communities and their functions [4]. The GI microbiome is a community of microorganisms and has been called "a hidden organ" [5]. This community of microorganisms is responsible for maintaining colonization resistance and produces substances with an impact on the host's metabolism, immune system development and response, and appears to participate in the communication among different organs as well as in the manifestation and progression of diseases [6–14].The term GI dysbiosis is used to describe the compositional and functional alterations of the GI microbiome in response to exogenous factors and/or the health status of the host [15]. Antibiotic-induced dysbiosis is characterized by a decrease in bacteria beneficial for the host ("health-associated bacteria"), allowing overgrowth of potentially pathogenic bacteria, and a shift in microbially derived metabolic products [15,16]. Antibiotic-induced microbial shifts can persist long term, and the abundances of some bacterial taxa might never return to their initial state. Other members of the microbiome, including the mycobiome and the virome are also affected by antibiotics, highlighting a global imbalance among members of microorganisms not directly inhibited by antibiotics [17]. Antibiotic-induced dysbiosis depends on the spectrum of antibacterial activity, type, duration, dosage, and route of administration in addition to individual host characteristics [18,19].

The GI microbiome appears to be more susceptible to antibiotics when administered early in life [20]. During that period, maturation of the immune system takes place concurrently with microbiome maturation. Antibiotics result in exposure of the host to a reduced number of microbes in the gut, which also results in changes in the microbially produced metabolites that the host is exposed to [21]. A depletion of bacteria known to ferment fiber and carbohydrates for short chain fatty acids (SCFAs) (*Faecalibacterium* spp., *Turicibacter* spp., *Blautia* spp., *Bacteroides* spp.), or convert primary into secondary bile acids (*Clostridium hiranonis*) is a common effect of antibiotic therapy in dogs [8,22–24]. In addition, bacteria that have been associated with GI diseases (*Proteobacteria* spp., *Fusobacterium* spp., *Escherichia coli*) or lactid-acid-producing bacteria (*Streptococcus* spp.) have been found upregulated after antibiotic therapy in dogs and cats [8,23–28]. In humans, antibiotics administered early in life appear to delay the developmental progression of the microbiome into an adult-like state [29,30]. Previous studies have shown that children exposed to antibiotics were more likely to develop inflammatory bowel disease [31,32], obesity [33,34], or asthma [35,36] during childhood. Currently, limited data are available for cats. In one-study, all cats previously treated with amoxicillin/clavulanic acid and pradofloxacin developed diarrhea after experimental infection with enteropathogenic *E.coli* in contrast to non-treated cats, none of which developed clinical signs [37]. This study highlights that similarly to humans, antibiotic-induced dysbiosis likely reduces colonization resistance in cats.

Feline upper respiratory tract disease (URTD) is a condition of mainly viral etiologies and clinical signs can vary in severity. Acute URTD can manifest with conjunctivitis, ocular or nasal discharge, and sneezing. In some cases, signs of other system involvement or systemic disease might occur [38]. Published guidelines suggest the use of either amoxicillin (with or without clavulanic acid) or doxycycline as a first line of treatment for the acute form of URTD [39]. Amoxicillin is a semisynthetic penicillin that is active against some non-beta-lactamase producing gram-positive bacteria and few gram-negative bacteria. The addition of a beta

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lactamase inhibitor, such as clavulanic acid, increases the spectrum of activity of amoxicillin [40]. From a microbiome perspective, amoxicillin, with or without clavulanic acid, commonly increases fecal abundances of Proteobacteria members and decreases Firmicutes and Actinobacteria members in humans and gnotobiotic animals [41–44]. Discordant findings have been reported in members of the phylum Bacteroides with some studies reporting an increase [20,41,43] and others a decrease [44–46] in members of this phylum. Some studies suggest that amoxicillin-induced microbial shifts are only temporary and subside within 2 to 4 weeks after its withdrawal [42]. Other studies suggest long-term changes including a persistent reduction in Lachnospiraceae 6 months after amoxicillin discontinuation [44]. Doxycycline belongs to tetracyclines, a class of bacteriostatic antibiotics with broad spectrum activity against bacteria, rickettsiae, and protozoal organisms. [47]. Doxycycline administration in humans and rodents has been associated with reduced fecal abundance of the phylum Firmicutes and an increased or reduced abundance of the phylum Bacteroidetes [48–50]. In mice treated with doxycycline, microbial shifts were still detected 1 month after doxycycline withdrawal [49] yet no published studies present results for a longer follow-up period.

Previous molecular studies investigating the effects of antibiotics on the feline GI microbiome have enrolled healthy cats under laboratory-controlled conditions. In these studies, cats were adults, but belonged to various age groups and were fed the same diet for the duration of each study [25,26,51]. In humans, antibiotics with an anaerobic spectrum of activity, such as amoxicillin and clindamycin, seem to have a more profound and prolonged effect on the gut microbiome, given that 95% of the GI bacteria are anaerobic [52]. In cats, administration of clindamycin affected the microbiome and metabolome long-term, with a persistent reduction in the families Prevotellaceae, Veillonelaceae, Enterobacteriaceae, and Porphyromonadaceae as well as deoxycholic acid, a secondary bile acid, for at least 2 years after withdrawal of the antibiotic [25]. In another study in cats, amoxicillin-clavulanic acid caused an increase in Enterobacteriaceae and *Enterococcus* spp. and these changes were still detected 7 days after withdrawal of the antibiotic [51]. No studies to date have investigated the effect of doxycycline and antibiotic treatment in general on the gastrointestinal microbiome of young cats until they reach maturity.

The aim of this study was to describe and compare the fecal microbiome of cats receiving amoxicillin/clavulanic acid or doxycycline and control cats not receiving antibiotics and follow them over a period of 10 months. A second goal was to describe the normal age-related changes of the feline microbiome during development.

Materials and methods

Study population

The protocol was reviewed and approved by the Animal Ethics Committee of the University of Thessaly, Greece (AUP number: 54/13.2.2018). A total of 72 eight-week-old rescue domestic shorthair (DSH) cats were enrolled in the study. Forty-four out of 72 cats were diagnosed with upper respiratory tract disease (URTD) before inclusion into the study. Diagnosis was based on a typical clinical presentation, including conjunctivitis, blepharospasm, ocular or nasal discharges, nasal congestion, sneezing, and coughing. The cats were treated with antibiotics (see Treatment) as part of the standard treatment for this condition. In addition, 26 clinically healthy cats or cats with very mild URTD that did not require antibiotic treatment were enrolled as controls.

Cats were either housed in foster homes or in individual cages at the Clinic of Medicine at the Faculty of Veterinary Science of the University of Thessaly. All cats were eventually adopted into private homes by the end of the study and owners signed an informed owner

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consent form. Upon initial enrollment, cats were kept under observation for a few days in case they developed clinical signs of GI disease. A physical examination was performed and anti-parasitic treatment (Broadline, Boehringer Ingelheim) was administered to each cat before inclusion into the study. Data including sex, body weight, body condition score (BCS), presence of diarrhea and vomiting, temperature, and heart rate were recorded (S1 Table). Evaluation of BCS and fecal score (FS) was based on previously published scoring systems [53,54]. Concurrent health conditions were recorded, and cats were excluded if these were severe enough to require hospitalization. All cats were on the same diet (GEMON Cat Breeder Kitten) for the duration of the study, to ensure that diet did not influence results. No more than two related cats were included in the same treatment group to ensure that relatedness did not bias results. All cats were vaccinated according to recent vaccination guidelines [55] and clinical data were collected throughout the study period (S1 Table).

Treatments

Cats with URTD were randomly allocated to receive either amoxicillin/clavulanate at 20 mg/kg q 12 h for 20 days (n = 23, AMC group) or doxycycline at 10 mg/kg q 24 h for 28 days (n = 21, DOX group). These antibiotics were chosen because they are first line treatments for URTD in cats [39]. In addition, 26 clinically healthy cats were enrolled as controls and did not receive any antibiotics during the study period (n = 26, CON group).

Sample collection and follow-up period

Fecal samples were collected from each cat on days: 0 (all groups; one day after initial presentation and antiparasitic treatment), 20 (AMC group; last day of antibiotic treatment for AMC group), 28 (DOX and CON groups, last day of antibiotic treatment for DOX group), 60 (all groups), 120 (all groups), and 300 (all groups). Naturally voided fecal samples were collected from the litter box and placed into Eppendorf tubes. For cats that were adopted, owners were instructed to collect fecal samples from the litter box, freeze them over night and either bring them to the clinic or ship them packed with icepacks by overnight courier. In case other animals were living in the same household, owners were asked to properly isolate their cat before sample collection. Upon receipt, samples were immediately stored at -80°C pending analysis. On each sampling day, cats underwent a physical examination and the same data as for initial presentation were collected for all cats.

DNA extraction

Genomic DNA was extracted from 100 mg of each fecal sample using a MoBio PowerSoil® DNA isolation kit (Mo Bio Laboratories, USA) according to the manufacturer's instructions.

16S rRNA sequencing

Illumina sequencing of the bacterial 16S rRNA genes was performed using primers 515F (5'-GTGYCAGCMGCCGCGGTAA) [56] to 806RB (5'-GGACTACNVGGGTWTCTAAT) [57] at the MR DNA laboratory (Shallowater, TX).

Sequences were processed and analyzed using a Quantitative Insights Into Microbial Ecology 2 (QIIME 2) [58] v 2018.6 pipeline. Briefly, the sequences were demultiplexed and the amplicon sequence variant (ASV) table was created using DADA2 [59]. Prior to downstream analysis, sequences assigned as chloroplast, mitochondria, and low quality and unassigned ASVs in the dataset were removed. A filter was used to remove rare taxa, defined as taxa that

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were not present in at least 50% of samples of at least one group or time point. All samples were rarefied to even sequencing depth, based on the lowest read depth of samples, to 8,275 sequences per sample. The raw sequences were uploaded to NCBI Sequence Read Archive under project number SRP16253.

Alpha diversity was measured with the Chao1 (non-parametric estimator of the number of rare or infrequent ASVs), Shannon diversity (evenness estimator; takes into account the proportion of each species) and observed ASVs (richness estimator) metrics within QIIME2. Beta diversity was evaluated with the weighted and unweighted phylogeny-based UniFrac [60] distance metric and visualized using Principal Coordinate Analysis (PCoA) plots, generated within QIIME2.

Quantitative PCR (qPCR)

The qPCRs assays for total bacteria, *Faecalibacterium* spp., *Turicibacter* spp., *Streptococcus* spp., *Escherichia coli*, *Blautia* spp., *Fusobacterium* spp., *Clostridium hiranonis*, and *Bifidobacterium spp.* were performed using previously published primers and probes, cycling and annealing conditions [61,62]. Extracted DNA was also used as the template for PCR amplification in a thermocycler (Bio-rad Gradient Thermal Cycler, Bio-rad Laboratories Inc., Hercules, California) of an approximately 184 bp of the *Bacteroides* spp. 16SrRNA with group-specific bacterial primers Bacteroides gen 16SF (TCGGCTAACTCCGTGCCAGC) and Bacteroides gen 16SF (ACACCACGAATTCCGCCCACC). Samples were amplified using the following protocol: initial denaturation at 95˚C for 2 min; 40 cycles of denaturation at 95˚C for 5 s, and annealing at 52˚C for 4 s.

Statistical analysis

Statistical analyses were performed using statistical software packages (SPSS version 23.0; and Prism version 9.0, GraphPad Software). For clinical data, a Kolmogorov-Smirnov test was used to assess the normality assumption. Clinical data did not pass normality testing, and therefore Kruskal-Wallis tests were used for among group comparisons while Friedman tests were used for within group comparisons. Pairwise comparisons were performed using Dunn's post hoc tests to determine which group categories were significantly different from each other as well as which time points were significantly different.

To determine differences in microbiome composition among and within the study groups, the analysis of similarities (ANOSIM) was performed using the statistical software package PRIMER 7 (PRIMER-E Ltd., Lutton, UK), and PERMANOVA was performed on QIIME2, based on the unweighted and weighted UniFrac distance matrices. Differences in alpha diversity indices were evaluated using Kruskal-Wallis tests for baseline values and linear mixed model followed by within group post hoc comparisons using Wilcoxon signed-rank tests and Bonferroni correction of p values. Differences in the abundances of bacterial taxa among and within groups were determined using Kruskal-Wallis tests for baseline values and linear mixed models. Data were rank transformed prior to fitting linear mixed models. Microbial compositions were initially screened for differences among groups with p values adjusted for multiple hypothesis testing using the Benjamini and Hochberg false discovery rate (FDR) and overall significance set at $p < 0.05$. For comparisons that were significant after FDR adjustment, a linear mixed model was fit including time, group, and the interaction between time and group as fixed effects and cat as a random effect. Multiple pairwise post hoc comparisons were adjusted using Bonferroni correction.

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Results

Clinical data

Twenty-seven cats were excluded from the study because of owner non-compliance (7/72), death (9/72; 2 due to accidents, 1 due to feline infectious peritonitis, 1 due to heart failure, while 5 had unknown cause of death), a required second course of antibiotics (5/72), antifungal treatments (3/72), or escape from home (3/72). Fifteen cats in each treatment group (45 cats total) completed the study. These included 25 males and 20 females. Microbiome analysis and clinical data assessment were only performed for the cats that completed the study (S1 Table).

On day 0, cats of the AMC group had significantly lower body weights (BW) (median 0.61 kg, range 0.37–0.95 kg) compared to CON cats (median 0.74 kg, range 0.52–1.4 kg) ($p = 0.026$; Table 1). No other BW or BCS differences were identified among groups. On day 0, cats belonging to the DOX group had a significantly higher fecal score (FS) (median 4/7, range 2/7-7/7), i.e., had more commonly abnormal fecal consistency, compared to CON cats (median 2/7, range 1/7-6/7) ($p = 0.045$). On days 20/28 and 60, AMC cats had a significantly higher FS (day 20, median 4/7, range 1/7-6/7; day 60, median 3/7, range 1/7-6/7) compared to CON cats (days 28 and 60, median 2/7, range 1/7-3/7) ($p < 0.05$).

1. Effect of aging on the microbiome of untreated cats. *1.A) Sequence analysis—alpha and beta diversity.* High interindividual variations in bacterial abundances were observed in all

Table 1. Clinical characteristics of cats included in the study.

	Body weight (kg)						
	AMC		DOX		CON		P value
	Median	Range	Median	Range	Median	Range	
Day 0	0.61	0.37–0.95	0.68	0.39–1.20	0.74	0.52–1.40	**0.026**
Day 20/28	1.00	0.80–1.56	1.18	0.87–1.73	1.26	0.77–1.60	0.217
Day 60	1.70	1.36–1.80	1.70	1.25–2.00	1.92	1.15–2.50	0.120
Day 120	2.50	1.98–3.79	2.62	1.99–3.05	2.80	1.69–3.80	0.746
Day 300	4.10	2.70–5.75	4.19	3.33–5.80	4.00	2.30–6.00	0.797
	Body condition score (1 to 9)						
	AMC		DOX		CON		P value
	Median	Range	Median	Range	Median	Range	
Day 0	4	2–6	4	3–5	4	3–5	0.107
Day 20/28	4	4–5	4	4–5	4	4–5	0.717
Day 60	4	4–6	4	4–5	4	3–5	0.651
Day 120	4	4–6	4	4–6	4	4–6	0.935
Day 300	4	3–7	5	4–6	5	3–6	0.281
	Fecal score (1 to 7)						
	AMC		DOX		CON		P value
	Median	Range	Median	Range	Median	Range	
Day 0	3	2–6	4	2–7	2	1–6	**0.045**
Day 20/28	4	1–6	3	2–5	2	1–3	**<0.001**
Day 60	3	1–6	3	1–5	2	1–3	**0.035**
Day 120	2	1–5	2	1–5	2	1–4	0.221
Day 300	2	1–5	2	1–3	2	1–3	0.195

AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days; CON, healthy cats that did not receive antibiotics. Bolded p-values indicate a statistically significant difference between groups.

https://doi.org/10.1371/journal.pone.0253031.t001

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groups on day 0 and within the CON group significant changes occurred over time. These changes were attributed to the process of microbial maturation, therefore results from this group are discussed separately. In total, the sequence analysis of the 225 fecal samples yielded 1,861,875 quality sequences. There were no significant differences in any of the species richness and evenness indices over time in control cats (Fig 1, S2 Table). However, the phylogenetic community structure clustered differently over time ($p < 0.05$) and was increasingly more distinct as cats were getting older based on the increasing ANOSIM effect size of unweighted and weighted UniFrac distances (Fig 2, S3 Table). PERMANOVA analysis also showed a distinct microbial composition over time in cats of the CON group (Fig 2, S4 Table).

1.B) Sequence analysis–abundance of individual bacterial taxa. At 2 months of age (day 0) the most prevalent phylum (regardless of the group) was Firmicutes (63.5%), followed by Actinobacteria (13.9%), Bacteroidetes (11.6%), Proteobacteria (6.0%), and Fusobacteria (4.9%). The abundance of Proteobacteria was significantly reduced to less than 1% ($p = 0.009$) by 4 months of age in the control cats (Fig 3). S5 Table contains summary statistics for all taxonomic classifications (i.e., phylum, class, order, family, genus, and species).

Clostridia, Clostridiales, and Lachnospiraceae, were the most prevalent class, order, and family, respectively, present in fecal samples from control cats during their first year of age. In addition, *Blautia* spp., *Collinsella* spp., *Lactobacillus* spp., *Bifidobacterium* spp., *Bacteroides* spp., and unclassified Lachnospiraceae constituted the predominant genera.

The majority of differences in the abundances of bacteria within the control cats occurred between 2 and 6 months of age. The abundance of Gammaproteobacteria significantly decreased from 5.5% at 2 months to 3.2% at 3 months of age ($p = 0.007$) and that of Enterobacteriales from 3.7% to less than 0.5% ($p = 0.009$) during the same period. The abundance of Erysipelotrichi increased from 1.9% at 2 months to 5% at 3 months of age ($p = 0.030$) (Fig 3). The abundance of Bacilli reduced from 16.4% at 3 months to 3.7% at 4 months of age ($p = 0.018$). The only changes observed after 6 months of age included an increase in the abundance of Aeromonadales ($p = 0.002$) (Fig 3).

1.C) Quantitative polymerase chain reaction (qPCR) for selected bacterial groups. In the CON group, E.coli decreased ($p < 0.001$), and Faecalibacterium spp. increased ($p = 0.032$) from 2 to 3 months of age (Fig 4). No other significant differences were identified in bacteria quantified with PCR in CON cats. S6 Table contains a summary of all bacterial taxa analyzed by qPCR.

2. Effect of antibiotics on the GI microbiome. Visualization of the data suggested a high interindividual variation of bacterial abundances in all groups on day 0. The alpha diversity indices (S2 Table), the ANOSIM and PERMANOVA of unweighted and weighted UniFrac distances (S1 Fig, S3 and S4 Tables), and bacterial abundances (S5 and S6 Tables) did not differ significantly among groups on day 0.

2.1.Amoxicillin/Clavulanic acid group. **2.1.A) Sequence analysis—alpha and beta diversity.** The AMC group had reduced evenness on the last day of treatment (day 20) compared to DOX and CON groups, but this decrease did not reach statistical significance (Shannon index, $p = 0.061$) (Fig 5, S2 Table). Alpha diversity indices did not vary over time in AMC cats (S2 Table). The microbial community composition on the last day of treatment (day 20) was different for AMC cats compared to both DOX (ANOSIM $R = 0.109$, $p = 0.011$; PERMANOVA $p = 0.008$, $q = 0.022$) and CON (ANOSIM $R = 0.188$, $p = 0.001$; PERMANOVA $p = 0.001$, $q = 0.006$) cats based on unweighted analysis (Fig 6, S3 and S4 Tables). On days 60 and 300, there was a less distinct clustering of the microbiome in AMC cats compared to CON cats (based on decreasing ANOSIM effect size) as demonstrated by unweighted (day 60, ANOSIM $R = 0.056$, $p = 0.075$; PERMANOVA $p = 0.086$, $q = 0.143$ and day 300, ANOSIM $R = 0.077$, $p = 0.058$; PERMANOVA $p = 0.056$, $q = 0.100$) and weighted distances (day 300, ANOSIM

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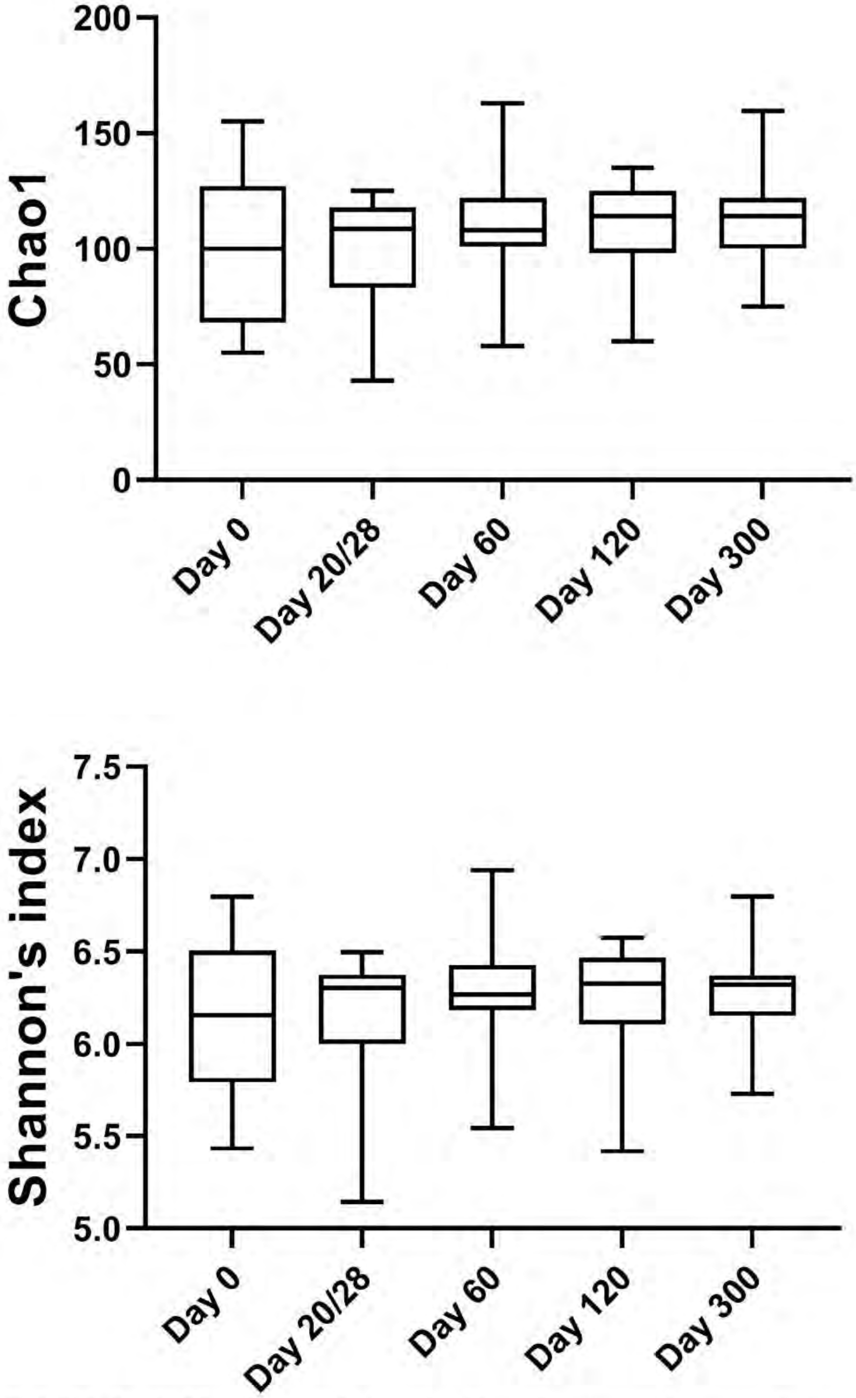

Fig 1. Alpha diversity differences in control cats over time. Means with minimums and maximums values are displayed at each sampling day.

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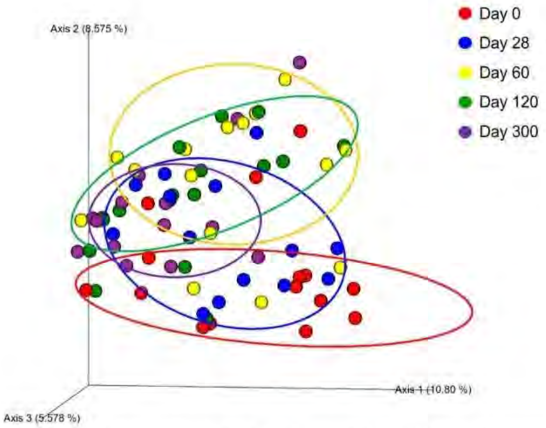

ANOSIM analysis		
Comparisons	R value	P value
D0 vs D28	0.092	0.034
D0 vs D60	0.150	0.006
D0 vs D120	0.158	0.003
D0 vs D300	0.223	0.001

PERMANOVA analysis		
Comparisons	p value	q value
D0 vs D28	0.038	0.074
D0 vs D60	0.002	0.008
D0 vs D120	0.002	0.008
D0 vs D300	0.001	0.006

Fig 2. Principal Coordinate Analysis of unweighted UniFrac distances of 16S rRNA genes representing the differences in microbial community composition within the control group on day 0 (red circles), day 28 (blue circles), 60 (yellow circles), 120 (green circles), and 300 (purple circles). R values and P values calculated with ANOSIM and PERMANOVA p and q values are displayed.

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R = 0.057, p = 0.074; PERMANOVA p = 0.127, q = 0.238), but this difference did not reach statistical significance (S1 Fig).

2.1.B) Sequence analysis—abundance of individual bacterial taxa. Amoxicillin/clavulanic acid had a significant impact on the GI microbiome. In fact, the normal age-related changes of the microbiome observed in CON cats were not observed in this group. Erysipelotrichi (p = 0.008), *Catenibacterium* spp. (p = 0.045), and unclassified Lachnospiraceae (p = 0.002) were detected in significantly lower abundances, whereas Enterobacteriales (p = 0.010) was found in significantly higher abundances in feces from AMC cats compared to CON cats on the last day of treatment (day 20/28) (Figs 6 and 7). Three (day 120) and 9 months (day 300) after amoxicillin/clavulanic acid discontinuation, AMC cats harbored significantly higher abundances of unclassified *Collinsella* spp. compared to CON cats (Fig 8).

Most of the differences in bacterial abundances between AMC and CON groups were found during treatment, (from 2 to 3 months of age), while after that period only minor changes were observed. In AMC cats, Gammaproteobacteria abundances remained the same during treatment (i.e., from 2 to 3 months) representing approximately 9% of total sequences, while in CON cats they decreased during the same period, representing 3% of total sequences (p = 0.009). At 1 month after antibiotic withdrawal (4 months of age), Gammaproteobacteria decreased to <1% in AMC cats (p = 0.030), reaching similar levels to those in CON cats at this age (Fig 8). Erysipelotrichi abundances represented 2.5% of the total sequences in AMC cats before treatment, and decreased to less than 2% after treatment, while in CON cats, Erysipelotrichi abundances increased at this age. On day 60, both groups harbored similar abundances of this bacterium (Fig 7).

2.1.C) qPCR for selected bacterial groups. On the last day of treatment, lower total bacterial counts (p = 0.003) and higher abundances of *E. coli* (p = 0.002) were detected in the feces of AMC cats compared to CON cats (Fig 9).

Bacterial abundances in the AMC group demonstrated a different pattern compared to the CON group. In the AMC group, *E. coli* abundances did not change between 2 to 3 months of age (i.e., during treatment), and then significantly decreased at 4 months of age (p = 0.012) (Fig 9).

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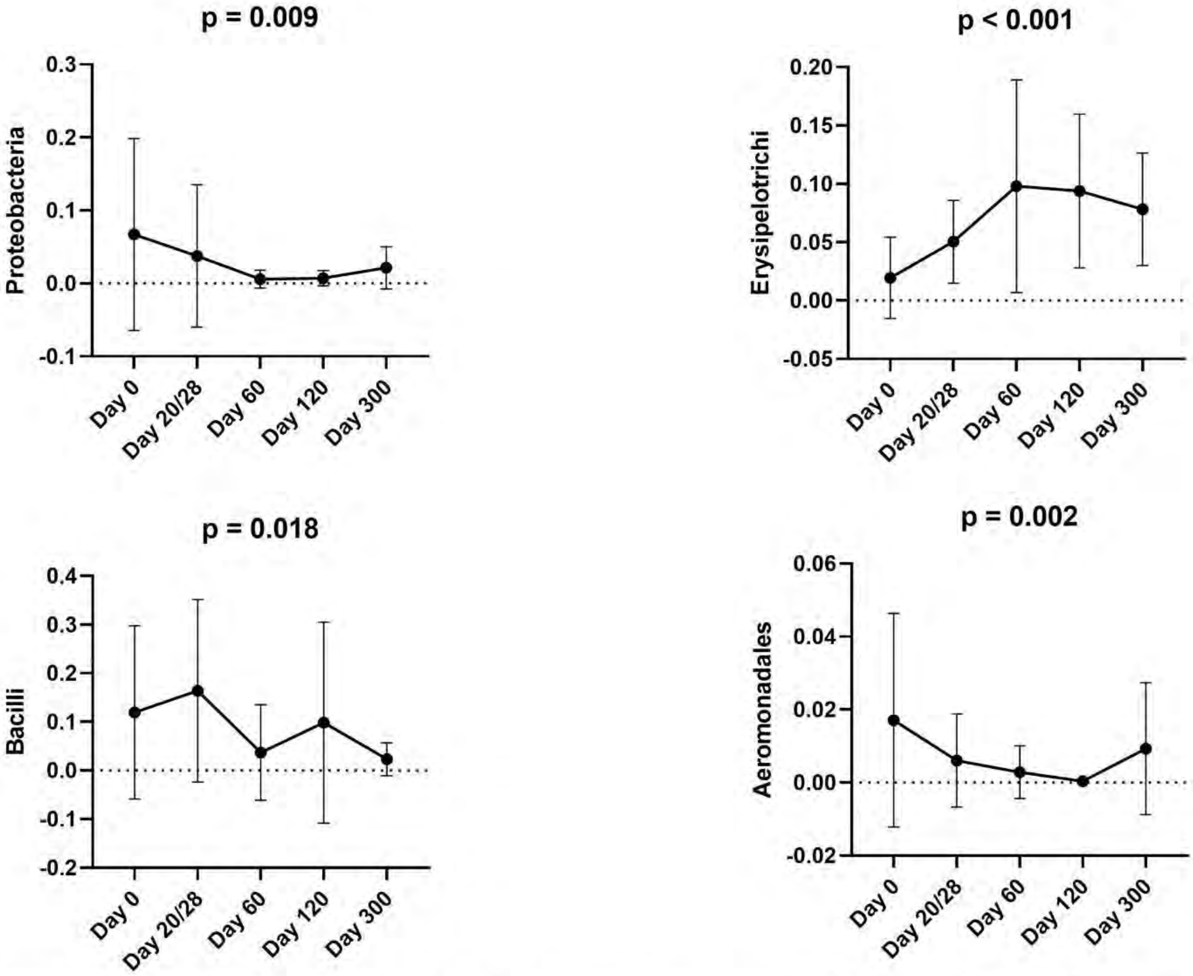

Fig 3. Bacterial groups that significantly changed over time within the control group based on sequence analysis. Means and standard deviations are displayed.

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2.2. Doxycycline group. **2.2.A) Sequence analysis–alpha and beta diversity.** DOX cats had a significantly higher species richness (observed ASVs, p = 0.025; Chao1, p = 0.029) (Fig 5, S2 Table) on the last day of treatment and a different clustering of the microbiome 1 month after treatment (day 60) compared to CON cats (ANOSIM R = 0.100, p = 0.021; PERMANOVA p = 0.033, q = 0.144) (Fig 10, S3 and S4 Tables). Species richness and evenness indices were also significantly higher within the DOX cats on day 300 compared to day 0 (observed ASVs; Chao1; Shannon p = 0.010).

2.2.B) Sequence analysis–abundance of individual bacterial taxa. Doxycycline caused pronounced changes in the abundances of bacterial communities, but its effects appeared 1 month after its discontinuation. *Catenibacterim* spp., and unclassified *Lachnospiraceae* spp. (both p = 0.039) were detected at significantly lower abundances whereas Proteobacteria (p = 0.001) and Enterobacteriales (p = 0.018) at significantly higher abundances in the feces of DOX cats compared to CON cats on day 60 (Figs 7 and 8). The increase in the abundance of

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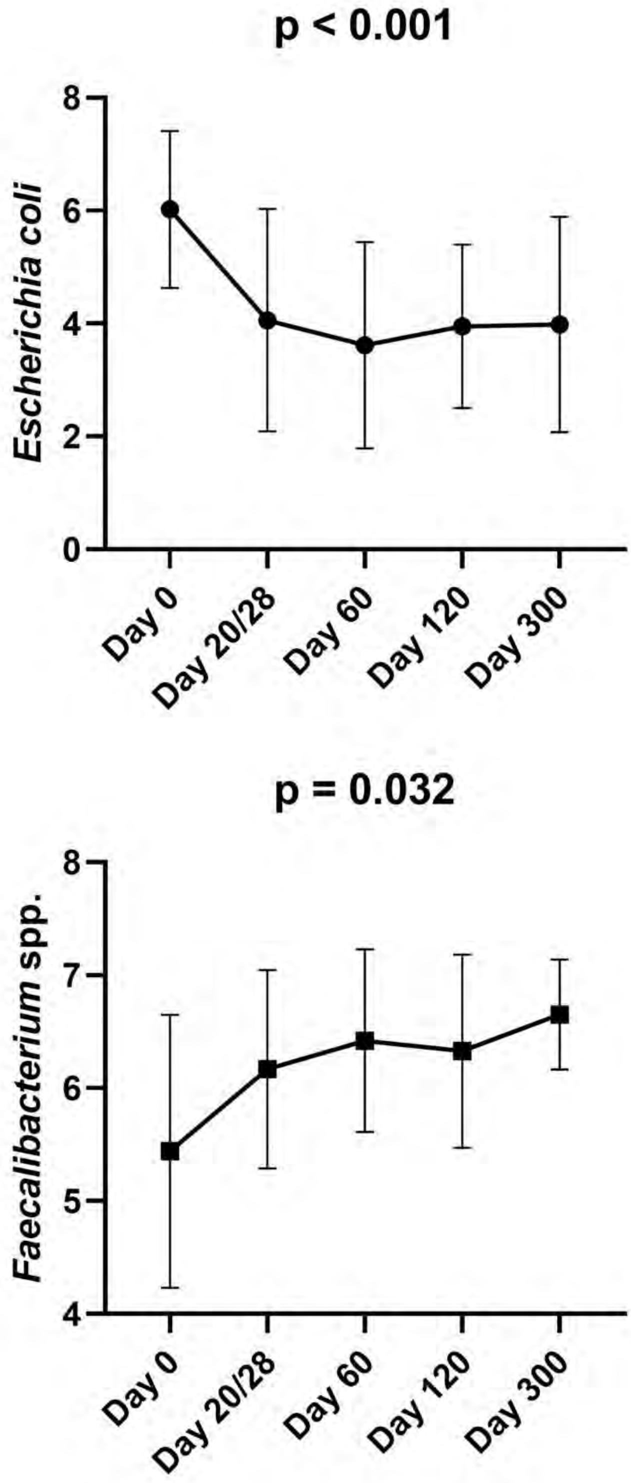

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Fig 4. Bacterial groups that significantly changed over time within the control group based on qPCR analysis. Means and standard deviations are displayed.

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Proteobacteria persisted for 3 months after antibiotic withdrawal (p = 0.026). In addition, at 3 and 9 months after antibiotic withdrawal, the abundance of unclassified *Collinsella* spp. was significantly higher in cats of the DOX group compared to cats of the CON group (p = 0.025) (Fig 8). Unclassified *Bulleidia* spp. were detected at higher abundances (p = 0.023) in DOX cats 9 months after its discontinuation (Fig 7). Fig 11 shows a percentage plot of bacterial abundances at a class level among groups.

2.2.C) qPCR for selected bacterial groups. On day 60, higher *E. coli* abundances (p = 0.035) were found in DOX cats compared to CON cats (Fig 9).

Discussion

Our goals were to describe the effects of treatment with amoxicillin/clavulanic acid or doxycycline on the GI microbiome of young cats and the microbial recovery after antibiotic exposure early in life. Our study showed substantial changes in the GI microbiome from 2 months until one year of age in cats, with antibiotics having a differential impact on the developing GI microbiome. Amoxicillin/clavulanic acid caused pronounced effects during treatment while the effects of doxycycline appeared 1 month after its withdrawal. Both antibiotics mainly affected members of Firmicutes and Proteobacteria and resulted in a delay in the developmental progression of the microbiome compared to the pattern of microbial changes observed over time in cats not treated with antibiotics.

Importantly, a high interindividual variation in bacterial abundances was observed in cats at 2 months of age (before exposure to antibiotics). In humans and dogs, during the phase of microbiota maturation, high-interindividual differences in bacterial abundances occur [63–65], therefore the large variation observed in our study likely represents an immature microbiome in cats at 2 months of age. In addition, the largest shifts in the GI microbiota in the control cats occurred during the age of 2 to 6-months suggesting that the normal GI microbiome evolves in kittens and reaches maturity around the age of 6 months. Although conflicting evidence exists about whether the microbiome reaches an adult-like state at the end of the weaning period in dogs and cats [8,66,67], in a previous canine study, 2-month-old puppies still harbored a significantly different microbiome compared to adult dogs [63].

In adult humans, the abundances of approximately 70% of the GI bacterial members are relatively stable for at least 12 months [8]. Therefore, in contrast to adult cats, the duration of antibiotic effects on the developing GI microbiome could only be investigated by evaluating a control group to adjust for age-related changes. The fact that there was a large variation in microbial community composition at baseline among cats likely led to unique responses to antibiotics. The microbiome is considered as unique as an individual's fingerprint [68], and during the maturation period, unpredictable shifts could occur that have not been adequately described in cats. Despite the high variability, the core bacterial taxa in cats of our study were Firmicutes and Actinobacteria from 2 months until 1 year of age. This is in agreement with previous studies investigating the effects of dietary nutrient composition [66,69,70], sex, and sexual status [67] on the fecal microbiome of young cats.

Current knowledge suggests that the first microbes colonizing the GI tract are mainly facultative anaerobic bacteria that reduce oxygen concentrations in the gut and allow for successful colonization of the obligative anaerobic bacteria [71]. The phylum Proteobacteria, which is comprised by facultative and obligative anaerobic bacteria, is among the first colonizers of the GI tract in humans [71,72]. At the weaning period and after the introduction of a solid diet

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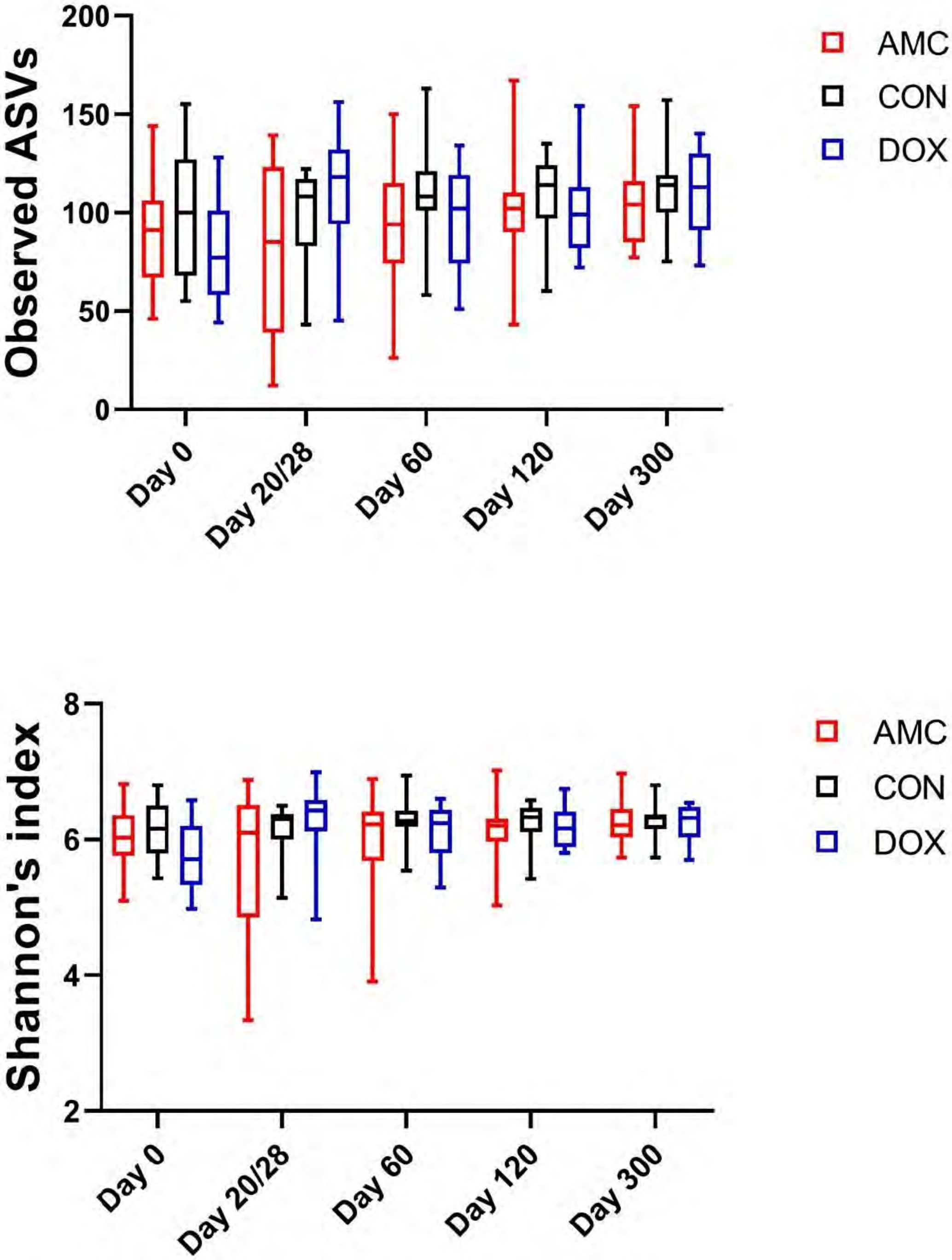

Fig 5. Alpha diversity differences between cats treated with amoxicillin/clavulanic acid (black), cats treated with doxycycline (blue), and healthy control cats (red). Means and standard deviations within each group are displayed.

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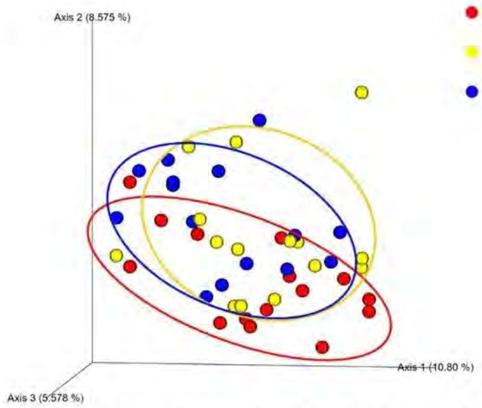

ANOSIM analysis		
Comparisons	R value	P value
AMC vs CON	0.188	0.001
AMC vs DOX	0.109	0.011
CON vs DOX	0.044	0.174

PERMANOVA analysis		
Comparisons	p value	q value
AMC vs CON	0.001	0.006
AMC vs DOX	0.008	0.022
CON vs DOX	0.195	0.269

Fig 6. Principal Coordinate analysis (PCoA) plot of unweighted Unifrac distance in cats treated with amoxicillin clavulanic acid (red = AMC), cats treated with doxycycline (yellow = DOX), and control cats (blue = CON) on day 20/28. R values and P values calculated with ANOSIM and PERMANOVA p and q values are displayed.

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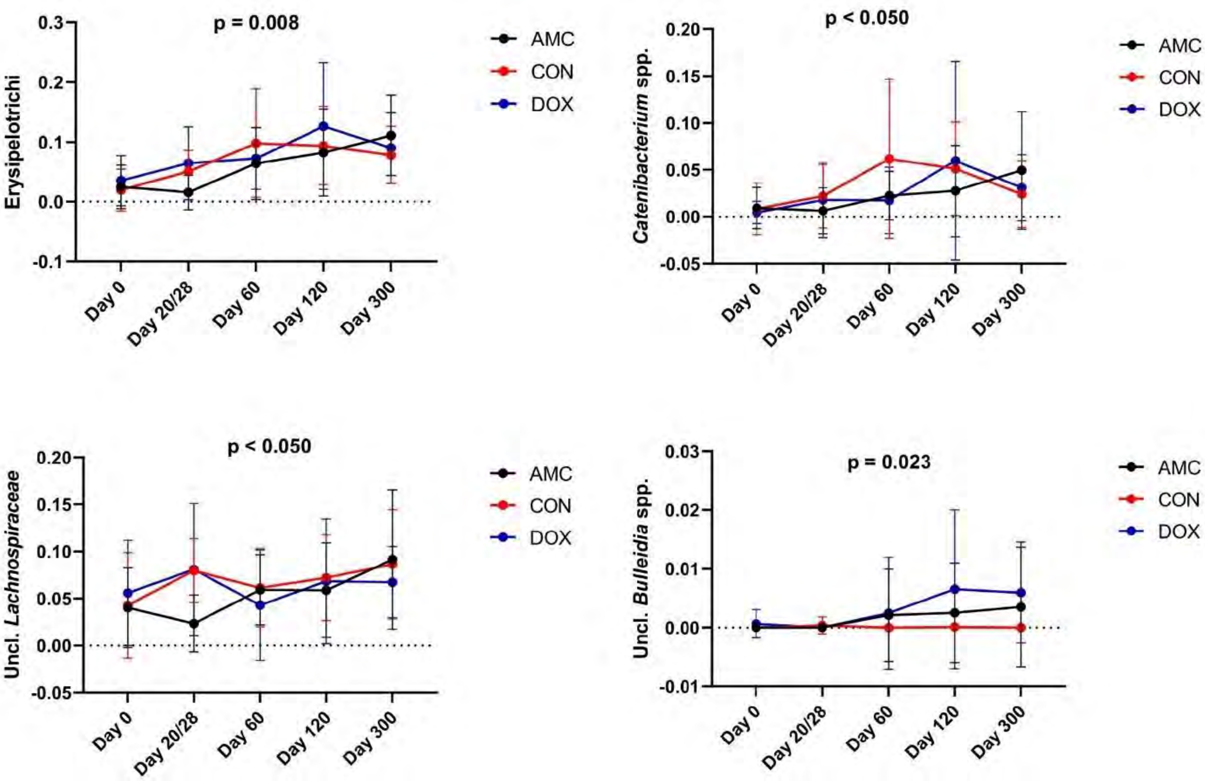

Fig 7. Bacterial groups that showed a significantly decreased abundance after antibiotic treatment (AMC and DOX group) compared to the control group (CON group). Means and standard deviations within each group are displayed.

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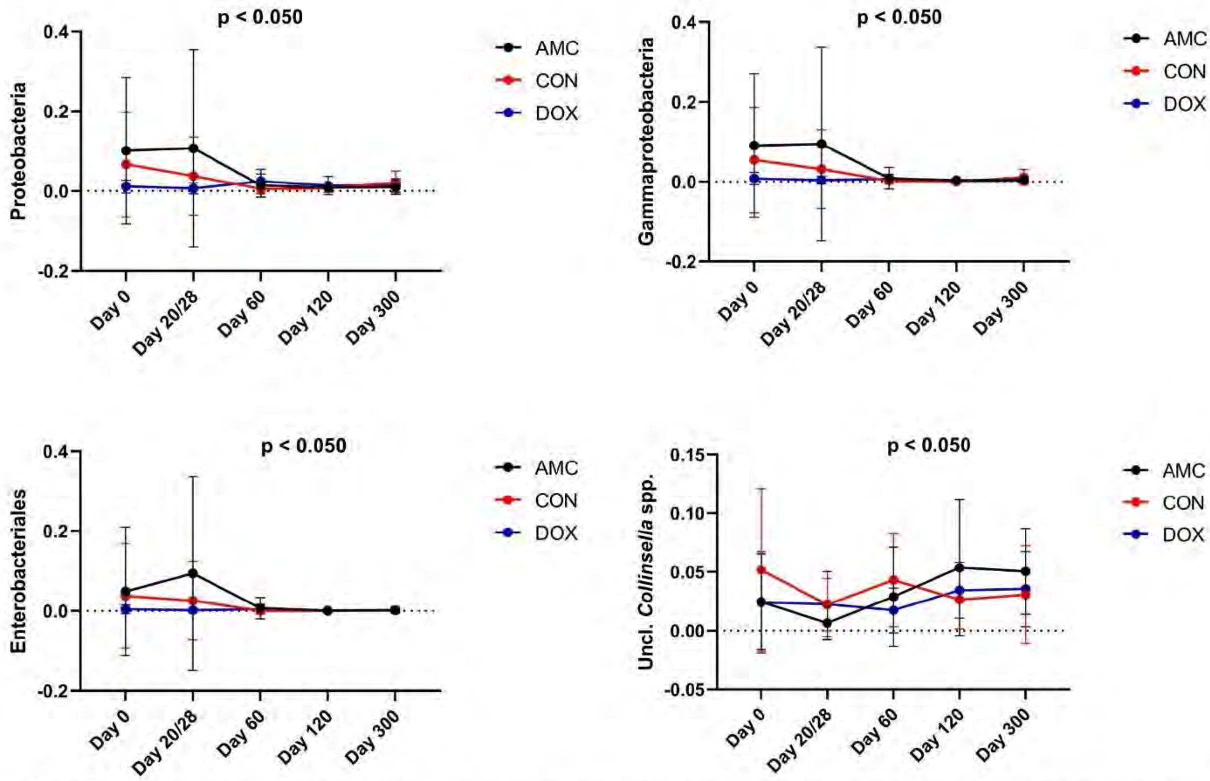

Fig 8. Bacterial groups that showed a significantly increased abundance after antibiotic treatment (AMC and DOX groups) compared to the control group (CON group). Means and standard deviations within each group are displayed.

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(i.e., around 5–6 months of age), the abundance of Proteobacteria gradually decreases [73]. Our finding of an age-dependent decrease in bacterial taxa belonging to Proteobacteria (i.e., Enterobacteriales, Escherichia coli) observed between 2 to 4 months of age in control cats in this study is in agreement with these data in humans. In addition, a concurrent increase in the abundance of taxa belonging to Firmicutes (i.e., Erysipelotrichales) occurred in the same group during the same period, which has also been reported by another study in cats of a similar age and reflects the introduction of dietary macronutrients that are utilized by these bacteria [69].

Treatment with amoxicillin/clavulanic acid led to a reduced species richness and evenness, although this varied among cats and it did not reach statistical significance, while doxycycline let to a significant increase in species richness. Antibiotics, including amoxicillin and doxycycline are most commonly reported to either decrease [41,43,50,74,75] or have no effect on species richness [76]. Only a few studies have reported an increase in species richness indices [46,77]. In adult laboratory cats, amoxicillin/clavulanic acid administration for 7 days reduced the number of different species observed and this effect persisted for 7 days after discontinuation of the antibiotic [51]. In our study, species richness indices were indistinguishable from untreated cats by 1 month after discontinuation of amoxicillin/clavulanic acid Doxycycline had no effect on bacterial abundances and community composition at the last day of the treatment period (day 28). Alternatively, the lack of an effect of doxycycline on bacterial genera

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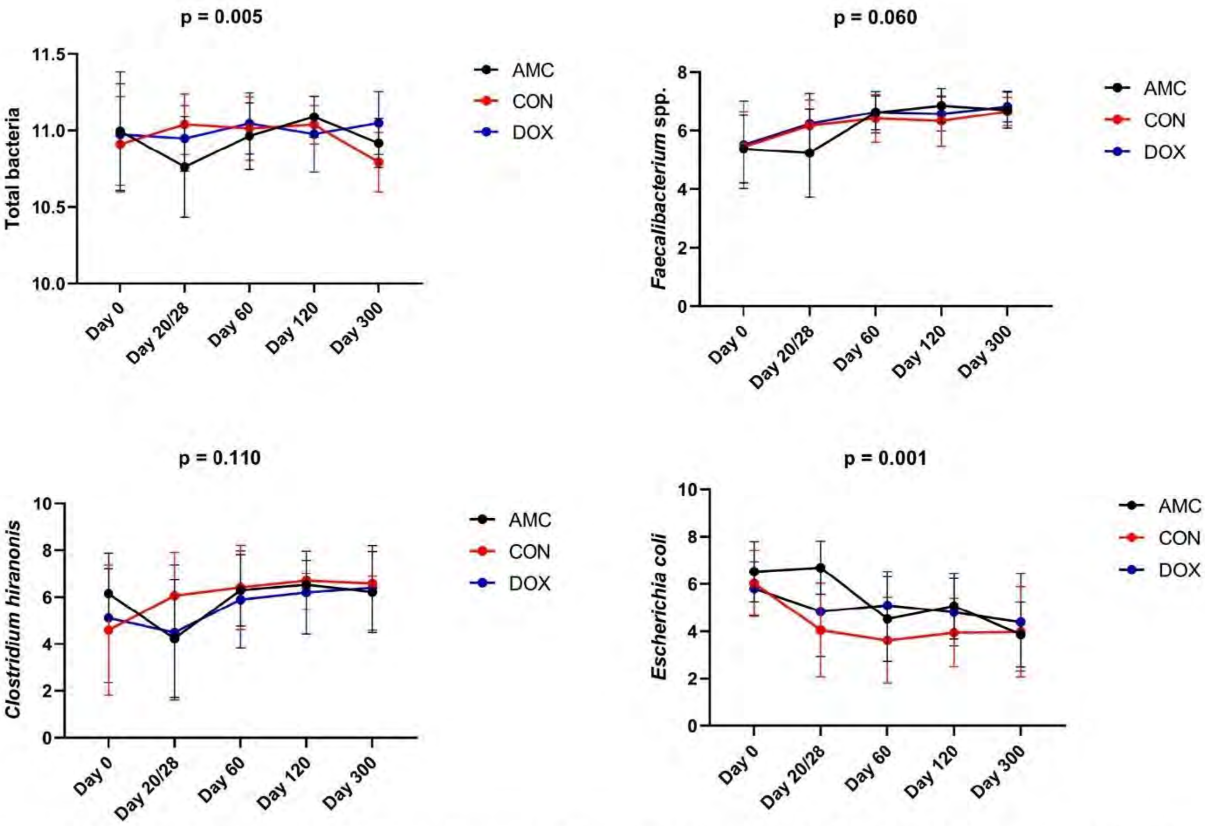

Fig 9. Fecal abundances of selected bacterial taxa among cats treated with amoxicillin/clavulanic acid (AMC), cats treated with doxycycline (DOX), and healthy cats (CON) analyzed with qPCR. Means and standard deviations within each group are displayed.

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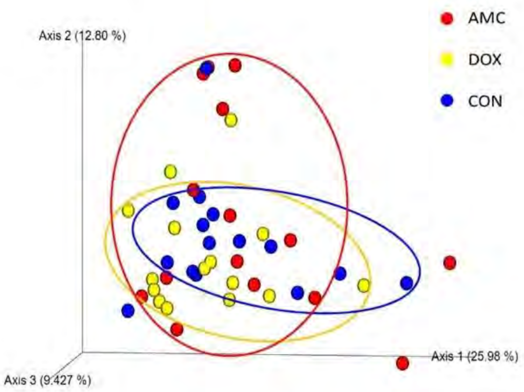

ANOSIM analysis		
Comparisons	R value	P value
AMC vs CON	0.007	0.356
AMC vs DOX	0.040	0.111
CON vs DOX	0.100	0.021

PERMANOVA analysis		
Comparisons	p value	q value
AMC vs CON	0.255	0.341
AMC vs DOX	0.166	0.282
CON vs DOX	0.033	0.144

Fig 10. Principal Coordinate analysis (PCoA) plot of weighted Unifrac distances in cats treated with amoxicillin/clavulanic acid (red = AMC), cats treated with doxycycline (yellow = DOX), and control cats (blue = CON) on day 60. R values and P values calculated with ANOSIM and PERMANOVA p and q values are displayed.

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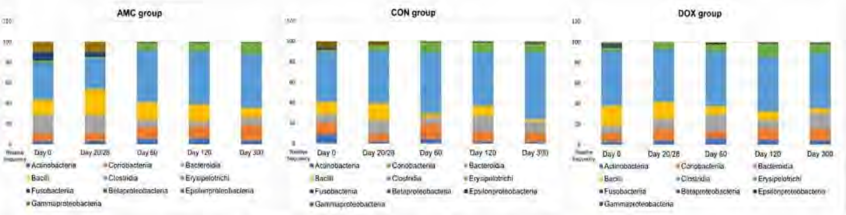

Fig 11. Relative abundance of bacterial taxa at a class level among groups.

https://doi.org/10.1371/journal.pone.0253031.g011

that would be expected to decrease as shown in control cats, could be responsible for the observed increased species richness in doxycycline-treated cats. The bloom of these genera might be attributed either to resistance to tetracyclines or to the concurrent decrease of some bacteria that produce antimicrobial peptides thus allowing members of these genera to remain at increased levels [78].

Microbial community composition was distinct in cats treated with amoxicillin/clavulanic acid and indistinguishable in cats treated with doxycycline compared to control cats on the last day of treatment. Interestingly, the effect of doxycycline was not evident until 1 month after drug discontinuation. Similar results have been described in a single study in mice, where the most profound changes in microbial community composition started 1 month after doxycycline discontinuation [49]. In addition, in our study, a trend for significant differences in microbial community composition were observed in amoxicillin/clavulanic acid-treated cats 3 and 9 months after antibiotic withdrawal. Contradictory findings exist in the literature with humans, laboratory animals and in vitro studies reporting high interindividual effects [79], no effects [44,80], only short-term effects [41,46], or both short- and long-term effects on microbial composition [20,45,75] after administration of amoxicillin with or without clavulanic acid. In a study in rats, a 7-day course of amoxicillin during the weaning period caused transient alterations in microbial composition that resolved by 20 days after its discontinuation [43]. In another study in infants, a 5- to 8-day course of amoxicillin caused long-term changes in microbial composition that persisted for 6 months after treatment withdrawal [20].

While the total abundance of the phylum Firmicutes was not significantly altered, certain bacterial members of this phylum showed significant shifts in response to antibiotics. Amoxicillin/clavulanic acid and doxycycline administration caused a transient decrease of the abundance of the order Erysipelotrichales and its sub-groups Erysipelotrichaceae and *Catenibacterium* spp. The family Erysipelotrichaceae contains bile salt hydrolase (BSH) genes, and this enzyme is responsible for the deconjugation of primary bile acids [81,82]. Thus, the decrease observed could potentially lead to increased concentrations of deconjugated primary bile acids in the gut. In addition to potential bile acid dysmetabolism in cats treated with antibiotics, one of the main converters of primary bile acids into secondary bile acids in dogs and cats is *Clostridium hiranonis*, which showed a decreased abundance in response to both antibiotics in our study, although this change did not reach statistical significance for either treatment [83]. Families belonging to Clostridiales were affected by antibiotics with a significant decrease in unclassified Lachnospiraceae. The family Lachnospiraceae was the predominant family present at all time points in all groups. Members of this family ferment carbohydrates leading to the production of butyrate [84]. Butyrate is one of the main short chain fatty acids (SCFAs) in the gut and has anti-inflammatory properties, is a major energy source for colonocytes, and its absence causes autophagy of epithelial intestinal cells in germ-free mice [85,86]. As a result, SCFAs might be another main metabolic class influenced by antibiotic treatment.

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The mechanisms by which antibiotics affect the abundance of bacteria as well as the impact of this reduction on microbial metabolites could be unraveled by applying other "omics" approaches including resistome and metabolomic analysis in future studies.

Among Actinobacteria, the abundance of unclassified *Collinsella* spp. was higher in both antibiotic-treated groups than in controls at 3 months after discontinuation of treatment. This effect persisted in the amoxicillin-clavulanic acid group for 9 months. Early colonization with *Collinsella* spp. within the first 6 months of life is associated with increased adiposity in humans, [73] and also increased *Collinsella* spp. abundances have been reported in cats with diarrhea [87,88].

Based both on sequencing and qPCR analysis, bacterial taxa belonging to Proteobacteria (Gammaproteobacteria, order Enterobacteriales, family Enterobacteriaceae, *Escherichia coli*) were found at significantly higher abundances on the last day of treatment (20 days) for amoxicillin/clavulanic acid and at 3 months after discontinuation of doxycycline before decreasing to similar abundances to that of control cats. The family Enterobacteriaceae is the most common microbial member that increases in abundance after antibiotic treatment in humans regardless of the antibiotic class [89]. In dogs, metronidazole [27] and amoxicillin [24], but not tylosin [23,28], are reported to increase the abundance of Enterobacteriaceae. In cats, this effect has been observed for amoxicillin [51] and clindamycin [25,26] with the latter leading to a 2-months persistent increase in Enterobacteriaceae [26]. The phylum Proteobacteria encompasses some of the most well-known pathogens [72] and members of this phylum are commonly increased in dogs [90–95] and cats with GI disease [87,88,96–98], as well as during consumption of high-protein, canned and raw diets [66,69,70,99]. Both antibiotic treated groups had higher fecal scores during treatment compared to healthy cats, therefore episodes of diarrhea may be associated with increased abundances of Proteobacteria members.

Previous studies in humans have shown that antibiotics delay the developmental progression of the microbiome into an adult-like state [29,30]. In agreement with these findings and compared to untreated cats of our study, a delay in maturation was observed in both antibiotic-treated groups. This delay was characterized by reduced abundances of taxa belonging to Firmicutes and increased abundances of taxa belonging to Proteobacteria. The most profound delay occurred between 2 to 3 months of age in the amoxicillin/clavulanic acid-treated cats and between 3 to 6 months of age in the doxycycline-treated cats.

Antibiotic treatment prenatally or during early life in humans has been associated with weight gain and obesity [33,34,100]. Both penicillins and tetracyclines have been used in livestock for facilitation of weight gain and growth [48,101]. Facilitation of weight gain has also been observed in severely malnourished children after receiving antibiotics [35]. In our study, no differences in weight gain and body condition scores were observed in any group, though a larger sample size might be required for investigating such effects.

Our study had some limitations. A larger number of animals could have helped in minimizing the interindividual differences observed in microbiome composition. However, previous studies investigating the effects of antibiotics have enrolled similar numbers of animals. All cats were stray at study initiation; thus, their exact date of birth was unknown and slight differences in the enrollment age might have influenced the microbiota composition. Differences in ambient could have also interfered with our results [102]. Some cats were malnourished, and malnourishment has been associated with a persistently immature microbiome in children [103]. In addition, some cats were found at a very young age and required formula feeding, which in children is also reported to impact microbiome colonization compared to breastfeeding [104]. The maternal diet of cats also has an impact on the microbiome of the offspring until its 17th week of age [105] and in our study the maternal dietary status was unknown. Although the above factors have been investigated in humans, no studies regarding their

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impact on the feline microbiota exist. Finally, cats treated with doxycycline had a significantly higher fecal scores at baseline, which might also have influenced the abundance of some bacterial taxa.

Conclusion

Overall, our results indicate that the GI microbiome of cats changes after 2 months of age and reaches an adult-like state around 6 months of age. Amoxicillin/clavulanic acid and doxycycline treatment early in life significantly affected the developing microbiome richness and composition in cats. The abundance of members of Firmicutes decreased and that of members of Proteobacteria increased after 20 days of amoxicillin/clavulanic acid treatment and 1 month after a 28-day course of doxycycline. Only minor changes were observed 9 months after amoxicillin/clavulanic acid or doxycycline discontinuation with an increase in the abundance of unclassified *Collinsella* spp. and unclassified *Bulleidia* spp., respectively. Our results suggest that doxycycline had a delayed impact whereas amoxicillin/clavulanic acid had a more immediate impact on bacterial community composition and only minor changes persisted 9 months after discontinuation of either antibiotic. Future studies utilizing additional approaches to gain a better understanding of the microbial functional changes caused by antibiotics would be useful.

Supporting information

S1 Fig. Beta diversity indices among groups. A) Principal Coordinate Analysis of unweighted UniFrac distances of 16S rRNA genes representing the difference in microbial communities among cats treated with amoxicillin clavulanic acid (blue circles), cats treated with doxycycline (yellow circles), and healthy control cats (red circles) on days 20/28 (last day of treatment), 60, 120, and 300. B) Principal Coordinate Analysis of weighted UniFrac distances of 16S rRNA genes representing the difference in microbial communities among cats treated with amoxicillin clavulanic acid (blue circles), cats treated with doxycycline (yellow circles), and healthy control cats (red circles) on days 20/28 (last day of treatment), 60, 120, and 300.
(DOCX)

S2 Fig. Rarefaction curves for A) Chao1, B) Observed ASVs, and C) Shannon Index.
(DOCX)

S1 Table. Clinical data of cats participating to the study.
(XLSX)

S2 Table. Alpha diversity metrics (mean ± standard deviation) with summary statistics; CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.
(XLSX)

S3 Table. Beta diversity differences based on ANOSIM analysis. CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.
(XLSX)

S4 Table. Beta diversity differences based on PERMANOVA analysis. CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.
(XLSX)

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S5 Table. Summary statistics of sequencing data describing the mean percent and standard deviation of sequences belonging to antibiotic-treated (AMC and DOX groups) and healthy (CON group) cats.
(XLSX)

S6 Table. Summary statistics of qPCR data describing the mean log abundance and standard deviation of bacterial groups belonging to antibiotic-treated (AMC and DOX groups) and healthy (CON group) cats.
(XLSX)

Acknowledgments

Preliminary results were presented at the: a) 29th European College of Veterinary Internal Medicine Congress, Milan, Italy, September 19th to 21st 2019; b) the 38th Forum of the American College of Veterinary Internal Medicine (ACVIM), June 10th to13th 2020; and c) the 39th Forum of the American College of Veterinary Internal Medicine (ACVIM), June 9th to12th 2021.

The authors would like to thank Gerolymatos International S.A. for providing products for antiparasitic treatment (Broadline) and vaccines (Purevax RCPh, Purevax Rabies) for the cats in this study.

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Supplementary data-Table S1. Clinical data of cats participating to the study.

			Body weight (BW)					Body condition scoring (BCS)					Fecal scoring (FS)				
CatID	Sex	Group	Day 0	Day 20/28	Day 60	Day 120	Day 300	Day 0	Day 20/28	Day 60	Day 120	Day 300	Day 0	Day 20/28	Day 60	Day 120	Day 300
FM7	M	AMC	0.95	1.56		3.78	5.75	5	5		6	7	3	4			5
FM13	M	AMC	0.37	1	1.74	3	4.1	2	4	6	6	6	3	4	2	2	2
FM18	M	AMC	0.72	1.42	2.3	3.79	5.41	4	5		6	5	2	3			2
FM20	F	AMC	0.63	1	1.6	2.39	4.41	6	5		4	5	2	2		2	2
FM22	F	AMC	0.42	8	1.2	2.09	3.6	3	4		4	4	3	4		2	2
FM24	F	AMC	0.4	0.95	1.7	2	4.27	3	5	5	4	6	3	5	3	5	3
FM29	F	AMC	0.39	0.8	1.36	1.98	3.03	3	4	4	4	4	5	4	3	3	2
FM32	M	AMC	0.61	1	1.74	2.65	4.49	3	4	4	4	5	4	5	6	4	2
FM34	M	AMC	0.9	1.19	1.8	2.87	4.1	4	4	4	4	4	3	4	5	4	2
FM56	M	AMC	0.6	1	1.79	2.42	3.15	4	4	4	4	3	6	4	3	2	3
FM58	F	AMC	0.76	1.18	1.68	2.35	3	4	4	4	4	4	4	6	1	1	1
FM67	F	AMC	0.53	1.11	1.7	2.3	2.7	3	4		4	4	6	3		2	4
FM68	M	AMC	0.61	1.16	1.7	2.83	5	3	4	4	5	5	4	2	1	2	2
FM70	F	AMC	0.48	0.84	1.5	2.5	3.5	4	4	5	4	4	2	3	2	3	3
FM74	M	AMC	0.37	0.83	1.49	2.66	4.1	4	4	4	4	4	2	1	4	3	2
FM8	M	DOX	0.72	1.3	1.98			4	4	5			3	2	3		
FM9	M	DOX	0.65	1.24				5	5				3	2			
FM14	M	DOX	0.52	0.92	1.45	2.58	5.05	3	4	5	5	6	3	3	3	2	2
FM15	F	DOX	0.71	1.15	1.85	2.71	4.19	4	5	4	6	6	3	2	2	3	2
FM16	F	DOX	0.68	1.25	2.1	2.93	4.69	4	5		6	6	4	3		2	2
FM33	M	DOX	1.2	1.73	2		4.41	4	5	4	4	5	4	3	5	2	3
FM35	M	DOX	0.9	1.58	1.89	2.85	4.25	4	4	4	4	6	5	4	3	5	2
FM37	F	DOX	0.8	1.43	1.93	2.72	3.82	4	4	4	4	5	4	5	4	2	2
FM41	M	DOX	0.64	1.2	1.25	2.5	3.33	4	5	4	4	4	7	3	4	2	1
FM45	F	DOX	0.77	1.16	1.7	2.33	3.5	4	4	4	4	4	3	2	2	4	3
FM55	F	DOX	0.69	1.29	1.85	2.55	4.55	4	4	4	4	6	4	3	3	3	1
FM63	M	DOX	0.48	0.87	1.33	1.99	3.7	4	4	4	4	4	6	2	2	2	2
FM66	F	DOX	0.61	1.15	1.6	2.5	3.76	4	4	4	4	5	2	2	2	1	2
FM71	M	DOX	0.49	1.11	1.65	3.05	5.8	4	4	5	4	6	5	4	3	4	3
FM75	M	DOX	0.39	1.03	1.46	2.65	3.7	4	4	4	4	4	5	2	1	2	2
FM4	M	CON	1.2	1.6	2.5	3.8	6	5	5	5	6	5	2	1			2
FM6	M	CON	0.8	1.4	1.93	2.8	4.45	4	4	4	5	5	2	1			2
FM23	M	CON	1.1	1.2	1.85	2.3	4.23	4	4	5	4	5	1	1	2	2	3
FM26	M	CON	0.65	1.23	1.1			4	4	4	4		2	2	3	2	
FM31	F	CON	0.9	1.46	1.72	2.49	2.89	4	4	4	4	4	1	2	2	1	2
FM36	F	CON	0.77	1.33	1.95		2.3	4	4	4		3	3	2	2		
FM38	F	CON	0.62	1.28	1.54	3.43	5.7	4	5	5	6	6	2	2	1	2	1
FM43	M	CON	0.54	0.9	2.1			3	4	4	4	4	4	2	2	2	2
FM47	F	CON	0.62	1.06	1.52		2.49	4	4	4	4	4	3	2	2	2	2
FM48	F	CON	1.15	1.6	1.3	3.15	5.2	4	5	4	4	6	2	2	2	4	3
FM49	M	CON	0.7	1.16	1.93	2.63	4	4	4	4	4	5	3	1	1	2	1
FM59	M	CON	0.87	1.41	1.92	2.85	4.7	4	4	4	4	6	4	3	3	2	1
FM61	F	CON	0.52	0.92	1.39	2.05	3.15	4	4	4	4	4	6	3	1	2	2
FM62	F	CON	0.54	0.77	1.15	1.69	3.3	4	4	3	4	4	6	2	1	2	1
FM64	M	CON	1.4		2.5	2.9	4	4	4	4	4	4	2	2	2	2	2

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Supplementary data-Table S2. Alpha diversity metrics (mean ± standard deviation) with summary statistics.

CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.

	P values								
	Chao1			Observed ASVs			Shannon's index		
	AMC	CON	DOX	AMC	CON	DOX	AMC	CON	DOX
Day 0 vs Day 28	0.999	0.999	0.090	0.999	0.999	0.090	0.999	0.999	0.200
Day 0 vs Day 60	0.999	0.999	0.350	0.999	0.999	0.380	0.999	0.999	0.310
Day 0 vs Day 120	0.999	0.999	0.410	0.999	0.999	0.410	0.999	0.999	0.310
Day 0 vs Day 300	0.999	0.999	0.010	0.999	0.999	0.010	0.999	0.999	0.010
Day 28 vs Day 60	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Day 28 vs Day 120	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Day 28 vs Day 300	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Day 60 vs Day 120	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Day 60 vs Day 300	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Day 120 vs Day 300	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999

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Supplementary data-Table S3. Beta diversity differences based on ANOSIM analysis. CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.

Comparisons	Weighted		Unweighted	
	R statistic	P value	R statistic	P value
CON day 0 versus AMC day 0	0.017	0.291	0.028	0.219
CON day 28 versus AMC day 20	0.032	0.167	0.188	0.001
CON day 60 versus AMC day 60	0.007	0.356	0.056	0.075
CON day 120 versus AMC day 120	0.056	0.085	0.018	0.245
CON day 300 versus AMC day 300	0.057	0.074	0.077	0.058
CON day 0 versus DOX day 0	0.005	0.398	-0.015	0.581
CON day 28 versus DOX day 28	0.003	0.388	0.044	0.174
CON day 60 versus DOX day 60	0.100	0.021	0.024	0.246
CON day 120 versus DOX day 120	0.008	0.355	-0.017	0.633
CON day 300 versus DOX day 300	0.03	0.199	-0.013	0.570
CON day 0 versus CON day 28	0.025	0.187	0.092	0.034
CON day 0 versus CON day 60	0.083	0.031	0.150	0.006
CON day 0 versus CON day 120	0.083	0.037	0.158	0.003
CON day 0 versus CON day 300	0.116	0.009	0.223	0.001
AMC day 0 versus AMC day 20	-0.041	0.841	0.124	0.006
AMC day 0 versus AMC day 60	0.114	0.031	0.214	0.002
AMC day 0 versus AMC day 120	0.171	0.003	0.164	0.009
AMC day 0 versus AMC day 300	0.193	0.003	0.258	0.001
DOX day 0 versus DOX day 28	0.054	0.083	0.050	0.103
DOX day 0 versus DOX day 60	0.100	0.019	0.060	0.083
DOX day 0 versus DOX day 120	0.125	0.005	0.130	0.005
DOX day 0 versus DOX day 300	0.140	0.005	0.204	0.001

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Supplementary data-Table S4. Beta diversity differences based on PERMANOVA analysis.

CON, healthy cats that did not receive antibiotics; AMC, cats treated with amoxicillin/clavulanic acid for 20 days; DOX, cats treated with doxycycline for 28 days.

Comparisons	Weighted			Unweighted		
	Psuedo F	p value	q value	Psuedo F	p value	q value
CON day 0 versus AMC day 0	1.38179437	0.221	0.318	1.034152115	0.381	0.471
CON day 28 versus AMC day 20	0.94181265	0.440	0.508	2.206913526	0.001	0.006
CON day 60 versus AMC day 60	1.19259041	0.255	0.341	1.383471718	0.086	0.143
CON day 120 versus AMC day 120	2.05897359	0.064	0.168	1.179396962	0.195	0.269
CON day 300 versus AMC day 300	1.53128619	0.127	0.238	1.485260906	0.056	0.100
CON day 0 versus DOX day 0	0.96502027	0.418	0.488	0.915131148	0.609	0.640
CON day 28 versus DOX day 28	1.21765673	0.268	0.342	1.163173743	0.195	0.269
CON day 60 versus DOX day 60	2.49225242	0.033	0.144	1.047198498	0.361	0.458
CON day 120 versus DOX day 120	1.36304924	0.205	0.308	0.891752238	0.627	0.652
CON day 300 versus DOX day 300	1.25799578	0.231	0.326	0.94317658	0.525	0.593
CON day 0 versus CON day 28	1.64387567	0.104	0.214	1.481609433	0.038	0.074
CON day 0 versus CON day 60	2.30766776	0.033	0.144	2.15668593	0.002	0.008
CON day 0 versus CON day 120	2.53142860	0.031	0.144	2.104270516	0.002	0.008
CON day 0 versus CON day 300	2.33570154	0.041	0.154	2.561190481	0.001	0.006
AMC day 0 versus AMC day 20	0.55063688	0.776	0.791	1.688599465	0.017	0.042
AMC day 0 versus AMC day 60	2.24275879	0.045	0.154	2.180991322	0.004	0.013
AMC day 0 versus AMC day 120	2.92410335	0.012	0.090	1.861087955	0.013	0.032
AMC day 0 versus AMC day 300	3.15967279	0.013	0.091	2.508131024	0.001	0.006
DOX day 0 versus DOX day 28	1.39161395	0.188	0.290	1.304421628	0.102	0.160
DOX day 0 versus DOX day 60	2.13801970	0.046	0.154	1.441276979	0.064	0.112
DOX day 0 versus DOX day 120	2.53976826	0.022	0.155	1.947365423	0.004	0.013
DOX day 0 versus DOX day 300	2.82989176	0.011	0.089	2.500491126	0.001	0.006

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Supplementary data-Table S5. Summary statistics of sequencing data describing the mean percent and standard deviation of sequences belonging to antibiotic-treated (AMC and DOX groups) and healthy (CON group) cats.

	Day 0						Day 20/28						Day 60						Day 120						Day 300						BH adjusted p values			Mixed model effects		
	AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX		AMC	CON	DOX	Sampling day	Group	Sampling day x Group
Taxa	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD						
Phylum																																				
Firmicutes	52.64	24.10	62.32	17.10	75.62	19.78	56.80	29.83	72.95	16.40	74.04	13.33	74.20	12.84	73.37	11.71	68.05	15.08	76.11	10.81	71.61	17.04	74.41	15.68	72.23	14.54	75.65	13.26	67.07	15.21	0.083	0.204	0.320			
Actinobacteria	10.81	13.58	19.88	19.46	11.15	10.06	11.05	13.15	9.32	7.98	15.00	9.60	16.84	12.21	19.10	10.09	13.41	15.82	17.31	13.28	11.47	8.44	15.67	9.61	18.58	11.62	10.61	8.50	15.39	9.98	0.134	0.065	0.416			
Bacteroidetes	18.09	19.52	9.08	13.56	7.60	12.77	17.53	21.76	13.66	19.15	10.24	13.22	7.25	12.80	6.73	10.54	15.95	17.25	5.16	4.87	15.79	19.07	8.24	13.68	7.76	12.70	11.01	10.96	15.57	15.70	0.278	0.274	0.428			
Fusobacteria	8.32	11.51	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.86	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Proteobacteria	10.11	18.38	6.70	13.13	1.15	1.62	10.71	24.65	3.76	9.76	0.69	1.38	1.41	2.92	0.58	1.24	2.47	3.01	0.90	0.98	0.71	1.04	1.38	2.28	0.99	1.82	2.14	2.89	1.45	1.72	0.053	0.029	0.420	**0.053**	0.471	**0.002**
Class																																				
Actinobacteria	3.07	7.72	8.92	11.98	3.16	5.09	3.24	4.39	2.16	3.20	4.08	5.94	5.72	5.65	4.47	5.61	6.25	13.41	5.86	8.35	2.11	3.27	4.80	6.22	4.03	4.83	1.86	2.45	4.27	6.13	0.153	0.236	0.519			
Coriobacteriia	7.74	9.73	10.96	9.35	7.98	9.19	7.80	10.24	7.16	5.74	10.92	6.76	11.11	10.81	14.63	9.51	7.16	4.96	11.44	9.70	9.36	5.99	10.87	5.29	14.55	8.46	8.75	7.27	11.12	8.04	0.076	0.181	0.254			
Bacteroidia	18.09	19.52	9.08	13.56	7.60	12.77	17.53	21.76	13.66	19.15	10.24	13.22	7.25	12.80	6.73	10.54	15.95	17.25	5.16	4.87	15.79	19.07	8.24	13.68	7.76	12.70	11.01	10.96	15.57	15.70	0.278	0.274	0.428			
Bacilli	14.75	22.83	11.93	17.81	19.28	25.98	25.19	37.49	16.36	18.76	16.80	25.59	16.97	23.90	3.70	9.82	8.62	12.32	16.31	19.71	9.82	20.66	8.75	10.49	9.26	18.43	2.31	3.37	4.52	7.43	0.997	0.043	0.456	0.064	0.321	0.364
Clostridia	35.40	15.46	48.44	23.89	52.82	30.07	30.07	24.98	51.54	21.80	50.80	19.42	50.82	18.62	59.86	13.06	52.19	17.42	51.54	19.22	52.40	17.77	53.01	16.01	51.85	14.73	65.52	13.58	53.49	13.85	0.031	0.143	0.999	**0.007**	0.098	0.118
Erysipelotrichi	2.49	3.64	1.95	3.49	3.51	4.21	1.54	2.88	5.04	3.56	6.44	6.11	6.41	6.05	9.81	9.10	7.24	5.18	8.25	7.30	9.39	6.59	12.66	10.61	11.12	6.74	7.82	4.81	9.06	5.93	0.012	0.012	0.012	**0.000**	0.411	**0.046**
Fusobacteriia	8.32	11.51	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.86	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Betaproteobacteria	0.34	0.51	0.44	0.70	0.12	0.29	0.04	0.09	0.38	0.85	0.09	0.19	0.10	0.26	0.20	0.36	0.41	0.50	0.13	0.19	0.41	0.62	0.17	0.38	0.16	0.37	0.34	0.66	0.78	1.23	0.234	0.976	0.083			
Epsilonproteobacteria	0.45	1.05	0.69	0.99	0.14	0.28	1.21	2.45	0.14	0.30	0.20	0.45	0.35	0.61	0.09	0.23	1.29	2.75	0.37	0.52	0.18	0.34	1.03	1.87	0.23	0.39	0.49	0.85	0.28	0.44	0.942	0.182	0.180			
Gammaproteobacteria	9.09	17.98	5.46	13.18	0.82	1.54	9.46	24.19	3.17	9.78	0.41	0.95	0.90	2.73	0.29	0.72	0.71	1.22	0.39	0.57	0.04	0.14	0.17	0.38	0.45	0.90	1.13	1.93	0.33	0.69	0.018	0.012	0.392	**0.000**	0.316	**0.004**
Order																																				
Bifidobacteriales	3.07	7.72	8.92	11.98	3.16	5.09	3.24	4.39	2.16	3.20	4.08	5.94	5.86	8.35	2.09	3.27	4.80	6.22	5.72	5.66	4.46	5.61	6.25	13.41	4.03	4.83	1.86	2.45	4.12	5.95	0.153	0.251	0.451			
Coriobacteriales	7.74	9.73	10.96	9.35	7.98	9.19	7.80	10.24	7.16	5.74	10.92	6.76	11.11	10.81	14.63	9.51	7.16	4.96	11.44	9.70	9.36	5.99	10.87	5.29	14.55	8.46	8.75	7.27	11.12	8.04	0.076	0.181	0.254			
Bacteroidales	18.09	19.52	9.08	13.56	7.60	12.77	17.53	21.76	13.66	19.15	10.24	13.22	7.25	12.80	6.73	10.54	15.95	17.25	5.16	4.87	15.79	19.07	8.24	13.68	7.76	12.70	11.01	10.96	15.57	15.70	0.278	0.274	0.428			
Lactobacillales	14.73	22.85	11.12	16.74	18.77	25.90	25.19	37.49	16.36	18.76	16.51	25.76	16.83	23.83	3.68	9.83	7.81	12.32	14.40	19.87	9.81	20.67	8.75	10.49	9.10	18.50	2.31	3.37	3.39	3.99	0.997	0.046	0.428	**0.049**	0.368	0.475
Clostridiales	35.40	15.46	48.44	23.89	52.82	30.07	30.07	24.98	51.54	21.80	50.80	19.42	50.82	18.62	59.86	13.06	52.19	17.42	51.54	19.22	52.40	17.77	53.01	16.01	51.85	14.73	65.52	13.58	53.49	13.85	0.031	0.143	0.999	**0.007**	0.098	0.118
Erysipelotrichales	2.49	3.64	1.95	3.49	3.51	4.21	1.54	2.88	5.04	3.56	6.44	6.11	6.41	6.05	9.81	9.10	7.24	5.18	8.25	7.30	9.39	6.59	12.66	10.61	11.12	6.74	7.82	4.81	9.06	5.93	0.012	0.012	0.012	**0.000**	0.411	**0.046**
Fusobacteriales	8.32	11.51	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.86	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Burkholderiales	0.34	0.51	0.44	0.70	0.12	0.29	0.04	0.09	0.38	0.85	0.09	0.19	0.10	0.26	0.20	0.36	0.41	0.50	0.13	0.19	0.41	0.62	0.17	0.38	0.16	0.37	0.34	0.66	0.78	1.23	0.234	0.976	0.083			
Campylobacteriales	0.45	1.05	0.69	0.99	0.14	0.28	1.21	2.45	0.14	0.30	0.20	0.45	0.35	0.61	0.09	0.23	1.29	2.75	0.37	0.52	0.18	0.34	1.03	1.87	0.23	0.39	0.49	0.85	0.28	0.44	0.942	0.182	0.180			
Aeromonadales	4.21	9.82	1.71	2.92	0.42	0.91	0.07	0.17	0.61	1.28	0.22	0.86	0.21	0.42	0.29	0.72	0.26	0.49	0.30	0.51	0.04	0.14	0.10	0.33	0.29	0.62	0.93	1.81	0.21	0.51	0.099	0.012	0.375	**0.000**	0.352	0.059
Enterobacteriales	4.89	16.08	3.73	13.08	0.41	1.08	9.39	24.22	2.57	9.86	0.18	0.44	0.69	2.66	0.01	0.02	0.45	1.22	0.09	0.34	0.00	0.00	0.05	0.18	0.16	0.54	0.20	0.77	0.13	0.40	0.012	0.012	0.481	**0.000**	0.468	**0.037**
Family																																				
Bifidobacteriaceae	3.07	7.72	8.92	11.98	3.16	5.09	3.24	4.39	2.16	3.20	4.08	5.94	5.72	5.66	4.46	5.61	6.25	13.41	5.86	8.35	2.09	3.27	4.80	6.22	4.03	4.83	1.86	2.45	4.12	5.95	0.153	0.251	0.451			
Coriobacteriaceae	7.74	9.73	10.96	9.35	7.98	9.19	7.80	10.24	7.16	5.74	10.92	6.76	11.11	10.81	14.63	9.51	7.16	4.96	11.44	9.70	9.36	5.99	10.87	5.29	14.55	8.46	8.75	7.27	11.12	8.04	0.076	0.181	0.254			
Bacteroidaceae	11.57	15.89	4.87	7.20	6.55	12.12	11.46	16.84	8.64	15.42	7.72	12.90	4.90	10.42	2.14	2.88	9.31	9.52	2.19	3.24	6.74	8.31	5.41	11.19	3.66	7.44	3.63	5.23	8.44	8.88	0.428	0.206	0.493			
Porphyromonadaceae	2.23	4.32	0.58	1.39	0.27	0.61	1.38	2.25	0.37	0.64	0.60	0.85	0.44	1.49	0.16	0.41	0.53	0.84	0.24	0.36	0.62	0.79	0.50	0.93	0.26	0.53	0.54	0.90	0.41	0.60	0.407	0.065	0.790			
Prevotellaceae	2.40	4.99	2.63	4.10	0.46	0.89	3.66	6.93	2.65	4.32	1.42	2.63	1.41	2.82	3.07	6.19	4.87	8.12	1.67	2.27	5.81	9.59	1.66	2.18	2.87	5.65	5.19	6.14	4.38	6.30	1.000	0.155	0.180			
Paraprevotellaceae	1.84	5.09	0.81	2.06	0.32	1.16	1.04	3.32	1.97	4.51	0.50	1.34	0.50	1.70	1.34	2.48	1.21	2.74	1.06	1.58	2.51	4.42	0.66	0.88	0.95	1.91	1.51	2.41	2.30	4.83	0.083	0.393	0.279			
Enterococcaceae	3.88	13.17	2.50	4.48	1.68	4.03	16.74	34.11	5.21	13.61	4.95	17.80	0.20	0.66	1.73	6.61	0.20	0.58	0.53	1.52	0.91	1.81	0.14	0.55	0.36	0.92	0.88	1.61	0.73	1.81	0.155	0.394	0.340			
Lactobacillaceae	10.58	20.69	8.52	15.01	16.17	25.84	8.10	16.63	10.94	15.10	11.44	20.43	16.63	23.77	1.95	4.67	7.38	11.97	12.89	18.86	5.87	10.90	8.15	10.22	8.74	18.46	1.27	2.77	2.08	3.58	0.284	0.081	0.364			
Clostridiales, unidentified family 1	0.08	0.20	0.18	0.62	0.13	0.37	0.12	0.43	0.05	0.10	0.39	1.03	0.08	0.28	0.49	0.73	0.03	0.08	0.48	1.27	0.35	0.81	0.14	0.45	0.91	1.55	0.58	1.11	0.25	0.40	0.138	0.281	0.138			
Clostridiales, unidentified family 2	0.20	0.34	1.48	2.07	0.66	1.39	0.58	1.04	1.30	1.51	1.15	1.29	1.37	1.15	1.11	1.36	1.48	1.44	0.86	0.97	1.28	1.42	1.35	1.82	1.01	1.11	2.82	3.23	1.23	1.30	0.018	0.264	0.230	**0.000**	0.298	0.430
Clostridiaceae	9.65	7.11	13.60	11.75	22.53	24.45	5.05	6.46	10.29	6.69	5.90	5.65	12.18	8.32	16.31	6.92	9.24	8.34	9.80	7.97	12.03	5.01	10.89	6.49	11.72	6.60	14.55	6.39	13.26	7.25	0.060	0.266	0.018	**0.000**	0.087	0.235
Lachnospiraceae	15.90	10.64	24.58	19.29	22.77	17.36	19.41	17.85	31.65	17.37	37.32	15.16	28.21	11.60	29.94	9.64	29.08	16.61	24.16	14.31	27.19	11.50	30.70	12.53	28.54	15.24	34.26	13.66	26.38	9.82	0.102	0.264	0.109			
Peptococcaceae	0.39	0.74	0.15	0.33	0.80	1.89	0.17	0.55	0.62	1.07	0.26	0.74	0.68	1.09	0.33	0.52	0.77	1.03	0.52	0.59	0.66	0.88	0.99	1.28	0.73	0.77	0.97	1.00	1.07	1.18	0.055	0.012	0.018	**0.000**	0.779	0.456
Peptostreptococcaceae	0.75	1.41	1.24	1.79	1.32	3.27	0.35	0.91	0.65	1.43	0.05	0.19	2.12	4.75	0.26	0.74	0.92	3.04	1.33	3.03	1.38	4.78	1.50	2.49	2.18	5.28	2.47	3.17	3.32	5.72	0.798	0.267	0.053			
Ruminococcaceae	1.74	2.44	1.65	1.81	2.26	4.27	2.31	3.62	2.29	1.78	2.68	2.52	2.81	2.12	3.32	3.74	2.50	2.01	3.45	2.15	3.11	3.08	2.98	2.84	3.67	3.21	4.39	3.56	4.10	3.40	0.063	0.227	0.169			
Veillonellaceae	6.69	16.05	5.47	6.70	2.32	4.65	2.05	3.75	4.50	4.98	2.96	5.50	3.33	4.28	7.95	10.67	8.08	9.21	10.94	13.52	6.28	7.67	4.38	7.18	3.01	4.35	5.35	7.15	3.60	3.53	0.055	0.979	0.340			
Mogibacteriaceae	0.00	0.01	0.10	0.30	0.02	0.07	0.04	0.14	0.19	0.42	0.09	0.36	0.05	0.14	0.17	0.40	0.09	0.14	0.01	0.05	0.10	0.16	0.07	0.17	0.09	0.18	0.12	0.20	0.28	0.66	0.395	0.338	0.084			
Erysipelotrichaceae	2.49	3.64	1.95	3.49	3.51	4.21	1.54	2.88	5.04	3.56	6.44	6.11	6.41	6.05	9.81	9.10	7.24	5.18	8.25	7.30	9.39	6.59	12.66	10.61	11.12	6.74	7.82	4.81	9.06	5.93	0.012	0.012	0.012	**0.000**	0.411	**0.046**
Fusobacteriaceae	8.32	11.51	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.86	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Alcaligenaceae	0.34	0.51	0.42	0.71	0.12	0.29	0.04	0.09	0.38	0.85	0.09	0.19	0.10	0.26	0.20	0.36	0.41	0.50	0.13	0.19	0.41	0.62	0.17	0.38	0.16	0.37	0.34	0.66	0.78	1.23	0.234	0.974	0.083			
Campylobacteriaceae	0.11	0.38	0.18	0.40	0.08	0.25	0.54	0.95	0.01	0.05	0.20	0.45	0.16	0.53	0.01	0.02	0.93	2.77	0.12	0.22	0.02	0.06	0.31	0.75	0.11	0.15	0.08	0.16	0.11	0.17	0.228	0.393	0.615			
Helicobacteraceae	0.34	1.02	0.51	0.88	0.07	0.14	0.67	2.39	0.12	0.30	0.00	0.00	0.19	0.33	0.09	0.22	0.36	0.80	0.25	0.47	0.16	0.35	0.72	1.21	0.13	0.38	0.42	0.80	0.17	0.37	0.895	0.263	0.058			
Succinivibrionaceae	4.21	9.82	1.71	2.92	0.42	0.91	0.07	0.17	0.61	1.28	0.22	0.86	0.21	0.42	0.29	0.72	0.26	0.49	0.30	0.51	0.04	0.14	0.10	0.33	0.29	0.62	0.93	1.81	0.21	0.51	0.099	0.012	0.375	**0.000**	0.352	0.059
Enterobacteriaceae	4.89	16.08	3.73	13.08	0.41	1.08	9.39	24.22	2.57	9.86	0.18	0.44	0.69	2.66	0.01	0.02	0.45	1.22	0.09	0.34	0.00	0.00	0.05	0.18	0.16	0.54	0.20	0.77	0.13	0.40	0.012	0.012	0.481	**0.000**	0.468	**0.037**

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Genus																																			
Bifidobacterium	3.07	7.72	8.92	11.98	3.16	5.09	3.24	4.39	2.16	3.20	4.08	5.94	5.72	5.66	4.46	5.61	6.25	13.41	5.86	8.35	2.09	3.27	4.80	6.22	4.03	4.83	1.86	2.45	4.12	5.95	0.153	0.251	0.451			
Coriobacteriaceae, unidentified genus	0.66	1.68	0.72	2.52	0.91	2.95	0.13	0.31	0.93	1.71	0.36	1.21	0.82	1.69	1.03	1.92	0.42	0.87	0.91	1.77	0.73	1.29	0.59	0.87	3.30	5.13	0.40	0.70	0.58	0.60	0.034	0.180	0.029	**0.000**	0.456	0,209
Adlercreutzia	0.04	0.15	0.09	0.19	0.14	0.32	0.06	0.19	0.08	0.16	0.10	0.18	0.13	0.22	0.20	0.27	0.07	0.12	0.33	0.49	0.33	0.38	0.31	0.35	0.39	0.44	0.34	0.30	0.36	0.32	0.012	0.034	0.012	**0.000**	0.452	0.670
Collinsella	6.94	9.57	10.06	8.42	6.75	7.79	7.53	10.10	5.99	4.93	10.30	6.14	10.04	9.72	13.15	8.83	6.56	4.57	9.98	8.80	8.10	5.28	9.75	4.97	10.61	4.95	7.79	6.74	9.92	7.33	0.149	0.153	0,230			
Slackia	0.08	0.12	0.09	0.12	0.18	0.19	0.05	0.08	0.15	0.31	0.14	0.13	0.12	0.13	0.25	0.35	0.11	0.14	0.22	0.27	0.17	0.21	0.19	0.19	0.24	0.21	0.22	0.19	0.26	0.20	0.083	0.083	0.153			
Bacteroides	11.57	15.89	4.87	7.20	6.55	12.12	11.46	16.84	8.64	15.42	7.72	12.90	4.90	10.42	2.14	2.88	9.31	9.52	2.19	3.24	6.74	8.31	5.41	11.19	3.66	7.44	3.63	5.23	8.44	8.88	0.428	0.206	0.493			
Parabacteroides	1.62	3.73	0.58	1.39	0.27	0.61	1.38	2.25	0.37	0.64	0.60	0.85	0.44	1.49	0.16	0.41	0.53	0.84	0.24	0.36	0.62	0.79	0.49	0.91	0.26	0.53	0.54	0.90	0.41	0.60	0.403	0.068	0.789			
Prevotella	2.40	4.99	2.63	4.10	0.46	0.89	3.66	6.93	2.65	4.32	1.42	2.63	1.41	2.82	3.07	6.19	4.87	8.12	1.67	2.27	5.81	9.59	1.66	2.18	2.87	5.65	5.19	6.14	4.38	6.30	0.083	0.320	0.279			
Paraprevotellaceae_Prevotella	1.84	5.09	0.81	2.06	0.32	1.16	1.04	3.32	1.87	4.54	0.50	1.34	0.50	1.70	1.34	2.48	1.21	2.74	1.06	1.58	2.51	4.42	0.66	0.88	0.95	1.91	1.51	2.41	2.30	4.83	1.000	0.155	0.180			
Enterococcus	3.50	12.36	2.18	3.88	1.43	3.54	15.48	31.39	4.07	11.92	4.53	16.47	0.00	0.00	0.69	2.55	0.03	0.08	0.12	0.48	0.44	1.10	0.00	0.00	0.12	0.46	0.30	1.15	0.19	0.70	0.012	0.430	0.234	**0.000**	0.445	0.234
Lactobacillus	10.58	20.69	8.52	15.01	16.17	25.84	7.29	16.22	10.94	15.10	11.44	20.43	16.63	23.77	1.95	4.67	7.38	11.97	12.89	18.86	5.87	10.90	8.15	10.22	8.74	18.46	1.27	2.77	2.08	3.58	0.269	0.081	0.364			
Clostridiales, unidentified genus 1	0.08	0.20	0.18	0.62	0.13	0.37	0.12	0.43	0.05	0.10	0.39	1.03	0.08	0.28	0.49	0.73	0.03	0.08	0.48	1.27	0.35	0.81	0.14	0.45	0.91	1.55	0.58	1.11	0.25	0.40	0.138	0.281	0.138			
Clostridiales, unidentified genus 2	0.20	0.34	1.48	2.07	0.66	1.39	0.58	1.04	1.30	1.51	1.15	1.29	1.37	1.15	1.11	1.36	1.48	1.44	0.86	0.97	1.28	1.42	1.35	1.82	1.01	1.11	2.82	3.23	1.23	1.30	0.018	0.264	0.230	**0.000**	0.298	0.430
Clostridiaceae, unidentified genus 1	4.57	2.39	5.16	4.91	7.37	9.27	2.46	2.84	4.48	3.06	2.58	2.62	6.40	4.48	6.80	3.53	4.28	3.45	4.95	4.28	4.95	2.48	5.03	2.77	6.31	3.77	6.43	2.45	6.17	3.56	0.034	0.269	0.065	**0.000**	0.393	0.567
Clostridiaceae, unidentified genus 2	1.95	2.61	4.92	5.75	6.06	7.48	2.50	4.06	5.63	4.13	3.21	3.27	5.10	4.39	8.45	4.18	3.55	3.43	4.29	4.41	6.38	3.06	5.47	4.04	5.12	3.17	6.79	4.00	5.88	4.29	0.076	0.176	0.236			
Clostridium	3.07	6.84	3.51	5.79	9.07	20.28	0.09	0.34	0.15	0.23	0.09	0.23	0.67	1.38	1.01	2.30	1.40	3.07	0.56	1.15	0.67	1.03	0.36	0.46	0.29	0.39	1.31	3.55	1.13	1.93	0.080	0.326	0.071			
Lachnospiraceae, unidentified genus 1	4.02	4.24	4.28	5.60	5.60	5.61	2.35	3.02	7.98	3.40	8.10	7.00	5.92	3.73	6.14	4.16	4.30	5.87	5.89	5.02	7.22	4.55	6.84	6.64	9.16	7.41	8.64	5.81	6.75	3.78	0.012	0.084	0.116	**0.001**	0.401	**0.002**
Lachnospiraceae, unidentified genus 2	0.96	1.34	2.09	1.70	1.30	1.51	1.26	2.63	2.08	1.39	2.15	2.35	1.95	2.29	2.16	1.62	2.80	2.56	1.46	2.33	1.94	1.53	1.48	1.32	2.02	1.71	2.58	2.03	2.53	2.47	0.279	0.965	0.417			
Blautia	6.59	6.79	13.38	11.32	11.69	11.69	12.64	14.76	15.91	9.96	21.70	9.14	16.54	7.58	18.38	6.07	16.69	9.89	12.78	8.73	14.55	6.93	16.62	8.68	12.75	7.55	18.90	9.82	13.46	7.20	0.043	0.233	0.087	**0.000**	0.175	0.207
Coprococcus	0.09	0.22	0.19	0.40	0.07	0.26	0.08	0.20	0.28	1.02	0.29	0.40	0.33	0.69	0.07	0.12	0.70	1.23	0.12	0.23	0.26	0.32	0.79	1.65	0.11	0.29	0.14	0.36	0.33	0.39	0.559	0.306	0.234			
Dorea	0.54	1.18	0.75	1.82	0.45	0.79	0.30	0.77	0.48	0.88	1.03	1.32	0.76	1.01	0.42	0.82	0.87	1.11	1.30	1.55	1.07	1.33	1.22	1.61	0.93	1.47	0.85	1.31	0.73	1.25	0.408	0.705	0.619			
Ruminoccus	3.58	3.84	3.76	3.24	3.63	3.43	2.77	3.31	4.81	6.36	4.05	1.95	2.66	2.38	2.67	2.91	3.52	3.51	2.56	2.32	1.88	2.33	3.24	2.61	3.31	2.98	3.08	3.33	2.46	2.93	0.895	0.083	0.443			
Peptococcus	0.39	0.74	0.15	0.33	0.80	1.89	0.17	0.55	0.62	1.07	0.26	0.74	0.68	1.09	0.33	0.52	0.77	1.03	0.52	0.59	0.66	0.88	0.99	1.28	0.73	0.77	0.97	1.00	1.07	1.18	0.055	0.012	0.018	**0.000**	0.779	0.456
Peptrostreptococcaceae, unidentified genus 1	0.12	0.36	1.24	1.79	0.42	0.98	0.15	0.40	0.65	1.43	0.05	0.19	2.01	4.75	0.26	0.74	0.92	3.04	1.30	3.01	1.38	4.78	1.50	2.49	2.18	5.28	2.47	3.17	3.32	5.72	0.275	0.274	0.076			
Ruminococcaceae, unidentified genus 1	0.06	0.19	0.03	0.12	0.00	0.00	0.20	0.77	0.02	0.04	0.17	0.43	0.02	0.10	0.16	0.52	0.06	0.08	0.07	0.13	0.02	0.05	0.08	0.17	0.10	0.15	0.21	0.56	0.09	0.21	0.234	0.629	0.188			
Ruminococcaceae, unidentified genus 2	1.30	1.69	0.97	1.26	1.93	4.21	1.53	2.23	1.58	1.23	1.53	1.70	2.09	1.60	2.32	3.52	1.73	1.60	2.78	1.85	2.12	1.90	2.51	2.64	3.04	2.87	3.14	2.73	2.38	1.43	0.060	0.101	0.116			
Faecalibacterium	0.20	0.67	0.24	0.46	0.02	0.09	0.40	0.81	0.51	0.87	0.79	1.16	0.68	1.03	0.69	0.95	0.51	0.63	0.52	0.65	0.78	1.39	0.26	0.41	0.36	0.62	0.65	0.99	1.27	2.60	0.312	0.556	0.132			
Oscillospira	0.11	0.15	0.33	0.56	0.14	0.28	0.14	0.30	0.10	0.16	0.17	0.47	0.01	0.02	0.15	0.30	0.13	0.31	0.06	0.12	0.14	0.24	0.08	0.12	0.13	0.22	0.24	0.36	0.30	0.41	0.272	0.941	0.306			
Runinococcus	0.07	0.19	0.08	0.27	0.17	0.41	0.05	0.13	0.08	0.28	0.02	0.07	0.01	0.02	0.00	0.01	0.07	0.15	0.02	0.05	0.06	0.14	0.05	0.10	0.05	0.11	0.14	0.28	0.07	0.15	0.944	0.346	0.188			
Dialister	0.43	0.61	1.12	1.80	0.06	0.20	0.02	0.08	0.90	2.67	0.63	1.97	0.27	0.65	1.09	2.28	0.89	2.30	0.57	1.00	0.92	1.75	1.16	3.22	0.12	0.15	1.05	2.09	0.30	1.01	0.080	0.883	0.532			
Megamonas	1.47	3.91	1.30	1.81	0.09	0.26	0.96	2.08	0.25	0.44	0.83	1.75	0.17	0.36	1.77	3.86	2.55	5.88	0.41	0.89	0.53	0.92	0.53	0.85	1.36	3.98	1.19	2.10	1.33	2.24	0.939	0.976	0.364			
Megasphaera	4.01	11.09	2.88	5.60	1.90	4.21	0.65	2.03	3.00	3.87	1.49	2.62	2.71	3.68	4.87	6.74	4.16	5.26	9.55	13.05	4.51	6.73	2.13	2.67	1.21	1.55	2.39	4.49	1.65	2.31	0.012	0.863	0.527	**0.007**	0.609	0.546
Rhascolarctobacterium	0.30	0.55	0.12	0.43	0.02	0.09	0.09	0.25	0.08	0.22	0.00	0.00	0.05	0.10	0.02	0.05	0.11	0.28	0.27	0.50	0.23	0.36	0.03	0.10	0.16	0.37	0.40	0.66	0.27	0.67	0.343	0.018	0.183	**0.001**	0.258	0.066
Mogibacteriaceae, unidentified genus	0.00	0.01	0.02	0.08	0.02	0.07	0.04	0.14	0.10	0.23	0.09	0.36	0.05	0.14	0.07	0.16	0.09	0.14	0.01	0.05	0.10	0.16	0.07	0.17	0.09	0.18	0.12	0.20	0.28	0.66	0.395	0.176	0.084			
Bulleidia	0.13	0.38	0.14	0.48	1.11	2.40	0.13	0.46	0.04	0.14	0.55	1.46	0.80	2.33	0.28	1.01	1.60	4.00	2.06	4.23	0.36	0.68	2.61	4.32	2.19	5.11	0.54	0.67	2.61	3.33	0.029	0.050	0.107	**0.000**	0.366	0.979
Catenibacterium	0.92	2.20	0.85	2.75	0.44	1.18	0.63	2.45	2.19	3.38	1.77	3.98	2.23	2.59	6.19	8.48	1.74	3.55	2.75	4.88	5.12	4.99	5.97	10.59	4.95	6.30	2.41	3.57	3.10	3.54	0.012	0.012	0.031	**0.000**	0.240	**0.028**
Eubacterium	1.29	1.65	0.92	2.44	1.92	3.45	0.60	0.94	1.74	2.45	3.53	4.38	2.62	3.95	2.86	2.92	3.38	3.58	2.71	3.91	3.68	2.93	3.51	3.01	3.01	3.56	3.21	2.91	3.17	2.25	0.084	0.012	0.181	**0.000**	0.248	0.340
Fusobacterium	8.30	11.48	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.85	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Sutterella	0.34	0.51	0.42	0.71	0.12	0.29	0.04	0.09	0.38	0.85	0.09	0.19	0.10	0.26	0.20	0.36	0.41	0.50	0.13	0.19	0.41	0.62	0.17	0.38	0.16	0.37	0.34	0.66	0.78	1.23	0.234	0.974	0.083			
Campylobacter	0.11	0.38	0.18	0.40	0.08	0.25	0.54	0.95	0.01	0.05	0.20	0.45	0.16	0.53	0.01	0.02	0.93	2.77	0.12	0.22	0.02	0.06	0.31	0.75	0.11	0.15	0.08	0.16	0.11	0.17	0.228	0.393	0.615			
Helicobacter	0.30	1.00	0.48	0.81	0.07	0.14	0.48	1.65	0.12	0.30	0.00	0.00	0.13	0.30	0.09	0.22	0.31	0.66	0.10	0.19	0.07	0.26	0.55	0.97	0.03	0.08	0.42	0.80	0.17	0.37	0.939	0.119	0.083			
Succinivibrionaceae, unidentified genus 1	3.34	9.62	0.42	0.83	0.30	0.86	0.06	0.17	0.11	0.25	0.22	0.86	0.06	0.17	0.08	0.30	0.04	0.14	0.21	0.46	0.02	0.06	0.09	0.33	0.22	0.54	0.03	0.07	0.09	0.23	0.235	0.138	0.921			
Succinivibrionaceae, unidentified genus 2	0.87	1.57	1.29	2.74	0.08	0.22	0.01	0.03	0.50	1.28	0.00	0.00	0.14	0.36	0.19	0.40	0.23	0.48	0.10	0.30	0.00	0.00	0.01	0.03	0.07	0.15	0.65	1.30	0.12	0.34	0.060	0.053	0.251			
Enterobacteriaceae, unidentified genus	4.89	16.08	3.48	12.08	0.41	1.08	3.16	6.25	2.57	9.86	0.18	0.44	0.69	2.66	0.01	0.02	0.45	1.22	0.09	0.34	0.00	0.00	0.05	0.18	0.14	0.54	0.20	0.77	0.13	0.40	0.012	0.012	0.481	**0.000**	0.594	**0.031**

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Species																																			
Bifidobacterium, unidentified species 1	2.14	6.84	5.21	8.91	1.25	2.64	0.59	1.28	0.48	1.48	0.97	1.88	1.36	3.09	0.69	1.49	2.21	7.06	1.55	2.35	0.15	0.47	1.99	4.21	0.79	1.28	0.08	0.33	1.54	3.22	0.710	0.139	0.926			
Bifidobacterium, unidentified species 2	0.93	1.84	3.71	4.90	1.91	3.59	2.65	3.68	1.67	2.12	3.10	4.30	4.36	3.85	3.77	4.50	4.05	6.75	4.31	6.87	1.94	2.86	2.80	2.68	3.23	3.68	1.77	2.28	2.58	4.50	0.046	0.581	0.366	**0.024**	0.749	0.109
Coriobacteriaceae, unidentified species	0.66	1.68	0.72	2.52	0.91	2.95	0.13	0.31	0.93	1.71	0.36	1.21	0.82	1.69	1.03	1.92	0.42	0.87	0.91	1.77	0.73	1.29	0.59	0.87	3.30	5.13	0.40	0.70	0.58	0.60	0.034	0.180	0.029	**0.000**	0.456	0.209
Adlecreutzia, unidentified species	0.04	0.15	0.09	0.19	0.14	0.32	0.06	0.19	0.08	0.16	0.10	0.18	0.13	0.22	0.20	0.27	0.07	0.12	0.33	0.49	0.33	0.38	0.31	0.35	0.39	0.44	0.34	0.30	0.36	0.32	0.012	0.034	0.012	**0.000**	0.452	0.670
Collinsella, unidentified species	2.46	4.06	5.17	6.92	2.41	4.31	0.67	1.44	2.22	2.23	2.26	2.76	2.89	4.23	4.30	3.94	1.74	1.89	5.37	5.77	2.64	2.48	3.45	2.37	5.04	3.65	3.07	4.16	3.55	3.19	0.012	0.451	0.131	**0.000**	0.560	**0.005**
Collinsella aerofaciens	1.19	1.41	2.47	3.52	2.86	4.00	0.21	0.51	1.74	1.60	2.64	2.79	4.28	7.89	4.07	3.24	2.42	2.97	1.55	2.46	1.72	1.61	3.53	3.23	1.73	1.79	1.30	1.50	3.33	3.42	0.029	0.139	0.451	**0.039**	**0.043**	**0.014**
Collinsella stercoris	3.20	5.39	2.41	2.97	1.47	1.74	6.66	9.38	2.04	1.60	5.37	4.91	2.87	2.59	4.77	5.43	2.40	3.08	3.06	3.52	3.74	3.54	2.77	2.22	3.80	2.76	3.43	2.38	3.00	1.81	0.429	0.232	0.029	**0.003**	0.811	0.187
Slackia, unidentified species	0.08	0.12	0.09	0.12	0.18	0.19	0.05	0.08	0.15	0.31	0.14	0.13	0.12	0.13	0.25	0.35	0.11	0.14	0.22	0.27	0.17	0.21	0.19	0.19	0.24	0.21	0.22	0.19	0.26	0.20	0.083	0.083	0.153			
Bacteroides, unidentified species	7.95	11.14	3.90	5.80	5.14	10.12	4.55	7.99	3.97	3.72	5.02	10.14	3.74	9.53	1.58	2.17	5.79	6.09	1.73	3.13	5.05	7.64	3.50	6.92	2.64	5.58	2.60	3.62	5.95	6.22	0.609	0.250	0.613			
Bacteroides plebeius	0.03	0.10	0.61	1.25	0.32	1.22	6.68	14.57	3.15	8.70	0.98	2.83	0.85	1.88	0.44	0.91	2.19	3.67	0.44	0.74	1.34	2.24	1.58	3.84	0.68	1.26	0.78	1.83	1.26	2.49	0.089	0.367	0.119			
Parabacteroides, unidentified species	1.56	3.74	0.48	1.14	0.27	0.61	1.15	1.98	0.34	0.59	0.52	0.75	0.44	1.49	0.15	0.40	0.48	0.75	0.24	0.36	0.57	0.75	0.47	0.84	0.24	0.47	0.53	0.90	0.32	0.48	0.615	0.080	0.833			
Prevotella copri	2.40	4.99	2.63	4.10	0.46	0.89	3.66	6.93	2.65	4.32	1.42	2.63	1.41	2.82	3.07	6.19	4.87	8.12	1.67	2.27	5.81	9.59	1.66	2.18	2.87	5.65	5.19	6.14	4.38	6.30	1.000	0.155	0.180			
Prevotella, unidentified species	1.84	5.09	0.81	2.06	0.32	1.16	1.04	3.32	1.87	4.54	0.50	1.34	0.50	1.70	1.34	2.48	1.21	2.74	1.06	1.58	2.51	4.42	0.66	0.88	0.95	1.91	1.51	2.41	2.30	4.83	0.083	0.320	0.279			
Enterococcus, unidentified species	3.32	11.73	2.02	3.77	1.43	3.54	15.34	31.15	3.93	11.95	4.53	16.47	0.00	0.00	0.00	0.00	0.02	0.07	0.00	0.00	0.43	1.10	0.00	0.00	0.12	0.46	0.30	1.15	0.00	0.00	0.012	0.180	0.068	**0.000**	0.419	0.210
Lactobacillus, unidentified species	10.58	20.69	8.52	15.01	16.15	25.84	7.29	16.22	10.94	15.10	11.44	20.43	16.63	23.77	1.95	4.67	7.38	11.97	12.71	18.55	5.87	10.90	8.15	10.22	8.74	18.46	1.27	2.77	2.07	3.56	0.277	0.081	0.365			
Clostridiales, unidentified species 1	0.08	0.20	0.18	0.62	0.13	0.37	0.12	0.43	0.05	0.10	0.39	1.03	0.08	0.28	0.49	0.73	0.03	0.08	0.48	1.27	0.35	0.81	0.14	0.45	0.91	1.55	0.58	1.11	0.25	0.40	0.138	0.281	0.138			
Clostridiales, unidentified species 2	0.20	0.34	1.48	2.07	0.66	1.39	0.58	1.04	1.30	1.51	1.15	1.29	1.37	1.15	1.11	1.36	1.48	1.44	0.86	0.97	1.28	1.42	1.35	1.82	1.01	1.11	2.82	3.23	1.23	1.30	0.018	0.230	0.264	**0.000**	0.298	0.430
Clostridiaceae, unidentified species 1	4.57	2.39	5.16	4.91	7.37	9.27	2.46	2.84	4.48	3.06	2.58	2.62	6.40	4.48	6.80	3.53	4.28	3.45	4.95	4.28	4.95	2.48	5.03	2.77	6.31	3.77	6.43	2.45	6.17	3.56	0.034	0.065	0.269	**0.000**	0.393	0.567
Clostridiaceae, unidentified species 2	1.95	2.61	4.92	5.75	6.06	7.48	2.50	4.06	5.63	4.13	3.21	3.27	5.10	4.39	8.45	4.18	3.55	3.43	4.29	4.41	6.38	3.06	5.47	4.04	5.12	3.17	6.79	4.00	5.88	4.29	0.076	0.176	0.236			
Clostridium, unidentified species	2.27	5.01	2.08	3.61	6.49	15.41	0.00	0.00	0.10	0.23	0.07	0.22	0.18	0.71	0.25	0.66	0.54	1.80	0.01	0.06	0.19	0.35	0.07	0.19	0.03	0.10	0.58	2.23	0.28	0.88	0.012	0.376	0.102	**0.000**	0.387	0.612
Lachnospiraceae, unidentified species 1	4.02	4.24	4.28	5.60	5.60	5.61	2.35	3.02	7.98	3.40	8.10	7.00	5.92	3.73	6.14	4.16	4.30	5.87	5.89	5.02	7.22	4.55	6.84	6.64	9.16	7.41	8.64	5.81	6.75	3.78	0.012	0.084	0.116	**0.001**	0.401	**0.003**
Lachnospiraceae, unidentified species 2	0.96	1.34	2.09	1.70	1.30	1.51	1.26	2.63	2.08	1.39	2.15	2.35	1.95	2.29	2.16	1.62	2.80	2.56	1.46	2.33	1.94	1.53	1.48	1.32	2.02	1.71	2.58	2.03	2.53	2.47	0.279	0.417	0.965			
Blautia, unidentified species	3.56	3.67	8.37	6.22	7.10	8.66	9.97	13.13	10.32	7.08	14.94	7.24	11.74	6.39	12.49	6.39	12.17	8.33	9.52	6.12	10.26	5.41	12.22	7.99	8.63	5.78	11.61	7.28	9.03	5.66	0.031	0.456	0.058	**0.000**	0.302	0.261
Blautia producta	2.81	4.40	5.00	6.01	4.26	3.60	2.67	2.73	5.28	3.36	6.35	5.06	4.80	2.70	5.87	3.68	4.51	2.74	3.08	3.21	4.16	2.48	4.13	2.34	3.96	4.59	6.97	3.90	4.28	3.56	0.153	0.263	0.806			
Coprococcus, unidentified species	0.09	0.22	0.19	0.40	0.07	0.26	0.08	0.20	0.28	1.02	0.29	0.40	0.33	0.69	0.07	0.12	0.70	1.23	0.12	0.23	0.26	0.32	0.79	1.65	0.11	0.29	0.14	0.36	0.33	0.39	0.559	0.306	0.234			
Dorea, unidentified species	0.54	1.18	0.75	1.82	0.45	0.79	0.30	0.77	0.34	0.75	1.03	1.32	0.76	1.01	0.42	0.82	0.87	1.11	1.30	1.55	1.07	1.33	1.22	1.61	0.93	1.47	0.85	1.31	0.73	1.25	0.408	0.471	0.620			
Ruminococcus, unidentified species 1	0.00	0.02	0.32	1.00	0.62	1.36	0.27	0.75	0.70	2.00	0.19	0.47	0.51	1.15	0.28	0.80	0.90	1.33	0.51	1.46	0.39	1.04	0.73	1.66	0.88	1.02	1.19	1.67	0.74	1.30	0.137	0.121	0.558			
Ruminococcus, unidentified species 2	0.95	1.33	1.45	1.78	0.65	1.06	2.00	2.56	2.08	2.69	2.11	1.63	0.98	1.05	1.20	1.54	0.52	0.85	1.53	1.36	1.27	1.61	0.96	0.81	1.39	1.47	0.63	0.90	0.77	0.99	0.612	0.742	0.046			
Ruminococcus gravus	2.63	3.13	1.98	2.57	2.36	3.21	0.50	0.77	2.03	3.94	1.75	1.27	1.17	1.22	1.19	1.69	2.10	2.94	0.52	0.74	0.22	0.49	1.55	1.35	1.04	1.54	1.26	2.24	0.95	1.82	0.058	0.274	0.343			
Peptococcus, unidentified species	0.39	0.74	0.15	0.33	0.80	1.89	0.17	0.55	0.62	1.07	0.26	0.74	0.68	1.09	0.33	0.52	0.77	1.03	0.52	0.59	0.66	0.88	0.99	1.28	0.73	0.77	0.97	1.00	1.07	1.18	0.055	0.012	0.018	**0.000**	0.779	0.456
Peptostreptococcaceae, unidentified species	0.12	0.36	1.24	1.79	0.42	0.98	0.15	0.40	0.65	1.43	0.05	0.19	2.01	4.75	0.26	0.74	0.92	3.04	1.30	3.01	1.38	4.78	1.50	2.49	2.18	5.28	2.47	3.17	3.32	5.72	0.275	0.274	0.076			
Ruminococaceae, unidentified species 1	0.06	0.19	0.03	0.12	0.00	0.00	0.20	0.77	0.02	0.04	0.17	0.43	0.02	0.10	0.16	0.52	0.06	0.08	0.07	0.13	0.02	0.05	0.08	0.17	0.10	0.15	0.21	0.56	0.09	0.21	0.234	0.629	0.188			
Ruminococaceae, unidentified species 2	1.30	1.69	0.97	1.26	1.93	4.21	1.53	2.23	1.58	1.23	1.53	1.70	2.09	1.60	2.32	3.52	1.73	1.60	2.78	1.85	2.12	1.90	2.51	2.64	3.04	2.87	3.14	2.73	2.38	1.43	0.060	0.101	0.116			
Faecalibacterium prausntzii	0.20	0.67	0.24	0.46	0.02	0.09	0.40	0.81	0.51	0.87	0.79	1.16	0.68	1.03	0.69	0.95	0.51	0.63	0.52	0.65	0.78	1.39	0.26	0.41	0.36	0.62	0.65	0.99	1.27	2.60	0.264	0.559	0.131			
Oscillospira, unidentified species	0.11	0.15	0.33	0.56	0.14	0.28	0.14	0.30	0.10	0.16	0.17	0.47	0.01	0.02	0.15	0.30	0.13	0.31	0.06	0.12	0.14	0.24	0.08	0.12	0.13	0.22	0.24	0.36	0.30	0.41	0.272	0.941	0.306			
Ruminococcus, unidentified species	0.07	0.19	0.08	0.27	0.17	0.41	0.05	0.13	0.08	0.28	0.02	0.07	0.01	0.02	0.00	0.01	0.07	0.15	0.02	0.05	0.04	0.10	0.05	0.10	0.05	0.11	0.09	0.13	0.02	0.05	0.895	0.085	0.430	**0.047**	0.347	0.411
Dialister, unidentified species	0.43	0.61	1.12	1.80	0.06	0.20	0.02	0.08	0.90	2.67	0.63	1.97	0.27	0.65	1.09	2.28	0.89	2.30	0.57	1.00	0.92	1.75	1.16	3.22	0.12	0.15	1.05	2.09	0.30	1.01	0.080	0.883	0.532			
Megamonas, unidentified species	1.47	3.91	1.30	1.81	0.09	0.26	0.96	2.08	0.25	0.44	0.83	1.75	0.17	0.36	1.77	3.86	2.55	5.88	0.41	0.89	0.53	0.92	0.53	0.85	1.36	3.98	1.19	2.10	1.33	2.24	0.939	0.976	0.364			
Megasphaera, unidentified species	4.01	11.09	2.88	5.60	1.90	4.21	0.65	2.03	3.00	3.87	1.49	2.62	2.71	3.68	4.87	6.74	4.16	5.26	9.55	13.05	4.51	6.73	2.13	2.67	1.21	1.55	2.39	4.49	1.65	2.31	0.012	0.863	0.527	**0.007**	0.609	0.546
Phascolarctobacterium, unidentified species	0.30	0.55	0.12	0.43	0.02	0.09	0.09	0.25	0.08	0.22	0.00	0.00	0.05	0.10	0.02	0.05	0.11	0.28	0.27	0.50	0.23	0.36	0.03	0.10	0.16	0.37	0.40	0.66	0.27	0.67	0.343	0.018	0.183	**0.001**	0.258	0.066
Mogibacteriaceae, unidentified species	0.00	0.01	0.02	0.08	0.02	0.07	0.04	0.14	0.10	0.23	0.09	0.36	0.05	0.14	0.07	0.16	0.09	0.14	0.01	0.05	0.10	0.16	0.07	0.17	0.09	0.18	0.12	0.20	0.28	0.66	0.176	0.395	0.084			
Bulleidia, unidentified species 1	0.00	0.00	0.00	0.00	0.06	0.24	0.00	0.00	0.04	0.14	0.00	0.00	0.21	0.78	0.00	0.00	0.25	0.95	0.25	0.85	0.01	0.05	0.65	1.35	0.35	1.02	0.00	0.00	0.60	0.86	0.228	0.491	0.034	**0.002**	**0.022**	**0.021**
Bulleidia, unidentified species 2	0.13	0.38	0.14	0.48	1.05	2.25	0.13	0.46	0.00	0.00	0.55	1.46	0.59	1.56	0.28	1.01	1.35	3.18	1.80	3.46	0.34	0.65	1.96	3.04	1.84	4.10	0.54	0.67	2.01	2.58	0.055	0.031	0.235	**0.000**	0.387	0.994
Catenibacterium, unidentified species	0.92	2.20	0.85	2.75	0.44	1.18	0.63	2.45	2.19	3.38	1.77	3.98	2.23	2.59	6.19	8.48	1.74	3.55	2.75	4.88	5.12	4.99	5.97	10.59	4.95	6.30	2.41	3.57	3.10	3.54	0.012	0.012	0.031	**0.000**	0.240	**0.028**
Eubacterium biforme	1.19	1.71	0.92	2.44	1.87	3.46	0.42	0.90	1.62	2.46	3.51	4.39	2.59	3.97	2.86	2.92	3.35	3.60	2.69	3.92	3.68	2.93	3.49	3.02	2.96	3.59	3.15	2.98	3.11	2.30	0.029	0.012	0.180	**0.000**	0.173	0.253
Eubacterium dolichum	0.10	0.24	0.01	0.03	0.05	0.11	0.17	0.25	0.10	0.27	0.02	0.06	0.01	0.03	0.00	0.01	0.03	0.10	0.00	0.01	0.00	0.02	0.01	0.05	0.02	0.07	0.06	0.25	0.06	0.18	0.043	0.362	0.714	**0.003**	0.457	0.285
Fusobacterium, unidentified species	8.30	11.48	1.98	3.73	4.46	9.77	3.91	9.57	0.29	0.68	0.03	0.08	0.30	0.74	0.21	0.78	0.12	0.24	0.49	1.71	0.40	0.88	0.24	0.92	0.42	0.85	0.46	0.72	0.52	0.89	0.029	0.236	0.264	**0.002**	0.219	0.090
Sutterella, unidentified species	0.34	0.51	0.42	0.71	0.12	0.29	0.04	0.09	0.38	0.85	0.09	0.19	0.10	0.26	0.20	0.36	0.41	0.50	0.13	0.19	0.41	0.62	0.17	0.38	0.16	0.37	0.34	0.66	0.78	1.23	0.974	0.234	0.083			
Campylobacter, unidentified species	0.11	0.38	0.18	0.40	0.08	0.25	0.54	0.95	0.01	0.05	0.20	0.45	0.16	0.53	0.01	0.02	0.93	2.77	0.12	0.22	0.02	0.06	0.31	0.75	0.11	0.15	0.08	0.16	0.11	0.17	0.228	0.393	0.615			
Helicobacter, unidentified species	0.10	0.31	0.39	0.83	0.02	0.10	0.44	1.66	0.12	0.30	0.00	0.00	0.07	0.27	0.09	0.22	0.30	0.66	0.09	0.19	0.00	0.00	0.49	0.99	0.03	0.08	0.40	0.81	0.14	0.36	0.798	0.089	0.203			
Succinivibrionaceae, unidentified species 1	3.34	9.62	0.42	0.83	0.30	0.86	0.06	0.17	0.11	0.25	0.22	0.86	0.06	0.17	0.08	0.30	0.04	0.14	0.21	0.46	0.02	0.06	0.09	0.33	0.22	0.54	0.03	0.07	0.09	0.23	0.235	0.138	0.921			
Succinivibrionaceae, unidentified species 2	0.87	1.57	1.29	2.74	0.08	0.22	0.01	0.03	0.50	1.28	0.00	0.00	0.14	0.36	0.19	0.40	0.23	0.48	0.10	0.30	0.00	0.00	0.01	0.03	0.07	0.15	0.65	1.30	0.12	0.34	0.060	0.053	0.251			
Enterobacteriaceae, unidentified species	4.89	16.08	3.48	12.08	0.41	1.08	3.16	6.25	2.57	9.86	0.18	0.44	0.69	2.66	0.01	0.02	0.45	1.22	0.09	0.34	0.00	0.00	0.05	0.18	0.14	0.54	0.20	0.77	0.13	0.40	0.012	0.012	0.481	**0.000**	0.594	**0.031**

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Supplementary data-Table S6. Summary statistics of qPCR data describing the mean log abundance and standard deviation of bacterial groups belonging to antibiotic-treated (AMC and DOX groups) and healthy (CON group) cats.

	Day 0			**Day 20/28**			**Day 60**			**Day 120**			**Day 300**			**BH adjusted p values**	**Mixed model effects**		
	AMC	CON	DOX	AMC	CON	DOX	AMC	CON	DOX	AMC	CON	DOX	AMC	CON	DOX	AMC CON DOX	Sampling day	Group	Sampling day x Group
qPCR	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD	MeanSD				
Total bacteria	11.000.39	10.910.31	10.970.33	10.760.33	11.040.20	10.950.21	10.960.22	11.010.21	11.050.20	11.090.13	11.040.13	10.980.25	10.920.16	10.790.20	11.05 0.21	0.0430.0180.785	**0.019**	0.599	**0.005**
Faecalibacterium spp.	5.371.16	5.441.21	5.511.50	5.241.51	6.170.88	6.231.04	6.610.58	6.420.81	6.630.70	6.850.58	6.330.85	6.570.58	6.700.61	6.650.49	6.82 0.52	0.0120.0240.031	**0.000**	0.717	0.060
Turicibacter spp.	5.700.78	5.911.12	5.650.94	5.210.65	5.210.37	5.390.89	5.520.66	5.420.36	5.460.51	5.480.70	5.800.45	5.530.68	5.730.51	5.720.29	42.04139.69	0.2850.0120.024	**0.000**	0.533	0.199
Streptococcus spp.	4.521.16	4.171.12	5.161.68	4.191.24	4.911.33	4.311.22	3.930.55	4.230.75	4.251.10	4.991.50	4.601.44	4.871.27	4.461.20	4.251.00	4.25 1.36	0.2540.4330.188			
Escherichia coli	6.521.26	6.021.39	5.801.14	6.681.11	4.061.97	4.841.91	4.521.79	3.621.82	5.101.43	5.071.39	3.951.45	4.801.43	3.871.37	3.981.90	4.39 2.07	0.0120.0120.336	**0.000**	**0.029**	**0.001**
Blautia spp.	10.170.65	10.250.74	10.180.90	9.501.43	10.690.33	10.650.33	10.540.31	10.730.25	10.620.56	10.550.30	10.620.31	10.630.38	10.480.28	10.470.28	10.58 0.28	0.0890.0530.612			
Fusobacterium spp.	8.061.45	7.170.62	7.411.29	7.261.46	6.980.58	6.710.56	6.890.87	6.740.57	6.930.32	7.070.71	6.850.72	6.640.49	7.140.88	6.960.58	7.05 0.60	0.4750.5680.175			
Clostridium hiranonis	6.151.08	4.602.78	5.112.77	4.232.51	6.061.85	4.502.89	6.291.52	6.411.79	5.902.07	6.531.04	6.700.33	6.201.76	6.221.73	6.580.32	6.40 1.80	0.1810.0120.152	**0.000**	0.771	0.110
Bifidobacterium spp.	5.751.36	6.311.52	5.761.75	5.431.42	5.731.12	5.931.40	6.390.85	5.911.24	6.041.13	6.521.22	5.551.21	6.261.19	6.071.27	5.141.26	6.12 1.29	0.1530.1630.976			
Bacteroides spp.	6.840.89	6.381.19	6.330.96	6.441.28	7.050.54	6.770.67	6.430.90	6.570.66	6.920.77	6.710.54	6.830.78	6.690.50	6.390.80	6.770.70	6.92 0.74	0.3430.2750.366	0.250	0.179	0.273

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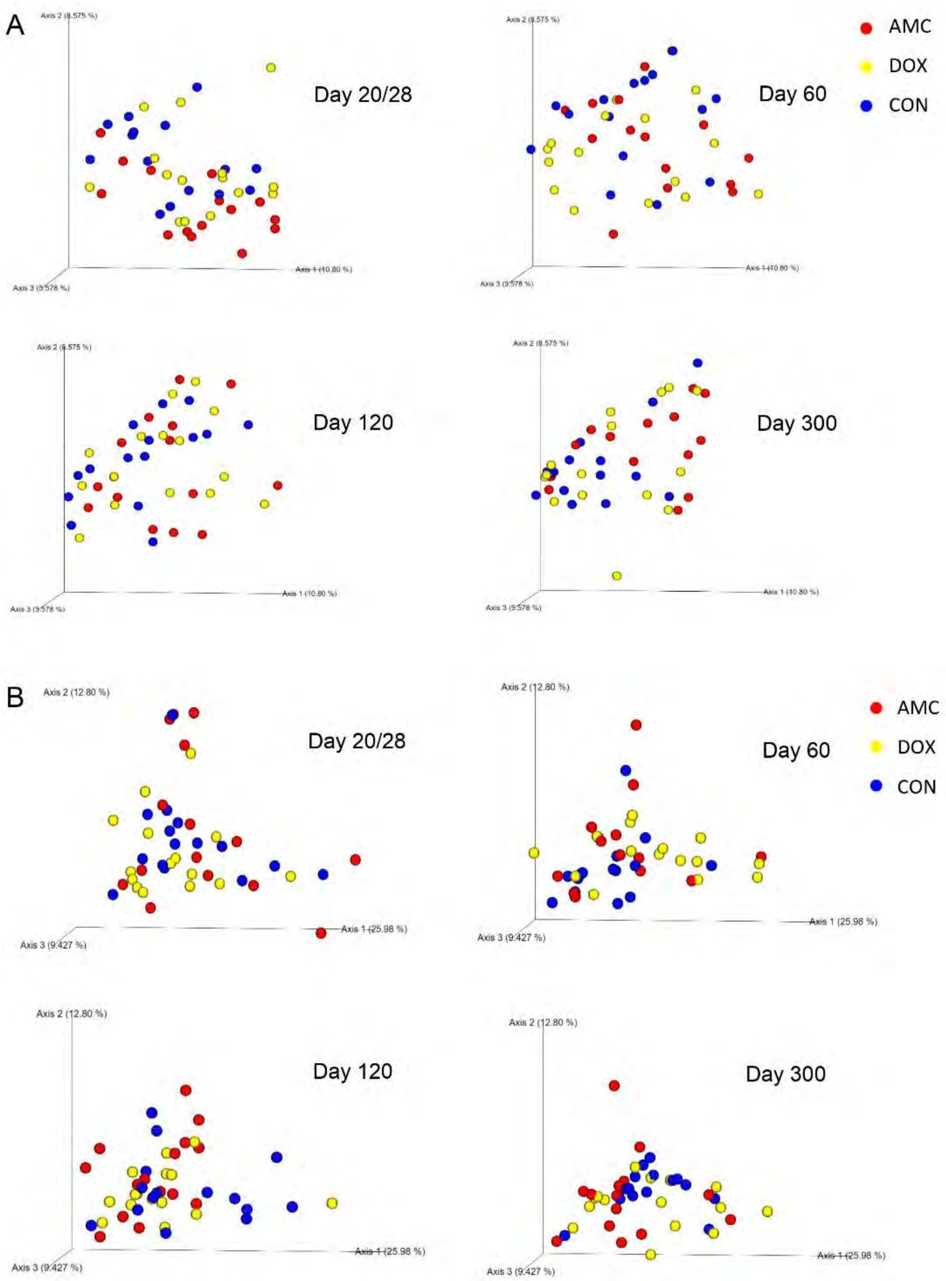
Supplementary data-Figure S1. Beta diversity indices among groups.

A) Principal Coordinate Analysis of unweighted UniFrac distances of 16S rRNA genes representing the difference in microbial communities among cats treated with amoxicillin clavulanic acid (blue circles), cats treated with doxycycline (yellow circles), and healthy control cats (red circles) on days 20/28 (last day of treatment), 60, 120, and 300. B) Principal Coordinate Analysis of weighted UniFrac distances of 16S rRNA genes representing the difference in microbial communities among cats treated with amoxicillin clavulanic acid (blue circles), cats treated with doxycycline (yellow circles), and healthy control cats (red circles) on days 20/28 (last day of treatment), 60, 120, and 300



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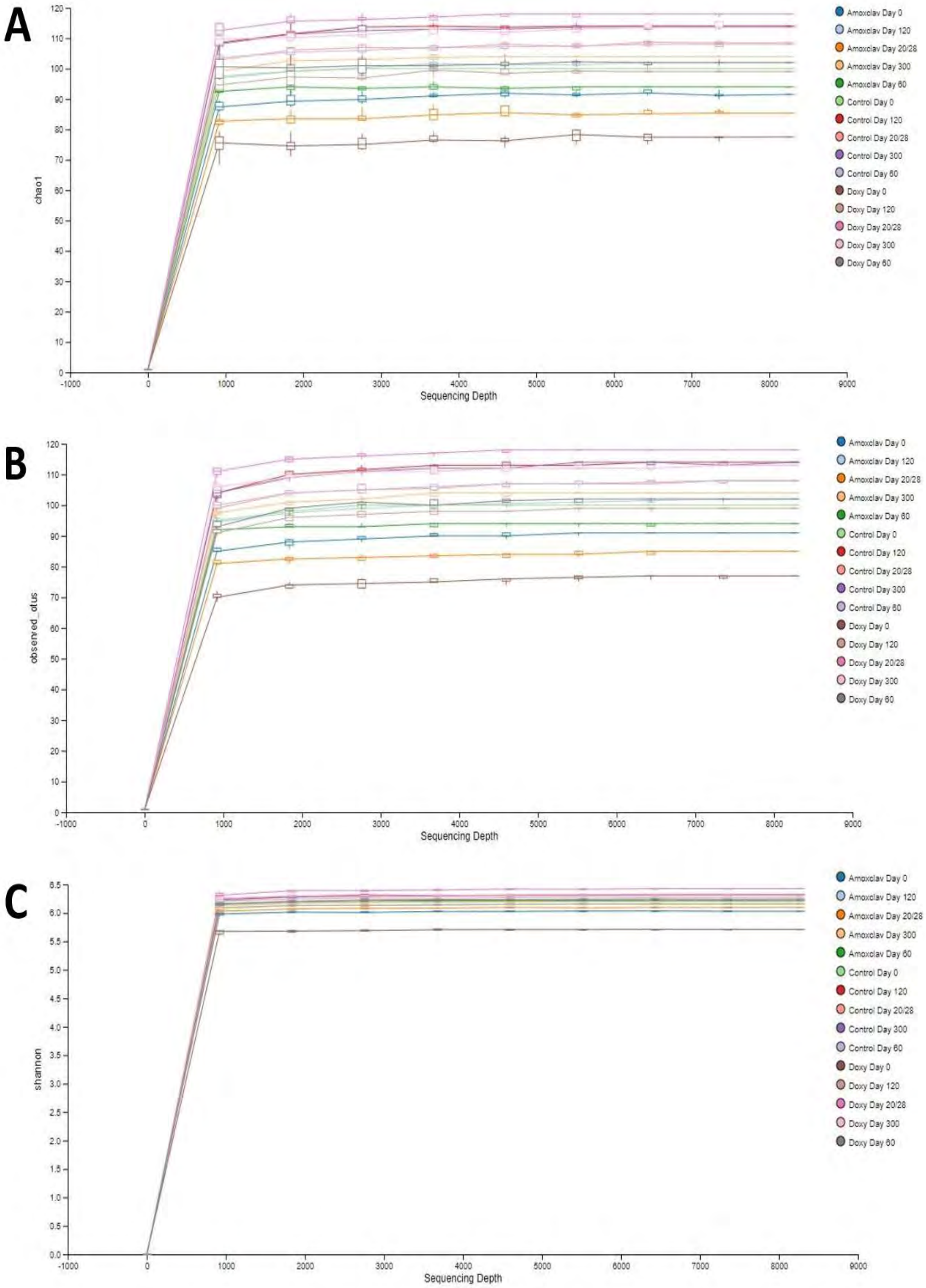
Supplementary data-Figure S2. Rarefaction curves for A) Chao1, B) Observed ASVs, and C) Shannon Index.



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3. Article No 2

The serum and fecal metabolomic profiles of growing kittens treated with amoxicillin/clavulanic acid or doxycycline. Animals 2022, 12: 330

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The Serum and Fecal Metabolomic Profiles of Growing Kittens Treated with Amoxicillin/Clavulanic Acid or Doxycycline

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Simple Summary: This study investigated the impact of antibiotic treatment on the serum and fecal metabolome (the collection of all small molecules produced by the gut bacteria and the host) of young cats. Thirty 2-month-old cats with an upper respiratory tract infection were treated with either amoxicillin/clavulanic acid for 20 days or doxycycline for 28 days. In addition, another 15 control cats that did not receive antibiotics were included. Blood was collected on days 0 (before treatment), 20/28 (last day of treatment), and 300 (10 months after the end of treatment), while feces were collected on days 0, 20/28, 60, 120, and 300. Seven serum and fecal metabolites differed between cats treated with antibiotics and control cats at the end of treatment period. Ten months after treatment, no metabolites differed from healthy cats, suggesting that amoxicillin/clavulanic acid or doxycycline treatment only temporarily affects the abundance of the serum and fecal metabolome.

Abstract: The long-term impact of antibiotics on the serum and fecal metabolome of kittens has not yet been investigated. Therefore, the objective of this study was to evaluate the serum and fecal metabolome of kittens with an upper respiratory tract infection (URTI) before, during, and after antibiotic treatment and compare it with that of healthy control cats. Thirty 2-month-old cats with a URTI were randomly assigned to receive either amoxicillin/clavulanic acid for 20 days or doxycycline for 28 days, and 15 cats of similar age were enrolled as controls. Fecal samples were collected on days 0, 20/28, 60, 120, and 300, while serum was collected on days 0, 20/28, and 300. Untargeted and targeted metabolomic analyses were performed on both serum and fecal samples. Seven metabolites differed significantly in antibiotic-treated cats compared to controls on day 20/28, with two differing on day 60, and two on day 120. Alterations in the pattern of serum amino acids, antioxidants, purines, and pyrimidines, as well as fecal bile acids, sterols, and fatty acids, were observed in antibiotic-treated groups that were not observed in control cats. However, the alterations caused by either amoxicillin/clavulanic acid or doxycycline of the fecal and serum metabolome were only temporary and were resolved by 10 months after their withdrawal.

Keywords: antibiotics; metabolomic profile; cats

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Citation: Stavroulaki, E.M.; Suchodolski, J.S.; Pilla, R.; Fosgate, G.T.; Sung, C.-H.; Lidbury, J.; Steiner, J.M.; Xenoulis, P.G. The Serum and Fecal Metabolomic Profiles of Growing Kittens Treated with Amoxicillin/Clavulanic Acid or Doxycycline. *Animals* **2022**, *12*, 330. https://doi.org/10.3390/ani12030330

Academic Editor: Elisabetta Giudice

Received: 14 December 2021
Accepted: 24 January 2022
Published: 29 January 2022

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1. Introduction

It is well known that the GI microbiome plays a central role in the host's metabolism [1]. The communication between the host and its microbiome occurs mainly through microbially derived metabolites that act as signaling molecules. Metabolomic analysis can detect and identify a wide range of small molecules that are present in biological samples, therefore allowing the assessment of both of microbial and host-derived metabolites [2]. Metabolomic

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analysis can be either targeted or untargeted, meaning that it either targets predefined metabolites or unknown metabolites, respectively. Feces may be more representative of the direct microbial metabolic products produced in the gut, compared to serum metabolites, representing those metabolites that eventually enter the systemic circulation and potentially have a greater impact on the host [3,4].

Antibiotics are used commonly for the treatment of upper respiratory tract infections (URTI) in kittens. In humans, the extensive use of antibiotics during early life is avoided based on the risk of the development of antibiotic resistance or because of the potential long-lasting effects of antibiotics on the gastrointestinal (GI) microbiome [5,6]. Secondary metabolic perturbations can occur due to antibiotic-induced dysbiosis in infants. A combination treatment of ampicillin and gentamycin caused reduced fecal concentrations of GABA, tryptophan, and ornithine in 2-day-old infants [7]. These metabolites play an important role in neurodevelopment and intestinal contractility, while ornithine is also an energy source for enterocytes [7]. In another study in 1-week-old infants, a combination of various beta-lactam antibiotics caused reduced fecal concentrations of microbially produced antibiotic compounds [8]. Antibiotics produced by the microbiome play an important role in colonization resistance [8]. The disruption of colonization resistance is a common consequence of antibiotic therapy and might be followed by the colonization or proliferation of pathogenic bacteria, leading to persistent gastrointestinal or systemic symptoms. The percentage of the known fecal end metabolic products that are altered by antibiotic treatment has been estimated to be between 4.4% and 87% in humans [9]. Commonly perturbed metabolic pathways following antibiotic intervention relate to protein, carbohydrate, lipid, and bile acid (BA) metabolism [10].

No studies have previously investigated the effects of antibiotics on the serum or fecal metabolic profiles of young cats. Previous studies have focused on the taxonomical and compositional characterization of the GI microbiome in young cats [11–18]. More recent studies have also described the serum and fecal metabolites in cats in states of health [19–23] and disease [24–29], or following drug administration [30–33]. Investigating metabolic patterns under certain conditions has filled gaps in understanding cellular processes and has led to the discovery of new disease biomarkers, allowing an understanding of impaired signaling pathways in different disease states [9]. For example, increased concentrations of several amino acids, arachidonic acid, and simple sphingolipids, and reduced concentrations of indole derivatives, have been found in the feces from cats with inflammatory bowel disease and alimentary lymphoma [28]. These alterations add knowledge to the pathogenesis of feline chronic enteropathies, as well as highlight potential therapeutic strategies. In another study, Burmese cats, a breed at high risk for developing diabetes mellitus, had higher serum concentrations of tyrosine and 2-oxoisocaproic acid, which are precursors leading to insulin resistance in humans [34].

Antibiotic treatment has been shown to alter the abundance of serum and fecal metabolites in dogs. Tylosin and metronidazole constitute the antibiotics of choice in dogs with antibiotic-responsive enteropathy, although their effects on the microbiome and secondary metabolites suggest the maintenance of GI dysbiosis. Metronidazole administration in dogs decreased fecal vitamins, antioxidants, secondary BAs, and increased oxidative stress molecules [35,36]. A combination therapy with metronidazole and enrofloxacin led to alterations of various metabolic profiles, including short chain fatty acids (SCFAs), tryptophan, and sphingolipid metabolites, as well as reductions in secondary BAs and increases in primary BAs [37]. Treatment with tylosin also caused an increase in primary BAs [38]. In cats, only the effects of clindamycin have been investigated, and long-term changes described have included a reduction in deoxycholic acid, a secondary BA, 2 years after antibiotic withdrawal [31,32].

Although the mode of action of each antibiotic has been extensively studied, there is new evidence from metabolomic studies that the secondary metabolites produced during antibiotic intervention play a role in antibiotic lethality [39]. Antibiotics that target the intracellular bacterial metabolism affect different microbial metabolic pathways compared to antibiotics

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that target the microbial cell wall or which are bacteriostatic [40]. For example, altering amino acid metabolism is a mechanism by which bacteria acquire resistance to aminoglycosides. The exogenous administration of amino acids increases the permeability of the bacterial cell membrane, which further increases the uptake of aminoglycosides and increases their efficacy [41]. Identifying the metabolic pathways by which antibiotics kill bacterial cells can be used for the identification of molecules that strengthen antibiotic lethality.

The aim of the present study was to describe the short- and long-term effects of amoxicillin/clavulanic acid or doxycycline on the serum and fecal metabolome in young cats. A secondary aim was to describe the normal age-related changes on the abundance of feline serum and fecal metabolites during the first year of life.

2. Materials and Methods

2.1. Study Population

This was a prospective case–control study. Forty-five rescue kittens, approximately 2 months of age, were enrolled. All kittens were kept in individual cages in appropriately designed facilities of the Clinic of Medicine at the Faculty of Veterinary Science of the University of Thessaly until adoption into private homes. Prior to inclusion into the study, all kittens received the same antiparasitic treatment (fipronil, (S)-methoprene, eprinomectin, and praziquantel; Broadline, Boehringer Ingelheim) and remained on the same antiparasitic treatment monthly throughout the study period. In addition, all kittens were fed the same commercial dry cat food during the study (GEMON Cat Breeder Kitten, Monge Breeder, Turin, Italy) and were vaccinated (Purevax RCPh, Purevax Rabies, Gerolymatos International S.A., Athens, Greece) according to standard vaccination guidelines [42]. All cats were eventually adopted by the end of the study and owners signed an informed owner consent form.

All 45 kittens had clinical signs suggestive of an acute URTI, including sneezing, ocular and/or nasal discharge, and blepharospasm for less than 10 days [43]. Concurrent health conditions were documented, and kittens were excluded if these were severe enough to require hospitalization, or if they had conditions suspected to affect the GI microbiota (such as GI infections). In addition, no more than two related cats were included in the study to ensure that relatedness did not bias results. Kittens diagnosed with URTI were chosen because acute URTI is typically restricted to the upper respiratory system, and it was presumed that this disease will not affect the concentrations of serum or fecal metabolites in cats.

2.2. Group Allocation and Treatments

On day 0, kittens were randomly assigned to receive either amoxicillin/clavulanic acid at a dose of 20 mg/kg q12 h for 20 days (AMC group = 15 cats) or doxycycline at a dose of 10 mg/kg q24 h for 28 days (DOX group = 15 cats), each administered orally. Randomization was performed using Microsoft Excel (2017), with odd numbers corresponding to the AMC group, whereas even numbers corresponded to the DOX group. These antibiotics were chosen based on previously published guidelines for the treatment of URTI in cats [43]. In addition, 15 kittens that had mild clinical signs of URTI did not receive antibiotics and were assigned to the control group (CON group).

2.3. Sample Collection and Follow-Up Period

Blood samples were collected from the jugular vein, allowed to clot, centrifuged at $3000\times g$ for 10 min, and serum was collected and placed into Eppendorf tubes and stored at −80 °C, pending analysis. For cats in the AMC group, blood samples were collected on days 0, 20 (last day of amoxicillin/clavulanic acid treatment), and 300. For cats in the DOX and CON groups, blood samples were collected on days 0, 28 (last day of doxycycline treatment), and 300.

Fecal samples were collected from the litter box within 4 h of defecation, placed into Eppendorf tubes, and kept at −80 °C until analysis. For kittens that were adopted,

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owners were instructed to clean the litterbox prior to the day of each scheduled fecal sample collection, collect fresh feces on the scheduled day, and ship them packed on ice by overnight courier. For cats in the AMC group, feces were collected on days 0 (baseline), 20 (last day of amoxicillin/clavulanic acid treatment), 60, 120, and 300. For cats in the DOX and CON groups, feces were collected on days 0, 28 (last day of doxycycline treatment), 60, 120, and 300.

2.4. Metabolomic Analysis

2.4.1. Untargeted Metabolomic Analysis of Serum Samples

Serum samples were analyzed at the West Coast Metabolomics Center (University of California, Davis, CA, USA) using a gas chromatography–time-of-flight mass spectrometry (GC-TOF MS) method. Serum aliquots were extracted with degassed acetonitrile. Internal standards C08-C30 fatty acid methyl ethers (FAMEs) were added, and the samples were derivatized with methoxyamine hydrochloride in pyridine and subsequently with N-methyl-N-trimethylsilyltrifluoroacetamide for the trimethylsilylation of acidic protons. Analytes were separated using an Agilent 6890 gas chromatograph (Santa Clara, CA, USA), and mass spectrometry was performed on a Leco Pegasus IV time-of-flight mass spectrometer (St. Joseph, MI, USA), following a published protocol [44]. Unnamed peaks were excluded from statistical analysis and peak height data were obtained and uploaded to MetaboAnalyst 4.0 (Xia Lab, McGill University, Montreal, Canada). Then, the filtered data were normalized through log transformation and Pareto scaling [45,46].

2.4.2. Targeted Metabolomic Analysis of Fecal Samples

Lyophilized fecal samples were used to measure the concentrations of unconjugated fecal primary BAs (cholic acid (CA) and chenodeoxycholic acid (CDCA)) and secondary BAs (lithocholic acid (LCA), deoxycholic acid (DCA), and ursodeoxycholic acid (UDCA)), fatty acids (FAs), and sterols using a gas chromatography coupled with a mass spectrometry protocol, as previously described [47,48]. Fecal concentrations of BA were expressed as ng/mg of lyophilized feces, as well as percentage of total BA. Fecal concentrations of FAs and sterols were expressed as μg/mg of lyophilized feces.

2.5. Statistical Analysis

The log-transformed, Pareto-scaled untargeted serum metabolites were compared among groups using two-way ANOVA, and within groups with two-way repeated measures ANOVA. Multiple post hoc comparisons were adjusted using Tukey's tests. *p*-values for between group comparisons were adjusted with the Benjamini and Hochberg false discovery rate (FDR), and significance was set at $q < 0.05$ to account for the large number of analytes measured. *p*-values for within-group comparisons were adjusted with Bonferroni corrections and significance was set at $p < 0.05$.

Fecal metabolites were rank transformed prior to statistical analysis due to the failure of the normality assumptions. A linear mixed model was fitted, including time, group, and the interaction between time and group as fixed effects and cat as a random effect. Multiple pairwise post hoc comparisons were Bonferroni corrected, and significance was set at $p < 0.05$. All statistics were performed with the web-based metabolomic data processing tool Metaboanalyst 5.0. (www.metaboanalyst.ca (accessed on 29 November 2021)), GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA), and SPSS version 23.0. Principal coordinate analysis, and hierarchical clustering heatmaps were generated using Metaboanalyst 5.0.

3. Results

3.1. Serum Metabolomics

A total of 182 named serum metabolites were identified, 15 of which differed significantly ($q < 0.05$) among control cats, cats treated with amoxicillin/clavulanic acid, and cats treated with doxycycline on day 0 (pre-treatment; Table 1). Principal coordinate analysis

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plots showed the clustering of variables based on treatment group on day 0 (Figure 1). The development of gut microbiota is mirrored in the microbially driven serum metabolites during early life, and abundances individualize around 2 months of age. A table with the raw abundances, as well as a table with the mean abundances and standard deviation of the metabolites identified in serum, are available as Table S1 and Table S2, respectively.

Table 1. Peak heights of serum metabolites that significantly differed among the groups at each timepoint.

Metabolite	Classification	AMC Group	CON Group	DOX Group
		Day 0		
Glutamine	Amino acid	552,948 ^{a} ± 263,874	872,940 ^{a} ± 336,986	735,477 ± 296,472
Asparagine	Amino acid	28,024 ^{a,b} ± 8064	39,820 ^{a} ± 14,906	37,632 ^{b} ± 9713
Alanine	Amino acid	1,571,042 ^{a} ± 777,177	2,077,072 ^{a} ± 473,101	1,921,038 ± 581,830
Citric acid	Organic acid	257,011 ^{a,b} ± 124,738	332,840 ^{a} ± 112,121	346,138 ^{b} ± 99,573
Trans-4-hydroxyproline	Antioxidant	255,037 ^{a} ± 192,296	362,099 ^{a} ± 180,627	256,459 ± 126,726
Ribose	Sugar	17,584 ± 10,043	21,027 ^{a} ± 12,089	31,123 ^{a} ± 16,217
Threitol	Sugar alcohol	6119 ^{a} ± 8254	1801 ^{a} ± 585	2897 ± 2568
3-hydroxybutyric acid	Fatty acid	1,192,909 ^{a} ± 2,274,124	112,391 ^{a} ± 80,512	311,592 ± 407,090
Beta-sitosterol	Sterol	2458 ^{a} ± 1340	4459 ^{a} ± 2159	2766 ± 1602
Dehydrocholesterol	Zoosterol	2775 ^{a} ± 1484	5023 ^{a} ± 3152	3991 ± 1571
Phenylethylamine	Polyamine	86,072 ± 12,733	49,633 ^{a} ± 59,675	28,350 ^{a} ± 23,642
Glyceric acid	Trionic acid	27,312 ^{a} ± 11,511	18,797 ^{a,b} ± 5325	31,637 ^{b} ± 16,222
2-hydroxyglutaric acid	Glutaric acid	9528 ^{a} ± 4490	12,753 ^{a} ± 5398	10,048 ± 3521
2-hydroxybutanoic acid	Hydroxybutyric acid	193,658 ^{a} ± 170,262	93,973 ^{a} ± 61,660	123,541 ± 69,982
2-deoxypentitol	Tetrol	3796 ^{a,b} ± 5408	1187 ^{a} ± 292	1388 ^{b} ± 404
		Day 20/28		
Uracil	Pyrimidine	6180 ± 2823	4458 ^{a} ± 1647	8912 ^{a} ± 4261
Hypoxanthine	Purine	84,182 ± 35,210	58,815 ^{a} ± 23,693	94,958 ^{a} ± 28,239
Guanine	Purine	3031 ± 1878	2071 ^{a} ± 946	3936 ^{a} ± 2018
Inositol-4-monophosphate	Inositol phosphate	1289 ^{a,b} ± 466	2072 ^{a} ± 653	2058 ^{b} ± 872
Indole-3-propionic acid	Antioxidant	2624 ^{a,b} ± 3382	8815 ^{a} ± 3066	7491 ^{b} ± 3823
Glycolic acid	Lipid	16,124 ^{a} ± 2687	17,618 ± 4914	27,515 ^{a} ± 19,908

Values are mean ± SD; ^{a,b} indicate significant differences between groups after FDR adjustment. Values with different superscripts (^{a,b}) in the same row are significantly different ($p < 0.05$).

3.1.1. Control Group

Table 2 shows the complete list of serum metabolites that changed in their abundances within the first year of life in control cats. None of the metabolites changed significantly from 2 to 3 months of age. Figure 2 shows how samples from days 28 (3 months of age) and 300 (1 year of age) are different from those on day 0 (2 months of age). After 3 months of age, amino acid concentrations changed with an increase in tryptophan ($p = 0.025$) and a decrease in glycine ($p = 0.019$). Decreases in metabolites classified as antioxidants (trans-4-hydroxyproline ($p = 0.017$), methionine sulfoxide ($p = 0.013$); polyamines: putrescine ($p = 0.002$), phenylethylamine ($p = 0.037$)), as well as in metabolites related to sugar metabolism (maltose ($p = 0.008$), erythritol ($p = 0.031$), arabitol ($p = 0.008$), and threonic acid ($p = 0.038$)) were also noted.

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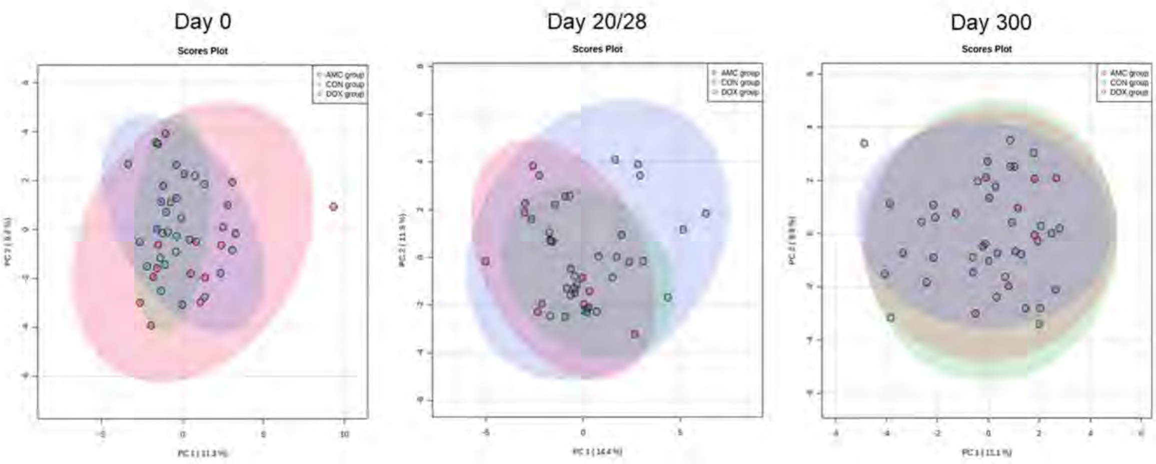

Figure 1. Principal coordinate analysis of serum metabolites on day 0 (before antibiotic administration), day 20/28 (last day of antibiotic treatment for the AMC and DOX groups, respectively), and day 300 for cats in the AMC, CON, and DOX groups.

Table 2. Peak heights of serum metabolites that differed significantly over time within CON cats.

Metabolites	Classification	Day 0	Day 28	Day 300
Tryptophan	Amino acid	255,630 ^{a} ± 96,825	344,259 ± 139,221	441,120 ^{a} ± 137,367
Glycine	Amino acid	883,554 ± 378,246	887,547 ^{b} ± 233,365	546,185 ^{b} ± 165,401
4-hydroxyphenylacetic Acid	Acetic acid	3015 ^{b} ± 1602	2829 ± 2052	1252 ^{b} ± 525
2-hydroxyglutaric Acid	Glutaric acid	12,753 ^{c} ± 5398	10,301 ^{d} ± 3394	4327 ^{c,d} ± 906
Pseudo uridine	Pyrimidine	15,377 ± 6106	17,688 ^{c} ± 2482	12,642 ^{c} ± 3254
Trans-4-Hydroxyproline	Antioxidant	362,099 ± 180,627	463,524 ^{b} ± 154,783	229,341 ^{b} ± 113,943
Methionine sulfoxide	Antioxidant	107,175 ^{b} ± 52,419	93,536 ± 35,520	59,856 ^{b} ± 33,237
Maltose	Sugar	15,491 ^{b} ± 7688	10,346 ± 4911	6515 ^{b} ± 2847
Erythritol	Sugar alcohol	12,511 ^{a} ± 4017	12,764 ± 1622	1048 ^{a} ± 1623
Arabitol	Sugar alcohol	9453 ± 3557	13,775 ^{c} ± 3221	8836 ^{c} ± 2273
Threonic acid	Sugar acid	31,888 ^{a} ± 21,050	16,298 ± 9022	13,589 ^{a} ± 7100
Putrescine	Polyamine	8201 ^{c} ± 2687	7366 ± 3102	5258 ^{c} ± 1630
Phenylethylamine	Polyamine	49,633 ± 59,675	31,497 ^{a} ± 119,931	11,004 ^{a} ± 8318
Serotonin	Hormone	83,366 ^{c} ± 36,347	85,772 ± 40,067	54,524 ^{c} ± 32,985
Phosphate	Ester	658,084 ^{b} ± 154,258	740,668 ^{a} ± 228,235	474,287 ^{a,b} ± 128,407
2-hydroxy-2-methylbutanoic acid	Organic acid	11,851 ^{a} ± 5531	9429 ± 3784	6686 ^{a} ± 1321
Creatinine		107,839 ^{b} ± 52,332	119,931 ± 39,720	188,484 ^{b} ± 41,887

Values are mean ± SD; ^{a,b,c,d} indicate significant differences over time in AMC cats after Bonferroni correction (^{a} $0.025 < p < 0.050$; ^{b} $0.005 \leq p < 0.025$; ^{c} $0.005 \leq p < 0.001$; ^{d} $p \leq 0.001$).

3.1.2. Amoxicillin/Clavulanic Acid Group

Table 3 shows the complete list of serum metabolites for which the abundance changed within the first year of life in cats treated with amoxicillin/clavulanic acid. Amoxicillin/clavulanic acid caused few changes to the serum metabolites of kittens when compared to the other groups of cats. Indole-3-propionic acid ($p < 0.001$), an antioxidant, and inositol-4-monophosphate ($q = 0.026$), an inositol lipid derivative, were detected at significantly lower concentrations in AMC cats compared to CON and DOX cats on the last day of treatment (Table 1, Figure 3).

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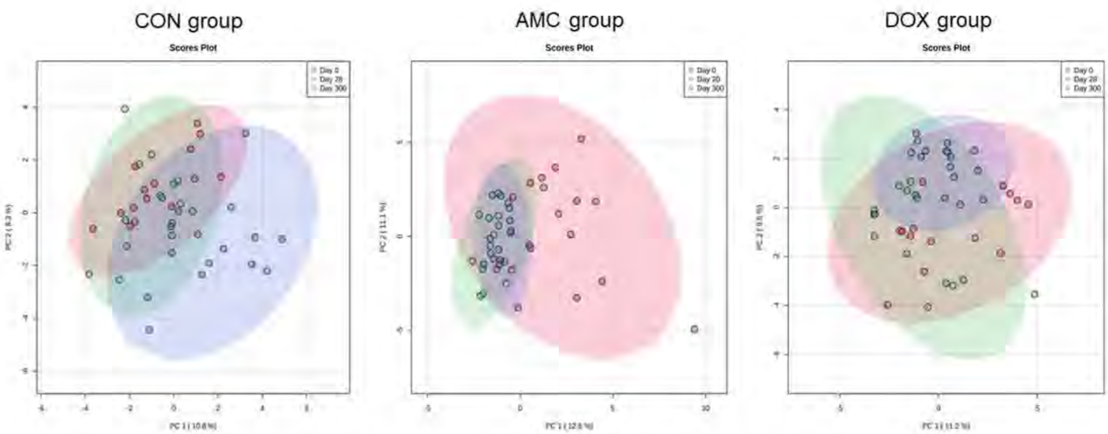

Figure 2. Principal coordinate analysis of serum metabolites for CON, AMC, and DOX groups on days 0, 20/28, and 300.

Table 3. Peak heights of serum metabolites that significantly differed over time in cats of the AMC group.

Metabolites	Classification	Day 0	Day 20	Day 300
Tryptophan	Amino acid	250,388 ^{d} ± 119,739	389,432 ^{c,d} ± 66,866	486,581 ^{d} ± 95,354
Threonine	Amino acid	200,577 ^{a} ± 108,054	317,721 ± 255,426	277,046 ^{a} ± 109,534
Oxoproline	Amino acid	721,708 ^{a} ± 174,709	815,968 ± 134,778	981,791 ^{a} ± 184,254
Isoleucine	Amino acid	514,101 ± 188,354	503,052 ^{b} ± 83,031	404,230 ^{b} ± 72,426
Tartaric acid	Organic acid	455 ± 348	380 ^{b} ± 139	1108 ^{b} ± 706 ± 882
Aconitic acid	Organic acid	2615 ^{a} ± 1457	1594 ^{a} ± 837	1614
2-hydroxyglutaric acid	Glutaric acid	9528 ^{c} ± 4490	12,206 ^{d} ± 3939	4244 ^{c,d} ± 1019
Trans-4-hydroxyproline	Antioxidant	255,037 ^{b} ± 192,296	460,027 ^{b} ± 112,402	291,014 ± 128,520
Glucose	Sugar	3,145,429 ± 643,471	3,215,996 ^{b} ± 497,544	4,251,770 ^{b} ± 1,155,169
Fucose	Sugar	7136 ± 1408	7344 ^{a} ± 1362	9371 ^{a} ± 2347
Phosphate	Ester	585,752 ± 180,423	724,383 ^{d} ± 135,884	461,411 ^{d} ± 112,401
Beta-sitosterol	Sterol	2458 ^{c} ± 1340	5775 ± 3217	6342 ^{c} ± 3243
Arachidonic acid	Fatty acid	20,304 ^{b} ± 7954	12,796 ^{a,b} ± 4318	19,069 ^{a} ± 5576
5-aminovaleric acid	Fatty acid	27,554 ^{a} ± 25,615	12,374 ± 10,395	4658 ^{a} ± 2946
5-hydroxymethyl-2-furoic acid	Furoic acid	5903 ± 9134	993 ^{b} ± 256	1571 ^{b} ± 388
Creatinine		169,183 ± 97,973	110,233 ^{a} ± 39,656	181,369 ^{a} ± 57,411

Values are mean ± SD; ^{a,b,c,d} indicate significant differences over time in AMC cats after Bonferroni correction (^{a} $0.025 < p < 0.050$; ^{b} $0.005 \leq p < 0.025$; ^{c} $0.005 \leq p < 0.001$; ^{d} $p \leq 0.001$).

In addition, changes in the abundance of metabolites were observed in AMC cats from 2 to 3 months of age, i.e., from day 0 to day 20, that were not observed within the control group at the same age. Aconitic acid ($p = 0.034$) and arachidonic acid ($p = 0.018$) decreased significantly after 20 days of treatment with amoxicillin/clavulanic acid. In addition, trans-4-hydroxyproline ($p = 0.012$), an antioxidant, increased by the last day of treatment (Figure 3).

A different pattern for the abundance of metabolites was also observed in AMC cats after 3 months of age (after day 20) when compared to the CON cats (Figure 2). Within the amino acid group, threonine significantly increased ($p = 0.025$), while isoleucine decreased ($p = 0.016$) in AMC cats after 3 months of age. The serum concentrations of metabolites belonging to sugars increased, including glucose ($p = 0.017$) and fucose ($p = 0.045$).

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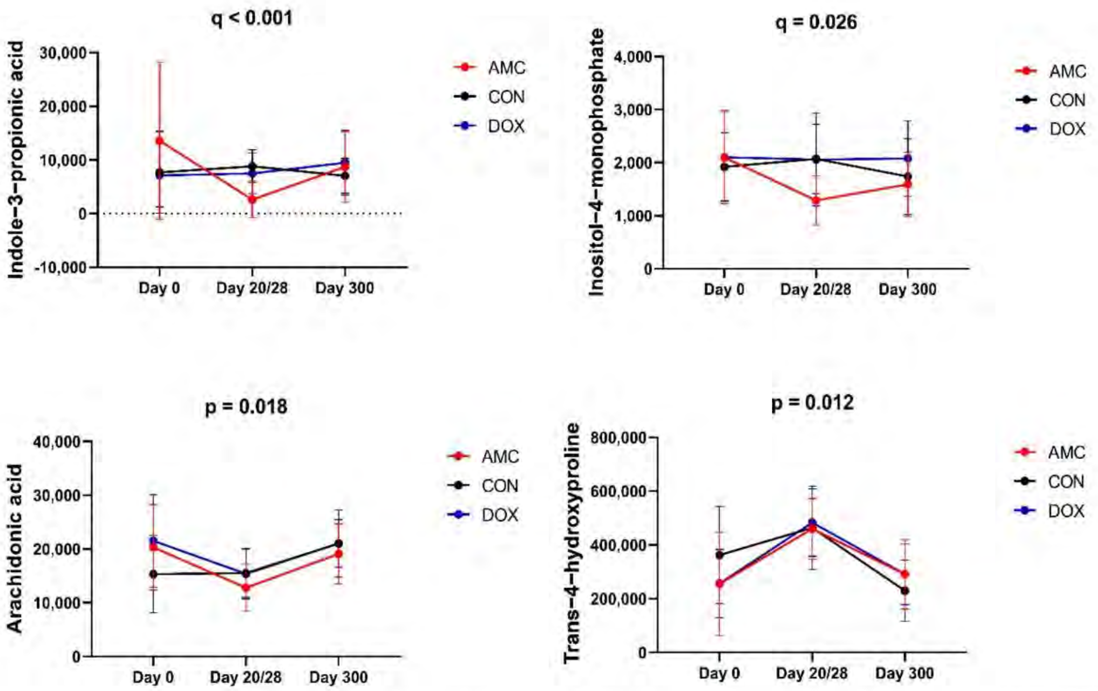

Figure 3. Abundance of serum metabolites that significantly differed between the AMC and CON groups on day 20/28 (indole-3-propionic acid, inositol-4-monophosphate) and from day 0 to day 20 within AMC cats (arachidonic acid, trans-4-hydroxyproline). Means and standard deviations are displayed.

3.1.3. Doxycycline Group

Table 4 contains the complete list of serum metabolites for which the abundance changed within the first year of life in cats treated with doxycycline. The concentrations of serum metabolites in 2-month-old cats were characterized by significant changes after 28 days of treatment with doxycycline, i.e., from 2 to 3 months of age. Concentrations of pyrimidines, including uracil ($q = 0.043$), and purines, including guanine ($q = 0.004$) and hypoxanthine ($q = 0.042$), were at significantly higher levels in DOX cats compared to CON cats on the last day of treatment (Table 1, Figure 4).

A different pattern in the concentrations of serum metabolites in DOX cats was observed from 2 to 3 months of age when compared to CON cats at this age. Similar to AMC cats, concentrations of trans-4-hydroxyproline increased in DOX cats ($p = 0.007$) (Figure 3). In addition, thymidine increased ($p = 0.032$), while metabolites classified as vitamins and sterols, including tocopherol-alpha ($p = 0.037$) and beta-sitosterol ($p = 0.027$), respectively, decreased from 2 to 3 months of age in DOX cats.

The pattern of the abundance of individual metabolites was also different in DOX cats compared to CON cats after the age of 3 months (i.e., day 28) (Figure 2). Within the amino acid group, threonine ($p < 0.001$) and glutamine ($p = 0.038$) increased, while aspartic acid ($p = 0.036$) decreased by the age of 1 year. Metabolites involved in sugar metabolism were also affected, including an increase in fructose ($p = 0.049$) and a reduction in isothreonic acid ($p = 0.002$) and gluconic acid ($p = 0.037$). A heatmap, which graphically represents variations in serum metabolite signal intensities among the three groups of cats, is presented in Figure 5.

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Table 4. Peak heights of serum metabolites that significantly differed over time within cats of the DOX group.

Metabolites	Classification	Day 0	Day 28	Day 300
Tryptophan	Amino acid	267,090 ^{d} ± 124,026	393,276 ± 108,905	534,822 ^{d} ± 126,493
Threonine	Amino acid	155,280 ^{d} ± 71,885	233,122 ± 125,192	232,976 ^{d} ± 55,123
Glutamine	Amino acid	735,477 ± 296,473	685,995 ^{a} ± 270,345	1,058,116 ^{a} ± 241,969
Aspartic acid	Amino acid	26,034 ± 7550	30,308 ^{a} ± 6213	22,840 ^{a} ± 4077
2-hydroxyglutaric acid	Glutaric acid	10,048 ^{c} ± 3521	12,499 ^{d} ± 3377	4425 ^{c,d} ± 1062
Uracil	Pyrimidine	6916 ^{a} ± 3400	8912 ^{c} ± 4261	3795 ^{a,c} ± 1863
Thymidine	Pyrimidine	30,479 ^{a} ± 11403	47,596 ^{a} ± 16,194	36,446 ± 8196
Pseudo uridine	Pyrimidine	18,234 ^{a} ± 4993	18,167 ± 7313	13,255 ^{a} ± 2608
Hypoxanthine	Purine	74,971 ± 24,171	94,958 ^{a} ± 28,239	61,218 ^{a} ± 23,140
Trans-4-hydroxyproline	Antioxidant	256,459 ^{b,c} ± 126,726	483,290 ^{c} ± 125,486	290,840 ^{b} ± 112,972
Fructose	Sugar	270,389 ^{a} ± 100,509	253,463 ± 69,322	446,898 ^{a} ± 206,582
Myo-inositol	Sugar alcohol	328,115 ± 196,034	404,677 ^{a} ± 133,018	265,394 ^{a} ± 128,091
Isothreonic acid	Sugar acid	12,508 ^{c} ± 3518	12,359 ^{b} ± 3379	7674 ^{c,b} ± 1083
Gluconic acid	Sugar acid	104,628 ^{a} ± 61,378	90,441 ± 47,982	43,425 ^{a} ± 43,335
Tocopherol alpha	Vitamin	41,000 ^{a} ± 22,358	20,256 ^{a} ± 8868	26,884 ± 12,928
Phosphate	Ester	646,227 ± 185,512	803,778 ^{b} ± 194,685	506,265 ^{b} ± 107,415
Lanosterol	Lanosterol	372 ± 180	257 ^{a} ± 60	344 ^{a} ± 66
Beta-sitosterol	Sterol	2766 ^{a,b} ± 1602	6238 ^{a} ± 2606	5392 ^{b} ± 2244
Arachidonic acid	Fatty acid	21,507 ± 8645	15,391 ^{a} ± 4627	21,035 ^{a} ± 4419
5-hydroxymethyl-2-furoic acid	Furoic acid	1799 ± 1639	980 ^{d} ± 267	1628 ^{d} ± 417
Creatinine		144,622 ± 108,647	117,559 ^{d} ± 42,094	207,931 ^{d} ± 51,552

Values are mean ± SD; ^{a,b,c,d} indicate significant differences over time in DOX cats after Bonferroni correction (^{a} $0.025 < p < 0.050$; ^{b} $0.005 \leq p < 0.025$; ^{c} $0.005 \leq p < 0.001$; ^{d} $p \leq 0.001$).

3.2. Fecal Metabolomics

The AMC and DOX cats had no significant differences in fecal BA concentrations compared to CON cats at any time point. There was only a tendency for decreased concentrations of secondary BAs in both antibiotic-treated groups on the last day of treatment compared to CON cats, but this did not reach statistical significance ($p = 0.090$). However, concentrations of fatty acids and sterols were significantly affected by antibiotics. Nervonic acid and cholesterol were detected at significantly lower concentrations in DOX cats compared to CON cats on the last day of treatment (nervonic acid, $p = 0.010$; cholesterol, $p = 0.005$) as well as 1 month (i.e., day 60) (nervonic acid, $p < 0.001$; cholesterol, $p = 0.001$) and 3 months (i.e., day 120) (nervonic acid, $p = 0.037$; cholesterol; $p = 0.048$) after antibiotic withdrawal. Nervonic acid concentrations were also significantly lower in AMC cats at 1 month ($p = 0.001$) and 3 months ($p = 0.032$) after antibiotic withdrawal compared to CON cats (Figure 6). A table with the raw metabolites and a table with the mean abundances and standard deviation with the metabolites identified in fecal samples are available as Table S3 and Table S4, respectively.

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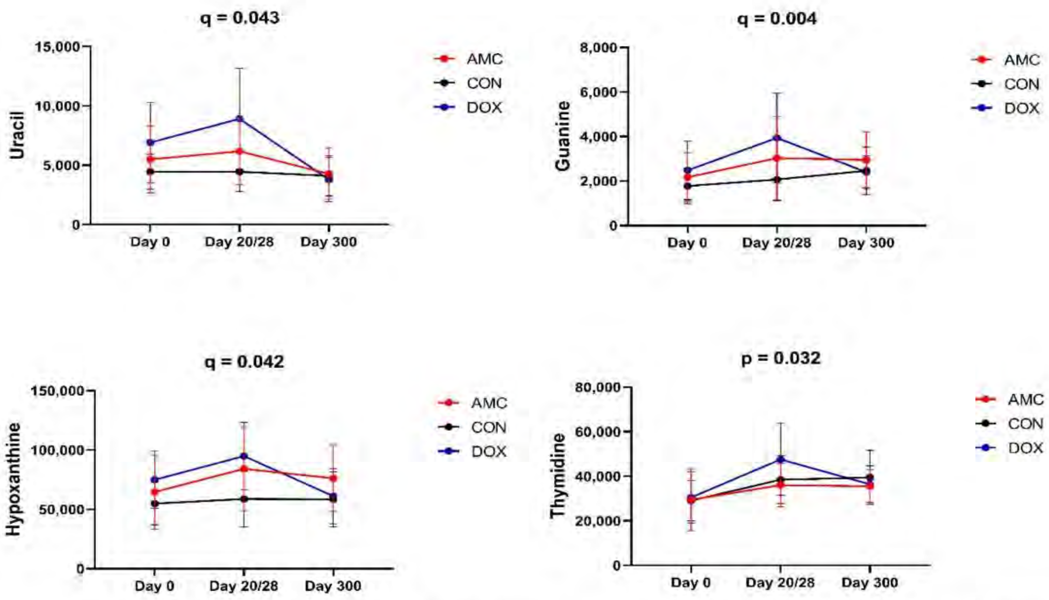

Figure 4. Changes in the abundance of serum metabolites that significantly differed between cats of the DOX and those of the CON group on day 20/28 (uracil, guanine, hypoxanthine) and from day 0 to day 28 within cats of the DOX group (thymidine). Means and standard deviations are displayed.

3.2.1. Control Group

Table 5 shows the complete list of fecal metabolites for which the abundances changed significantly within the first year of life in CON cats, presented as mean values with standard deviations. Within the CON cats, total secondary BAs ($p = 0.003$) as well as some individual secondary BAs (LA, $p = 0.038$; DCA, $p < 0.050$) increased, while some individual primary BAs (CDCA percentage, $p = 0.006$) decreased after 2 months of age (i.e., day 0) (Figure 7). The abundance of linoleic acid ($p = 0.013$), total sterols ($p = 0.039$), as well as some individual sterols (coprostanol, $p = 0.017$; campesterol, $p = 0.012$; stigmasterol, $p = 0.001$; fusosterol, $p = 0.016$; beta-sitosterol, $p = 0.004$; sitostanol, $p < 0.001$) significantly increased.

3.2.2. Amoxicillin/Clavulanic Acid Group

Fecal concentrations of total ($p < 0.001$) and individual secondary BAs (LA, $p = 0.004$; DCA, $p = 0.010$) increased, while individual primary BAs (CDCA percentage, $p = 0.006$) decreased after amoxicillin–clavulanic acid discontinuation (after the age of 3 months). In contrast to CON cats, where total secondary BAs increased and total primary BAs (CDCA percentage) decreased from 2 to 3 months of age, the age-related increase in secondary BAs and decrease in primary BAs was delayed by 1 month and started to appear after 3 months of age (Figure 8) in AMC cats. Individual fatty acids significantly decreased during treatment, as well as 1 month after the discontinuation of the antibiotic. Sterols changed over time and showed a similar pattern when compared to the pattern observed in CON cats (Table 6).

3.2.3. Doxycycline-Treated Cats

Similar to the AMC-treated cats, the fecal concentrations of total secondary bile acids ($p < 0.050$) and some individual secondary BAs (LA, $p = 0.006$; DCA, $p < 0.050$), as well as some individual primary BAs (CDCA percentage, $p = 0.004$), started to increase after the end of treatment with doxycycline (Figure 8). Individual fatty acids and sterols significantly decreased during doxycycline treatment (Table 7), which was not observed within the

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CON cats at this age. Heatmaps, which graphically represent variations in fecal metabolite concentrations within each group of cats, are presented in Figure 9.

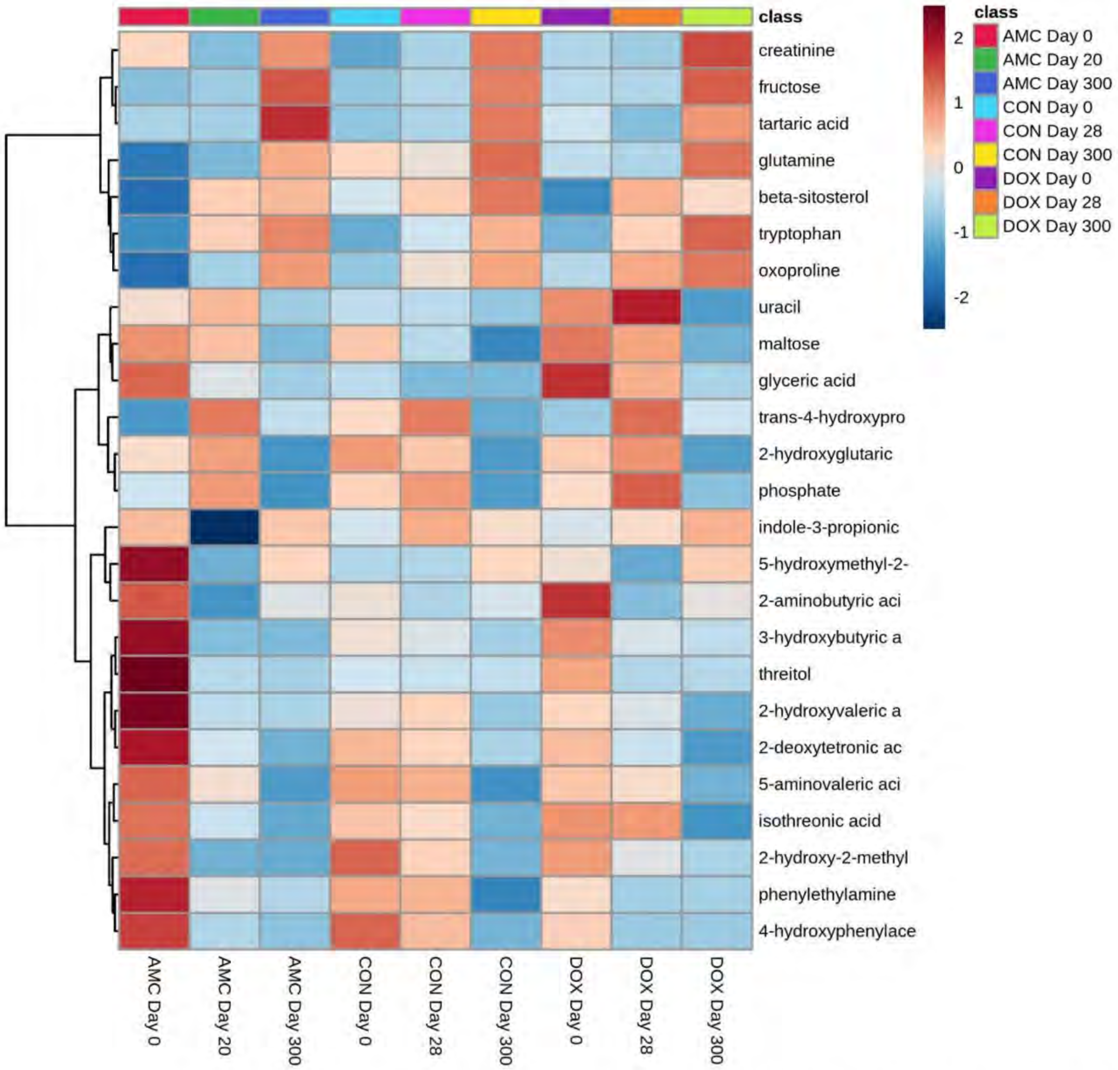

Figure 5. Heatmap clustering metabolites in serum of AMC, CON, and DOX cats over time (days 0, 20/28, 300). For simplicity, the figure only displays the average intensities of the top 25 metabolites that were different ($q < 0.05$) based on the ANOVA. The higher the signal intensity of a metabolite, the more intensely red the metabolite shows. The lower the signal intensity of a metabolite, the more intensely blue the metabolite shows in the heat map. Each row corresponds to a single metabolite. Each column represents the average intensity of a metabolite at a given sampling time within AMC, CON, and DOX groups, and samples are grouped by day within each treatment group along the x-axis.

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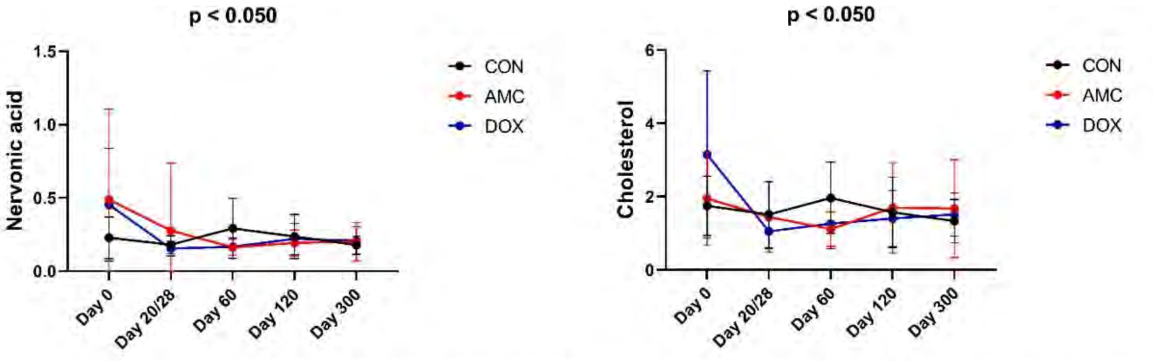

Figure 6. Fecal metabolites that significantly differed among AMC, DOX, and CON cats over the course of the study. Means and standard deviations are displayed.

Table 5. Concentrations of fecal metabolites that significantly differed over time within CON cats.

Metabolites	Classification	Day 0	Day 28	Day 60	Day 120	Day 300
Lithocholic acid	BA	244 ^{a} ± 346	313 ± 268	380 ± 236	355 ± 229	507 ^{a} ± 377
Deoxycholic acid	BA	1282 ^{a,d} ± 1576	1882 ± 1245	2082 ± 934	2281 ^{a} ± 781	3025 ^{d} ± 1705
Linoleic acid	Fatty Acid	6.54 ^{b} ± 3.87	7.92 ± 3.81	10.20 ^{b} ± 4.80	9.08 ± 4.69	7.95 ± 2.90
Coprostanol	Sterol	0.17 ^{a,b,c} ± 0.09	0.43 ± 0.75	0.91 ^{c} ± 1.21	0.90 ^{a} ± 1.31	0.68 ^{b} ± 0.93
Campesterol	Sterol	0.24 ^{b} ± 0.15	0.34 ± 0.17	0.42 ^{b} ± 0.19	0.38 ± 0.15	0.42 ± 0.17
Stigmasterol	Sterol	0.12 ^{b,c,d} ± 0.07	0.17 ± 0.08	0.20 ^{c} ± 0.06	0.20 ^{b} ± 0.09	0.21 ^{d} ± 0.05
Fucosterol	Sterol	0.03 ^{a,c} ± 0.04	0.06 ± 0.04	0.07 ^{a} ± 0.04	0.06 ± 0.04	0.07 ^{c} ± 0.04
Beta-sitosterol	Sterol	0.66 ^{c} ± 0.38	0.92 ± 0.47	1.05 ± 0.43	0.97 ± 0.40	1.17 ^{c} ± 0.43
Sitostanol	Sterol	0.37 ^{b,c,d} ± 0.27	0.63 ± 0.33	0.78 ^{b} ± 0.28	0.80 ^{c} ± 0.30	0.88 ^{d} ± 0.27
Secondary BAs	BA	1622 ^{a,c} ± 2003	2282 ± 1566	2636 ^{a} ± 1147	2761 ± 1027	3629 ^{c} ± 2086
Chenodeoxycholic acid (%)	BA	13.03 ^{b} ± 15.78	7.07 ± 5.70	5.06 ± 3.19	3.95 ± 1.78	3.52 ^{b} ± 2.15
Ursodeoxycholic acid (%)	BA	2.42 ^{a} ± 3.45	2.60 ± 2.87	4.94 ^{a} ± 4.05	3.62 ± 2.36	2.58 ± 1.64
Zoosterols	Sterol	1.42 ^{b,c,d} ± 0.86	2.13 ± 1.08	2.53 ^{c} ± 0.97	2.41 ^{b} ± 0.90	2.76 ^{d} ± 0.94
Sterols	Sterol	3.83 ^{a} ± 1.76	4.26 ± 1.57	5.63 ^{a} ± 2.20	5.12 ± 1.80	4.98 ± 1.43

Values are mean ± SD; ^{a,b,c,d} indicate significant differences over time in CON cats after Bonferroni correction (^{a} $0.025 < p < 0.050$; ^{b} $0.005 \leq p < 0.025$; ^{c} $0.005 \leq p < 0.001$; ^{d} $p \leq 0.001$).

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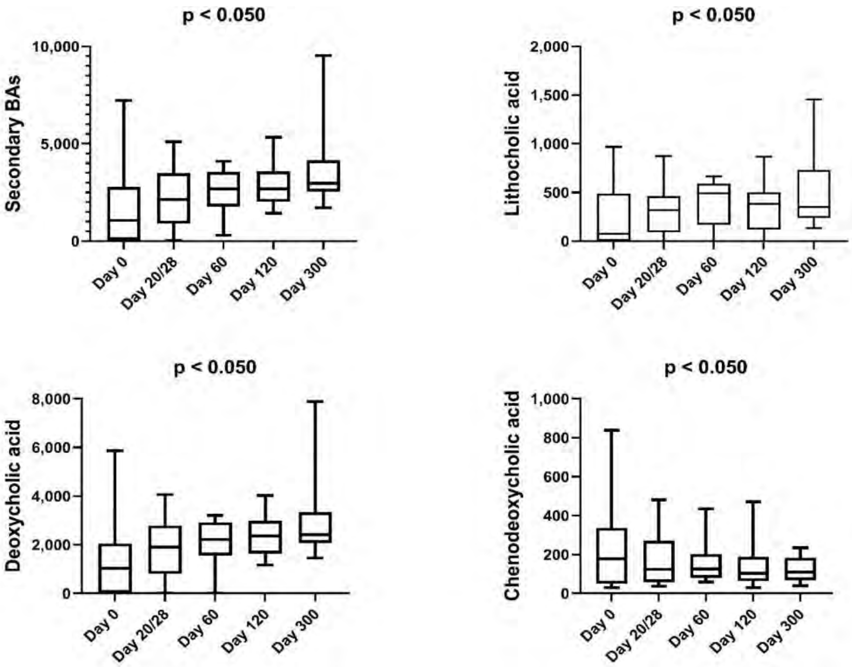

Figure 7. Fecal concentrations of BAs that significantly changed in CON cats over the course of the study. Minimums and maximums are displayed.

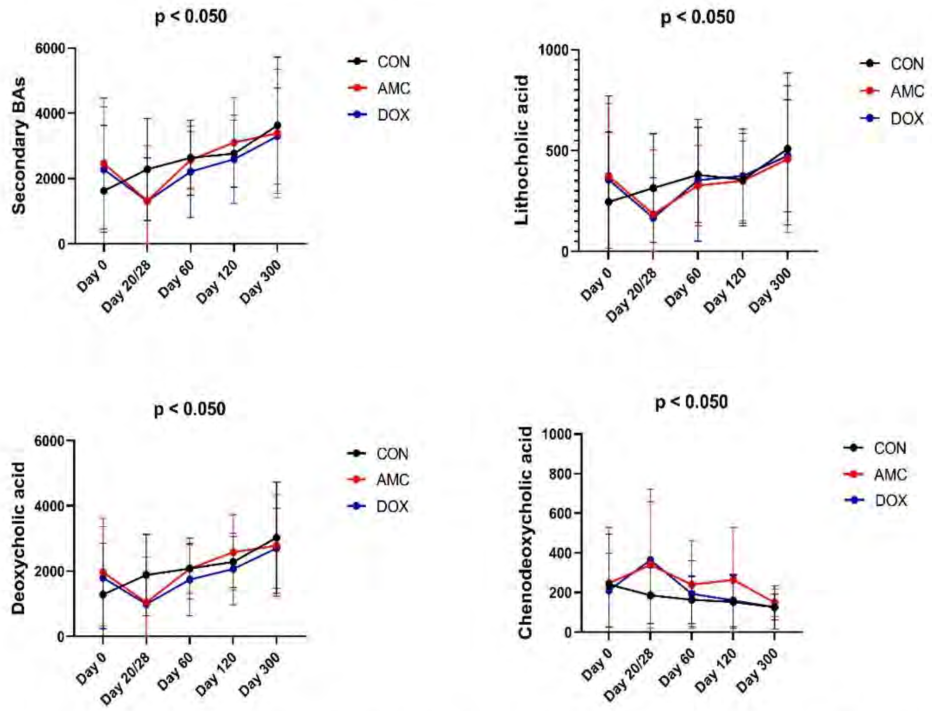

Figure 8. Fecal concentrations of BAs that significantly changed in CON cats over the course of the study. Means and standard deviations are displayed.

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Table 6. Concentrations of fecal metabolites that significantly differed over time within AMC cats.

Metabolites	Classification	Day 0	Day 20	Day 60	Day 120	Day 300
Lithocholic acid	BA	374 ± 359	184 [c] ± 319	325 ± 200	349 ± 198	458 [c] ± 364
Deoxycholic acid	BA	1968 ± 1652	1041 [b,c,d] ± 1392	2073 [b] ± 742	2584 [c] ± 1151	2783 [d] ± 1549
Palmitic acid	Fatty acid	12.61 [b] ± 5.95	9.15 ± 3.73	7.49 [b] ± 3.11	10.00 ± 4.90	9.81 ± 4.16
Stearic acid	Fatty acid	9.94 [c,d] ± 6.35	4.20 [d] ± 1.20	4.17 [c] ± 1.60	6.31 ± 4.34	6.29 ± 4.58
Nervonic acid	Fatty acid	0.49 [a] ± 0.62	0.28 ± 0.46	0.16 [a] ± 0.05	0.19 ± 0.09	0.20 ± 0.13
Campesterol	Sterol	0.19 [a,c,d] ± 0.11	0.30 ± 0.15	0.34 [a] ± 0.15	0.38 [c] ± 0.14	0.38 [d] ± 0.13
Stigmasterol	Sterol	0.11 [a,c,d] ± 0.07	0.18 ± 0.08	0.19 [a] ± 0.06	0.21 [d] ± 0.09	0.20 [c] ± 0.05
Fucosterol	Sterol	0.02 [a] ± 0.03	0.06 ± 0.06	0.10 [a] ± 0.10	0.07 ± 0.05	0.07 ± 0.03
Beta-sitosterol	Sterol	0.49 [b,c,d] ± 0.35	0.92 ± 0.53	1.00 [b] ± 0.42	1.04 [d] ± 0.45	1.03 [c] ± 0.35
Sitostanol	Sterol	0.29 [a,d] ± 0.33	0.61 [a] ± 0.34	0.77 [d] ± 0.19	0.82 [d] ± 0.25	0.81 ± 0.33
Secondary BA	BA	2463 ± 2002	1316 [c,d] ± 1688	2565 [c] ± 878	3109 [d] ± 1362	3387 [d] ± 1964
Chenodeoxycholic acid (%)	BA	9.15 ± 7.95	13.83 [b] ± 11.72	6.86 ± 5.35	6.31 ± 5.92	4.59 [b] ± 3.19
Zoosterols	Sterol	1.10 [c,d] ± 0.86	2.07 [c] ± 1.13	2.38 [d] ± 0.85	2.52 [d] ± 0.90	2.49 ± 0.81

Values are mean ± SD; [a,b,c,d] indicate significant differences over time in AMC cats after Bonferroni correction ([a] $0.025 < p < 0.050$; [b] $0.005 \leq p < 0.025$; [c] $0.005 \leq p < 0.001$; [d] $p \leq 0.001$).

Table 7. Concentrations of fecal metabolites that significantly differed over time within DOX cats.

Metabolites	Classification	Day 0	Day 28	Day 60	Day 120	Day 300
Lithocholic acid	BA	355 ± 415	166 [b] ± 198	352 ± 302	373 ± 233	474 [b] ± 278
Deoxycholic acid	BA	1798 ± 1562	985 [a,d] ± 988	1740 ± 1110	2065 [a] ± 1092	2702 [d] ± 1219
Myristic acid	Fatty acid	0.54 [a,d] ± 0.28	0.25 [d] ± 0.07	0.25 [d] ± 0.09	0.32 [a] ± 0.15	0.39 ± 0.25
Palmitic acid	Fatty acid	14.65 [b,c,d] ± 4.60	9.61 [b] ± 4.35	8.49 [d] ± 4.17	8.87 [c] ± 2.72	10.69 ± 5.05
Stearic acid	Fatty acid	11.73 [c,d] ± 6.10± 6.10	4.34 [d] ± 1.67	4.71 [d] ± 2.67	4.93 [c] ± 2.01	6.25 ± 3.80
Docosanoic acid	Fatty acid	0.29 [a,c,d] ± 0.21	0.12 [d] ± 0.03	0.13 [c] ± 0.04	0.16 [a] ± 0.08	0.16 ± 0.07
Gondoic acid	Fatty acid	0.60 [a,b] ± 0.44	0.26 [b] ± 0.08	0.27 [a] ± 0.14	0.33 ± 0.17	0.37 ± 0.25
Nervonic acid	Fatty acid	0.45 [b,c,d] ± 0.38	0.15 [d] ± 0.05	0.17 [c] ± 0.06	0.22 ± 0.11	0.21 [b] ± 0.09
Cholesterol	Sterol	3.15 [b,c,d] ± 2.28	1.05 [d] ± 0.47	1.26 [c] ± 0.69	1.40 [c] ± 0.77	1.51 [b] ± 0.58
Lathosterol	Sterol	0.02 [a,b] ± 0.00	0.02 [a] ± 0.00	0.02 [b] ± 0.00	0.02 ± 0.00	0.02 ± 0.00
Sitostanol	Sterol	0.34 [b,c] ± 0.37	0.75 ± 0.43	0.63 ± 0.24	0.83 [b] ± 0.31	0.82 [c] ± 0.50
Secondary BA	BA	2277 ± 1919	1307 [a,d] ± 1322	2212 ± 1405	2592 [a] ± 1352	3299 [d] ± 1471
Secondary BA (%)	BA	64.10 ± 40.69	49.94 [a] ± 38.40	76.56 ± 31.54	79.12 ± 27.13	84.76 [a] ± 20.83
Primary BA (%)	BA	35.90 ± 40.69	50.06 [a] ± 38.40	23.44 ± 31.54	20.88 ± 27.13	15.24 [a] ± 20.83
Chenodeoxycholic acid (%)	BA	6.84 ± 5.30	10.43 [c] ± 5.56	6.43 ± 4.08	5.80 ± 4.85	4.77 [c] ± 6.34
Deoxycholic acid (%)	BA	52.07 ± 35.48	39.43 [b] ± 33.36	60.77 ± 26.68	63.05 ± 22.05	69.04 [b] ± 19.09
Phytosterols	Sterol	4.02 [b,c] ± 2.78	1.57 [c] ± 0.74	1.78 [b] ± 0.73	2.48 ± 1.43	2.49 ± 1.41
Zoosterols	Sterol	1.37 [a] ± 0.97	2.40 ± 1.31	2.07 ± 0.74	2.56 [a] ± 0.86	2.52 [a] ± 1.34

Values are mean ± SD; [a,b,c,d] indicate significant differences over time in DOX cats after Bonferroni correction ([a] $0.025 < p < 0.050$; [b] $0.005 \leq p < 0.025$; [c] $0.005 \leq p < 0.001$; [d] $p \leq 0.001$).

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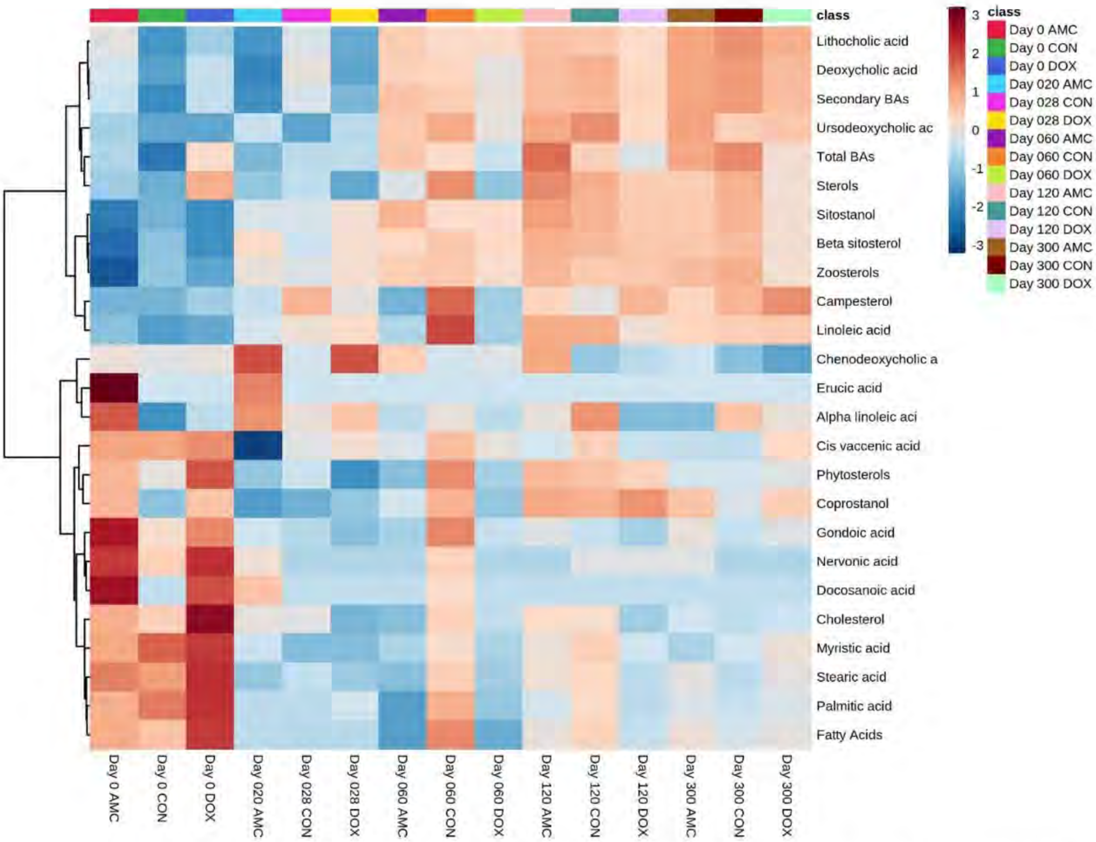

Figure 9. Heatmap clustering metabolites in feces of CON, AMC, and DOX cats over time (days 0, 20/28, 60, 120 300). For simplicity, the figure only displays the average concentrations of the top 25 metabolites that were different ($q < 0.05$) based on a liner mixed-effects analysis. Each row represents the average intensity of one metabolite for all three groups (CON, AMC, and DOX) and for all sampling times.

4. Discussion

This study showed that young cats treated with antibiotics had significant alterations of their serum and fecal metabolites compared to control cats. Amoxicillin/clavulanic acid and doxycycline caused perturbations in the pattern of concentrations of metabolites related to amino acids, carbohydrates, lipids, nucleotides, and bile acids that were not observed in control cats.

Alanine, leucine, and valine were the most prevalent amino acids in the serum of cats regardless of age or antibiotic treatment. Most amino acid concentrations did not significantly change during the first year of age, nor with antibiotic treatment (valine, tyrosine, serine, proline, phenylalanine, methionine, lysine, leucine, histidine, glutamic acid, cysteine, asparagine, and alanine). The concentration of other amino acids did not change in CON cats and, therefore, were not significantly affected by aging, but changed within the antibiotic-treated cats (threonine and isoleucine), while others were affected both by age and by antibiotic treatment (glycine, tryptophan, glutamine, and aspartic acid). Particular GI microorganisms produce amino acids through the fermentation of carbon and nitrogen sources, or consume them as nutrients, or use them for toxin synthesis [49,50]. For example, *E. coli* can produce threonine and consume serine or cysteine [51]. A study in infants showed a profound impact of beta-lactams on fecal amino acid concentrations

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with reductions in fecal serine, tyrosine, and lysine [52]. Another study in rats showed a reduction in the serum concentrations of glutamine, serine, and glutamate during a 28-day course with tetracyclines [53]. Therefore, antibiotics might interfere with microbial amino acid metabolism by altering the composition of GI microbial members that are amino acid producers or amino acid consumers. Glycine declined significantly within the first year in CON cats, and this reduction might be attributed to its high requirement for muscle growth, an effect that has been reported also in children during their first year of age [54].

The pattern in serum concentrations of metabolites classified as antioxidants (trans-4-hydroxyproline, methionine sulfoxide, and indole-3-propionic acid) also differed between control cats and cats treated with antibiotics. Trans-4-hydroxyproline is a hydrolysate derivative of hydroxyproline, and is highly abundant in collagen [55]. Trans-4-hydroxyproline increased significantly over time in both antibiotic-treated groups, while it decreased in control cats after 3 months of age. The degradation of collagen can cause increased concentrations of trans-4-hydroxyproline and takes place during oxidative stress [56]. Methionine sulfoxide concentrations decreased in control cats, and no changes were observed in antibiotic-treated cats. Methionine sulfoxide is formed by the oxidation of methionine in the presence of (ROS), and is also a potential marker of oxidative stress [57]. Trans-4-hydroxyproline and methionine sulfoxide serum concentrations are altered in horses with resistance to insulin [58] and obese mice [59]. The development of an oxidative stress state is a common effect of antibiotic treatment. Bactericidal (e.g., ampicillin, norfloxacin, gentamicin, and rifampin) antibiotic-induced alterations in mitochondrial morphology and function lead to the accumulation of reactive oxygen species (ROS) within the bacterial cell, which eventually leads to its disruption [60]. It is also important to mention that not only is it bacterial cells that undergo oxidative stress during treatment with bactericidal antibiotics, but also eukaryotic cells [61]. Indole-3-propionic acid was detected at significantly lower concentrations in cats treated with amoxicillin/clavulanic acid, compared to control cats on the last day of treatment. Indole-3-propionic acid is a tryptophan-derived microbial metabolite that exerts a protective role on the intestinal mucosal barrier through increasing mucin synthesis, and with other beneficial products produced by the intestinal goblet cells [62]. The reduced indole-3-propionic acid concentrations could also explain the increased serum concentrations of tryptophan in AMC cats at the end of treatment. Reduced indole 3-propionic acid concentrations have been found in mice treated with neomycin, which was significantly associated with weight gain. Exogenous indole-3-propionic acid administration led to a two-fold reduction in body weight gain in mice treated with neomycin compared to mice treated with neomycin alone, suggesting a potential link of antibiotic-induced alteration in the microbial metabolism of tryptophan and obesity [63].

Concentrations of purines (guanine) and pyrimidines (uracil, thymidine, and pseudouridine) significantly increased during treatment with doxycycline, and this might explain the reduced serum concentrations of aspartate, which is deaminated in the GI tract for the production of purines and pyrimidines. Nucleotide (purines and pyrimidines) biosynthesis pathways are suggested to be involved in antibiotic lethality. Bacterial nucleotide biosynthesis is stimulated during antibiotic treatment [64,65]. The synthesis of nucleotides for ATP storage requires more energy, followed by increasing cellular respiration, central carbon metabolism, and oxidative stress, and these metabolic disturbances eventually lead to bacterial cell death [39]. However, this mechanism has been described with bactericidal and not with bacteriostatic antibiotics, such as doxycycline. Therefore, these data may suggest that doxycycline may alter bacterial nucleotide metabolism, an effect that was not observed with amoxicillin treatment.

Cats treated with antibiotics also showed a different pattern in concentrations of the metabolites classified as carbohydrates or as derivatives of carbohydrate metabolism (sugar phosphates, deoxy and amino sugars, sugar alcohols, sugar acids, and inositol phosphate). Of the monosaccharides, serum glycose and fucose concentrations increased over time in AMC cats, and fructose concentrations increased in DOX cats. Monosaccharides can be utilized by the GI microbiota, and their consumption results in an increase in bacterial species that

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are beneficial for the host, such as *Bifidobacterium* spp. and *Bacteroides* spp. [66]. Therefore, the increased serum concentrations of fucose, fructose, and glycose might be attributed to an antibiotic-induced reduction of beneficial microbial species with the ability to ferment monosaccharides. Among the serum sugar alcohols, erythritol and arabitol decreased in control cats, while myoinositol concentration decreased in doxycycline-treated cats. Increased concentrations of serum sugar alcohols have been associated with disturbances in colonization resistance and susceptibility to infection with intestinal pathogens [67,68], liver disease [69], and obesity [70]. Therefore, an age-related reduction of serum sugar alcohol concentrations might be a marker of gut health. Inositol-4-monophosphate concentration decreased in AMC cats at the end of treatment, compared to the CON cats. Inositol and its phosphates play multiple beneficial roles for the host, including serving as co-factors for mRNA expression, maintaining phosphate homeostasis, and are involved in insulin signaling [71]. A possible explanation for the reduction of inositol phosphate may be reduced intestinal absorption, a process known to be orchestrated by the GI microbiome. It has been reported that a dysbiotic microbiome can reduce the absorption of inositol and its phosphates [72].

Serum arachidonic acid decreased in both antibiotic-treated groups during treatment, before reaching similar concentrations in control cats. Arachidonic acid is an omega-6 fatty acid and is the precursor of inflammatory mediators, namely the eicosanoids. Eicosanoids are a family of signaling molecules that include prostaglandins and leukotrienes [29]. In cats with inflammatory bowel disease (IBD), it has been suggested that large amounts of omega-6 fatty acids in the diet should be avoided, and instead be replaced with omega-3 fatty acids to avoid inflammation [73]. Many drugs target arachidonic acid metabolism [29]. For example, it has been shown in vitro that beta-lactams can suppress arachidonic acid release from platelets to form thromboxanes [74]. In another study, a combination of ampicillin and chloramphenicol increased eicosanoid concentrations [75]. Therefore, both antibiotics might have an impact on eicosanoid formation. Alternatively, some bacterial members are reported to be able to metabolize arachidonic acid. Serum arachidonic acid reduction during antibiotic treatment in our study might reflect an increase in bacteria that are able to metabolize it [76].

The concentration of both total and some individual secondary BAs significantly increased after the age of 2 months in the feces of CON cats. In one study, 9-week-old puppies had lower concentrations of fecal secondary BAs compared to 1-year-old dogs [77]. Therefore, similarly to young dogs, microbial converters of primary to secondary BAs in 2-month-old cats have not yet reached an adult plateau. In contrast, in both groups treated with antibiotics, the increase in secondary BAs appeared after the age of 3 months, i.e., after antibiotic discontinuation. This suggests that antibiotics caused a transient suppression of microbial bile acid converters. Secondary BAs are commonly decreased after antibiotic treatment in rodents [78], humans [79], adult dogs [36], and cats [31,32]. Mounting evidence suggests that secondary BAs can suppress the proliferation of GI pathogens and maintain colonization resistance [80]. Secondary BA have direct antimicrobial effects and can indirectly stimulate the production of antimicrobial peptides after interaction with the farnesoid X receptor (FXR) [80]. During immune system maturation, the microbiome also matures and informs the immune system about which bacteria can be considered to be harmful or pathogenic [81–83]. A reduction in secondary BAs at this critical developmental window of cats could therefore allow the proliferation of GI pathogens and engender a lack of a proper immune response due to the immune system immaturity at this age.

Fecal concentrations of cholesterol did not change within AMC or CON cats, but in DOX cats, cholesterol concentrations decreased significantly and remained decreased for 3 months after doxycycline withdrawal. Several possible mechanisms could lead to reduced concentrations of cholesterol in the feces of DOX cats. Cholesterol can be metabolized by bacteria within the large intestine, mainly producing the poorly absorbable compound coprostanol [84]. However, fecal coprostanol concentrations remained unchanged in DOX cats; moreover, in humans, the bacterial degradation of cholesterol to cholestanol starts after the age of 6 months [85,86]. Therefore, a doxycycline-induced decrease in the amount

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of coprostanol-producing bacteria could not explain the reduced fecal cholesterol concentrations identified in this study. The depletion of the GI microbiota by antibiotics is documented to increase the intestinal absorption of cholesterol, which could potentially explain the reduced concentrations of cholesterol in feces in DOX cats; yet this was not observed in AMC cats [87]. Lathosterol is a precursor of the endogenous cholesterol biosynthesis pathway, and this was also only reduced in DOX cats, suggesting a suppression of cholesterol biosynthesis and a secondary reduction of fecal cholesterol concentrations [88]. In humans, it has been shown that particular antibiotics, including metronidazole, can have lipid-lowering effects [89].

Interestingly, serum concentrations of some metabolites (15/185) were differentially abundant among the groups before exposure to antibiotics. The exact reason for these differences among groups is unknown. It could be considered that a URTI could have affected the GI microbiota in these cats. However, an acute URTI is a condition that is typically localized in the upper respiratory tract, and there is no evidence that it alters the composition of the GI microbiome or metabolite concentrations in cats. In addition, cats in the control group also had mild signs of URTI that did not require antibiotic treatment. Therefore, baseline differences in serum metabolic profiles are most likely attributable to individualized differences driven by the immaturity of the microbiome at this age, rather than URTI. In humans, individual differences in microbial and metabolic profiles have been identified before the microbiome reaches maturity, i.e., around 1 to 4 years of age [90]. Another potential limitation of the study that could at least partially explain the interindividual differences observed among the study groups is the small numbers of cats enrolled. However, previous studies applying similar methodologies have used similar numbers of cats [20,31,32]. Finally, the dose used for amoxicillin/clavulanic acid was higher (20 mg/kg) than the one recommended for upper respiratory tract infection in cats (11–13 mg/kg), but still within the normal range for amoxicillin/clavulanic acid. It is currently unknown whether a higher dose of antibiotics could be associated with a more profound impact on the metabolomic profiles of cats.

In summary, both antibiotics temporarily affected concentrations of serum and fecal metabolites in young cats, but these changes were no longer present at 10 months after antibiotic therapy. The long-term clinical consequences of these disturbances remain unknown. Further studies are required to investigate the impact of these changes on potential disease susceptibility and proneness to pathogen colonization in cats.

5. Conclusions

Both amoxicillin and doxycycline affected the concentrations of several fecal and serum metabolites during treatment. However, these changes were transient and did not persist at 10 months after the withdrawal of the antibiotics. Cats treated with amoxicillin/clavulanic acid for 20 days showed reduced serum concentrations of inositol-4-monophosphate, and increased serum concentrations of indole-3-propionic acid on the last day of treatment compared to control cats. Cats treated with doxycycline for 28 days showed increased serum concentrations of uracil, hypoxanthine, and guanine on the last day of treatment compared to control cats. Fecal nervonic acid was detected at significantly lower concentrations in both antibiotic-treated groups on the last day of treatment, and this effect lasted for 3 months after antibiotic withdrawal. Fecal cholesterol was also persistently reduced in doxycycline-treated cats compared to control cats for 3 months after doxycycline discontinuation. When the pattern in the concentrations of metabolites was compared within each group, amino acids, antioxidants, metabolites related to carbohydrate metabolism, bile acids, sterols, and fatty acids were differentially expressed over time in each group. Similar to the developing microbiome, the concentrations of serum and fecal metabolites are characterized by high interindividual variability at 2 months of age in cats, and antibiotics appeared to delay the maturation of the serum and fecal metabolome. Further studies are required to investigate a potential association between the changes in these metabolites and potential disease susceptibility later in life.

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Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/ani12030330/s1, Table S1: List of raw metabolites identified in serum samples by untargeted metabolomics. Table S2: List of metabolites identified in serum samples by untargeted metabolomics. Mean and standard deviation by group and time point. Table S3: List of raw metabolites identified in fecal samples by targeted metabolomics. Table S4: List of metabolites identified in fecal samples by targeted metabolomics. Mean and standard deviation by group and time point.

Author Contributions: Conceptualization, E.M.S., J.S.S., R.P. and P.G.X.; methodology, E.M.S., J.S.S., R.P., C.-H.S. and P.G.X.; software, E.M.S., J.S.S., R.P., C.-H.S., J.L. and J.M.S.; validation, E.M.S., J.S.S., R.P., G.T.F., C.-H.S. and P.G.X.; formal analysis, E.M.S., J.S.S., R.P., G.T.F., C.-H.S. and P.G.X.; investigation, J.S.S., R.P., C.-H.S. and P.G.X.; resources, J.S.S., R.P., G.T.F., C.-H.S., J.L., J.M.S. and P.G.X.; data curation, J.S.S., R.P., C.-H.S., J.M.S. and P.G.X.; writing—original draft preparation, E.M.S.; writing—review and editing, J.S.S., R.P., G.T.F., C.-H.S., J.L., J.M.S. and P.G.X.; visualization, E.M.S., J.S.S., R.P. and C.-H.S.; supervision, J.S.S., P.G.X. and R.P.; project administration, J.S.S. and P.G.X.; funding acquisition, E.M.S., J.S.S., J.M.S. and P.G.X. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Winn Feline Foundation, Miller Trust Award, grant number MT18-003 and the Operational Program "Human Resources Development, Education and Life Lifelong Learning", MIS 5048925.

Institutional Review Board Statement: This study was conducted at the Clinic of Medicine of the Faculty of Veterinary Science, University of Thessaly in Greece, and the protocol was reviewed and approved by the Animal Ethics Committee of the University of Thessaly (AUP number: 54/13.2.2018).

Data Availability Statement: Metabolomics raw data are available in supplementary files Tables S1 and S3.

Acknowledgments: The authors would like to thank Gerolymatos International S.A. for providing products for antiparasitic treatment (Broadline) and vaccines (Purevax RCPh, Purevax Rabies) for the cats in this study.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Supplementary-Table S1: List of raw metabolites identified in serum samples by untargeted metabolomics.

						Day 0 - AMC														
						579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855
						579901	579898	579895	579892	579889	579886	579883	579880	579877	579874	579871	579868	579904	579865	579862
						FMO13	FMO18	FMO20	FMO22	FMO24	FMO29	FMO32	FMO34	FMO56	FMO58	FMO67	FMO68	FMO7	FMO70	FMO74
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	2328	1530	1579	1676	1765	2185	2708	2841	2703	2670	1977	3058	1052	3326	1497
xylose	543267	103	169	135191	C00181	5985	11184	9385	16232	10810	27550	13034	8569	18935	14902	18088	21005	12357	16665	17948
xylitol	567437	217	5857	6912	C00379	16351	3000	6121	5094	3560	5317	4345	2471	3680	2497	3186	3623	3633	3951	4862
xanthine	701688	353	1669	1188	C00385	643	470	1372	297	1381	242	726	752	454	360	622	584	635	452	515
valine	313502	144	3	6287	C00183	970351	661520	712053	369208	1149180	1858254	1237006	1586526	781766	882622	849022	642132	837115	1132562	816667
uric acid	730691	441	23	1175	C00366	3994	6164	22019	3947	12166	4958	15438	2431	3846	2887	4855	5808	5784	5962	3280
urea	329351	189	145496	1176	C00086	347935	2344324	2332868	3529690	2621367	3047331	4437035	2788711	3663545	3336245	235552	2193249	2685313	3901677	2590680
uracil	385735	241	1664	1174	C00106	3760	3122	11556	4455	9618	2840	2703	6475	3903	7842	3965	7627	8117	3234	3417
tyrosine	671252	218	16	6057	C00082	125129	368716	288728	371461	197209	565540	380499	449466	319757	253313	348312	416012	368896	495946	278472
tryptophan	780482	202	14	6305	C00078	62282	78947	94188	226403	172279	354663	315157	284625	278232	247788	244258	398121	321171	489399	188310
trans-4-hydroxyproline	484934	140	97	5810	C01157	32024	99368	172433	237994	61824	79798	428683	191740	602291	605479	191868	158804	515441	160609	287211
tocopherol gamma-	1026121	223	4545	92729	C02483	571	847	1047	1441	540	901	1258	1950	811	1196	974	1023	576	1569	2005
tocopherol alpha-	1067809	237	100	14985	C02477	12864	20736	24550	48648	12614	63501	15993	39347	58637	14071	18943	20542	1958	83086	49743
thymine	420133	255	1692	1135	C00178	477	577	1057	661	1276	493	1014	858	206	484	553	545	950	844	390
thymidine	349402	170	87703	5789	C00214	13380	14658	11027	51943	32138	14090	16580	29562	29982	31216	34411	48806	23111	44299	47017
threonine	409568	218	26	6288	C00188	206115	110000	76163	68004	104831	330323	238221	316177	142962	356809	391654	262291	151223	121312	132584
threonic acid	497572	292	172	5460407	C01620	10995	17524	18485	20625	32512	17792	13016	8317	30285	14492	49016	40499	3828	34264	38217
threitol	467595	217	770	169019	C16884	1279	7788	5590	3878	1698	3942	2004	1584	2457	1602	23236	28466	2264	2658	3353
taurine	556690	326	411	1123	C00245	2549	1964	13884	230	49654	1887	15284	69559	39778	22412	114596	49592	7025	2085	7603
tartaric acid	534291	292	33985	444305	C00898	155	1351	874	1018	295	540	313	329	250	420	235	256	301	216	274
tagatose	631835	307	33981	439312	C00795	3134	1379	660	9744	1124	3324	1456	712	1147	596	1159	3129	1387	1450	1349
sucrose	915139	271	173	5988	C00089	694	10919	6338	1912	8271	280	2407	281	4565	1276	9091	6835	1122	1329	2974
succinic acid	370608	247	161	1110	C00042	5643	7335	27605	6555	5507	6761	8623	5998	22548	7102	8857	8314	5374	6545	9077
sophorose	962064	307	132242	441432	C08250	352	1244	663	377	368	269	392	305	253	89	2053	1569	392	298	315
shikimic acid	611100	204	286	8742	C00493	1821	7268	2059	3369	3018	3155	3543	3405	4799	8038	3811	5287	7878	18460	11403
serotonin	863824	174	364413	5202	C00780	281960	119461	91585	229167	239564	172542	28851	76519	158727	31529	71495	129911	72763	103214	90233
serine	395020	204	25	5951	C00065	292202	375962	593542	827531	466357	1048101	1427218	1419682	901276	1087593	755851	826708	799169	953728	752864
salicylic acid	480699	267	3063	338	C00805	2437	2704	1914	2807	1871	5102	5279	4088	3798	3745	11083	4862	1942	4366	4881
saccharic acid	699211	333	11214	33037	C00818	2784	2635	3409	3358	1160	1060	1926	645	1086	779	723	1477	1433	988	744
ribose	553071	217	384948	10975657		5068	11089	19243	33147	8851	5486	7981	10344	16384	31204	11238	30503	29942	24911	18376
ribonic acid	599680	292	1683	5460677	C01685	4425	5233	2352	7321	1433	7777	11169	6847	9158	5050	6695	7474	6654	9899	10442
ribitol	575497	217	7362	827	C00474	2665	1458	2736	1734	1929	3308	2989	1143	2438	1256	2385	2764	2237	1647	1869
raffinose	1120886	361	3190	439242	C00492	221	2010	1415	676	2493	307	3992	305	3413	843	1164	580	2201	1303	660
pyrophosphate	547021	451	88522	1023	C00013	2094	1143	2135	5216	2325	1769	5802	3243	3881	3914	3403	7749	1218	2422	252
putrescine	588119	174	21703	1045	C00138	7394	5707	8618	17845	4090	7536	12210	5752	11747	4238	10644	11345	4160	8947	6708
pseudo uridine	813899	217	1688	15047	C02067	13084	17235	10284	20556	25140	13120	16480	12550	16520	11602	16215	22963	15150	16003	17168
proline	364716	142	8	145742	C00148	81822	447361	694960	273116	232806	461663	948544	724591	667203	867370	616782	261475	854812	518260	894635
piperidone	275603	156	34023	12665		4221	3941	10186	2982	3346	4317	9472	1763	11075	83754	1988	1622	54020	4196	21022
pipecolinic acid	404121	156	2448	6931662		879	5074	2767	2954	4096	4940	18108	3724	1700	4376	2436	1227	4652	3058	5731
pimelic acid	523205	155	33429	385	C02656	904	990	1176	1627	1824	1084	1126	1809	1758	1784	3166	3281	1433	1315	2620
phthalic acid	567345	147	46142	1017	C01606	19076	9037	11559	12625	9592	8228	8856	9209	8632	8908	9256	14514	7110	22143	11668
phosphoethanolamine	603912	299	1723	1015	C00346	6682	1253	1569	2360	7142	11527	7312	3297	13182	4451	3812	9897	1368	3528	1405
phosphate	345365	314	4	1004	C00009	337114	334617	441384	551145	478469	726489	461436	525715	998625	781088	593384	669901	496185	768233	622497
phenylethylamine	510327	174	2005	1001	C05332	114937	22727	14343	101206	54414	47411	519877	42325	17916	26077	99878	150046	53043	11090	15799
phenylalanine	537804	192	33	6140	C00079	98739	149633	147217	213164	133238	239662	364823	207510	204230	234893	211290	236318	187844	279499	160856
pentose	540818	103	360841	229		1975	2525	1812	3082	3403	4698	11785	3174	4129	2180	3687	5725	2582	2161	2337
pelargonic acid	399229	215	50	8158	C01601	54560	15172	12409	30029	15067	19681	31990	25231	20822	20743	15383	39091	22723	26896	21925
palmitoleic acid	706508	311	96	445638	C08362	2634	4982	1493	3886	2027	2327	4420	1865	3165	2351	955	1107	2996	6896	2874
palmitic acid	713809	313	11	985	C00249	211042	192906	73488	167028	175036	133829	158997	148596	141945	130561	92420	118344	143176	199980	210042
oxoproline	485935	156	10	7405	C01879	529911	635480	594792	654927	517421	497539	683947	914601	844127	629016	905495	1081540	792405	639950	904471
oxalic acid	260513	190	4923	971	C00209	48174	24485	9555	7429	3315	15314	9845	7813	6352	5176	5795	11820	8260	8202	3238
ornithine 3TMS	527113	142	1821	6262	C00077	101260	138135	126434	230981	138818	551813	737023	221314	257408	238388	281528	242824	181006	288390	145176
oleic acid	779120	339	43	445639	C00712	164082	101086	16443	64932	75855	1293	2491	56089	2020	1426	1291	1061	1777	91269	62335
oleamide	849710	144	20961	5283387	C19670	9094	18562	9372	14250	29555	4271	13826	23478	15011	15237	31274	16154	29398	16125	25640
nonadecanoic acid	822782	117	46258	12591	C16535	7786	6037	2051	3836	4149	86	6169	3820	4389	4293	2654	4195	2878	3807	4767
nicotinic acid	353428	180	327312	938	C00253	282030	147768	153590	203721	412644	4607	10718	4303	3534	1807	29300	4640	237808	3313	1303
N-acetylglycine	356109	174	97747	10972		3667	1374	431	1281	2651	2881	1094	1156	1182	825	832	753	1496	1831	2751
myristic acid	634414	285	127	11005	C06424	8456	6341	2867	5611	5817	3416	5414	4029	3465	4023	3083	7325	5155	12542	5574
myo-inositol	730022	305	1741	892	C00137	514149	190195	129101	436213	654431	577740	260307	293487	229117	434582	489088	506435	163820	284031	364247
mevalonic acid	498785	247	127978	439230		5599	3352	872	887	3779	1257	8010	873	1753	2828	3095	3522	1372	947	2930
methionine sulfoxide	637588	128	1678	158980	C02989	19315	124160	132573	260104	28924	60388	205863	75512	133540	66076	165678	125424	65384	106461	110272
methionine	483560	176	45	6137	C00073	34390	470342	804318	397898	116675	249824	209352	98040	206202	230287	175207	207421	213175	79531	84059
methanolphosphate	289520	241	5393	13130		26553	26310	23089	29877	14933	31303	32952	30808	50849	28425	14252	33257	15525	38399	21378
mannose	645856	205	70	18950	C00159	78743	189368	160203	280694	111704	247187	184511	188541	194798	178148	259618	321594	183254	276257	275475
maltose	946601	204	1979	439186	C00208	2252	14782	32722	7706	22128	20592	14257	5938	24863	19092	209571	223595	9531	11907	5229
malonic acid	305372	233	16918	867	C00383	581	1169	248	626	670	625	643	97	436	320	565	140	593	352	610
malic acid	463180	233	1391	525	C00711	2714	3043	16981	3889	3713	3712	3505	4591	7235	8326	5318	4550	5971	3987	4271
maleimide	245118	154	1743	10935	C07272	7062	5306	8949	9401	11286	26950	8096	9871	12977	14866	10232	8793	19484	24220	31359
lyxitol	573587	217	233	439255	C00532	5964	7860	8407	10543	9791	8485	23939	8458	15549	15580	7567	10326	18308	11472	11003
lysine	663483	317	12	5962	C00047	23278	105538	76261	112261	46340	48606	43738	109995	52320	47070	37334	62577	27884	49236	27620
linoleic acid	777285	337	471765	5280450	C01595	42376	31635	8026	26712	20612	19584	28188	14440	28855	20800	11252	14094	19570	37845	28670
levoglucosan	569637	204	3169	2724705		790	1173	919	1560	581	957	939	1155	975	779	1910	950	1050	1214	5523
leucine	346101	158	9	6106	C00123	1259799	1407128	1237595	683597	1541638	1790318	1685836	1292351	1236652	833240	955570	784729	1364197	1333187	1198076
lauric acid	547906	117	49	3893	C02679	33250	11945	7045	15699	11958	11457	15531	15720	13404	12880	10816	229041	15707	238701	17230
lanosterol	1129573	393	133475	246983	C01724	226	978	394	187	397	312	1006	238	339	587	392	503	351	571	618
lactose	936998	204	217651	6134	C01970	1018	3453	3202	1713	1653	2282	1376	1469	2332	1893	8460	6552	2086	2054	1568
lactic acid	217657	191	80	612	C01432	1229753	2699684	4176338	3454270	3609567	1041538	902750	2106486	2666358	3247393	3580600	3212671	3792387	1810189	2939770
lactamide	265698	232	415	94220		1263	2755	3748	2332	3400	2350	1133	2454	2216	3496	3909	3536	3583	1631	2584
kynurenine	769709	218	210712	25245862	C01718	6012	8584	4919	10795	12710	19576	10887	10421	3688	8772	14097	24760	4944	5731	7859
isothreonic acid	489385	292	1679	151152	C00639	9169	12532	9067	13529	10033	14839	12094	7548	12620	14732	15836	31844	13801	10114	15262
isomaltose	983199	160	127715	439193	C00252	250	3271	924	690	302	485	200	472	789	654	991	730	457	764	319
isoleucine	359251	158	15	6306	C00407	805218	417576	366459	237060	741473	825734	664516	633440	426679	495016	307197	296219	448707	611601	434629
isocitric acid	616323	245	12267	5318532	C00451	2353	4190	5965	7165	3914	2892	6878	2841	8942	5573	3662	7264	7397	6450	7365
inositol-4-monophosphate	845976	315	4759	440043	C03546	3117	1384	1342	1617	1299	2450	3025	1963	2476	3135	1133	3635	831	2564	1482
inosine	897434	230	84524	6021	C00294	27944	35408	26157	52509	37318	29235	22268	26979	50663	33762	32165	52637	21126	24934	31865
indoxyl sulfate	577333	277	31543	10258		3253	2228	1233	1792	3310	4256	988	4806	6585	3379	847	1711	1063	1615	2244
indole-3-propionic acid	732249	202	112556	3744		4764	4833	9827	2285	3205	3526	39949	3089	9176	31353	7259	46955	820	19037	17564
indole-3-lactate	764079	202	390397	92904		1072	1740	6044	7892	1840	5667	33093	2913	4966	6081	4386	8883	12773	7665	5368
indole-3-acetate	684929	202	69	802	C00954	6000	7904	7251	17679	4533	4676	74549	3171	12278	11394	4826	11494	14088	17717	32111
hypoxanthine	619128	265	1663	790	C00262	34464	51740	80259	76737	81420	50411	30630	107580	74200	108967	88670	45010	97606	2085	40716
hydroxycarbamate	325318	278	130396	16639161		5679	3472	2583	6239	7034	5044	11740	5441	10585	4240	3857	8471	3766	6421	2469
homoserine	443878	218	2849	12647	C00263	463	762	1388	968	688	355	1755	1342	1208	1753	2333	1402	1327	973	1916

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homocystine	874865	128	2786	10010	C01817	344	827	1487	997	882	668	1612	1012	1053	1278	789	1340	942	896	851
histidine	663790	154	150	6274	C00135	18480	110392	80824	83546	66376	8833	56833	88462	50313	62415	52506	50605	107996	56776	42490
heptadecanoic acid	751309	117	727	10465		28399	21920	6657	18767	18940	11149	17135	17475	15222	14919	13980	14550	14489	16876	19580
guanosine	954962	324	1966	6802	C00387	864	2711	2304	4804	3754	1140	2264	2841	2962	3564	2328	4891	2484	2681	2719
guanine	744307	352	2519	764	C00242	471	1395	2358	1995	2343	1428	1329	4119	1709	4073	1969	1869	4089	1324	2056
glycyl proline	691357	174	18496	3013625		3154	1053	1465	3084	1254	1184	2372	1047	1891	1991	889	1364	892	974	1329
glycolic acid	227636	177	1971	757	C00160	9755	10320	8317	12521	11074	21036	19003	12017	16666	14663	25983	32814	19074	16784	18650
glycine	368707	248	6	750	C00037	194859	460908	612998	603829	349850	859810	1E+06	1E+06	807454	1E+06	916515	587027	879754	523058	1E+06
glycerol-alpha-phosphate	590747	357	1687	754	C03189	15505	24221	19355	38344	18366	49750	33673	29124	36726	33396	22762	26907	26674	36580	30660
glycerol-3-galactoside	800205	204	100875	16048618	C05401	2618	4904	2631	2324	1946	5884	3757	1562	6518	3683	11773	11233	7626	31890	8012
glycerol	344466	205	30	753	C00116	503656	531285	418271	537285	602798	466561	445664	269413	485054	458478	238207	367328	410481	563681	300901
glyceric acid	377308	189	394878	752	C00258	25836	29510	29593	25518	23702	19487	29674	13209	17927	24427	52783	53199	26780	21044	17002
glutaric acid	421260	261	1727	743	C00489	963	951	1095	640	683	1009	858	598	832	3615	987	998	1969	1054	1992
glutamine	600315	156	18	5961	C00064	232153	933394	781348	1E+06	245808	139143	400579	614974	418775	492737	340860	535673	821200	666996	646796
glutamic acid	529100	246	28	33032	C00025	35379	56866	105657	50666	57015	39611	49566	70161	40323	58914	82709	47085	67097	42521	64711
glucuronic acid	665901	333	344793	94715	C00191	12734	11842	12667	10414	8869	10875	8229	5978	8455	6790	5721	8554	9021	7875	8847
glucose-6-phosphate	808788	387	360626	5958	C00092	1961	2224	871	1217	1909	1025	2039	585	1097	1117	1280	1526	797	2473	1823
glucose-1-phosphate	594647	217	3167	65533	C00103	2062	3555	3316	3659	4328	4513	806	2570	4555	9401	2581	3685	4403	2988	3643
glucose	659798	319	22	64689	C00221	2E+06	3E+06	3E+06	4E+06	2E+06	4E+06	3E+06	2E+06	3E+06	3E+06	3E+06	4E+06	3E+06	4E+06	3E+06
gluconic acid lactone	645815	220	3502	7027	C00198	2703	10353	21156	8223	14534	20313	6585	5388	20853	25677	33215	25591	9770	11124	21603
gluconic acid	693148	333	7501	6857417	C00800	18818	59130	186082	56395	106987	165634	46234	24115	139840	179253	218088	156554	56247	60976	138659
galactinol	1017580	204	1975	11727586	C01235	816	1633	1426	1557	2087	846	4577	1186	3845	1479	2047	1252	1675	1608	1047
fumaric acid	390775	245	1718	444972	C00122	924	1354	1196	1696	1823	2550	4322	2459	4291	5462	1444	3323	1544	2544	4503
fucose	578299	160	3009	439650	C02095	4477	6177	8016	10025	6700	8919	7394	6511	6262	5572	6789	8662	6504	8018	7023
fructose	639442	307	21	439709	C02336	138192	240156	110012	360548	179232	322173	355272	136681	280220	106747	183598	403521	261254	318793	283928
ethanolamine	342561	174	342038	700	C00189	29715	25977	44642	24605	38412	32327	38775	26112	41526	39846	24754	53089	13783	51594	19629
erythritol	471922	217	92	222285	C00503	6832	12082	12032	14955	10022	9688	15662	6318	13420	8822	16196	21224	10410	10513	11821
epsilon-caprolactam	353069	170	3101	7768	C06593	2557	10060	5911	5697	10872	2958	4496	8913	4023	7804	18452	2768	9641	2769	10479
docosahexaenoic acid	902819	91	87709	445580	C06429	1972	2798	977	3489	3056	2105	2495	2039	2863	2438	2015	1432	2012	1973	2969
dihydrocholesterol	1082070	215	42937	66066	C12978	1053	1757	3552	3221	1087	3470	1138	2834	5357	2556	1044	2139	3480	5829	3109
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1042	867	1765	1108	1111	752	1427	1540	2154	1257	1121	1082	1178	807	892
cytosine	486724	254	2186	597	C00380	600	897	1522	1918	1200	1691	2632	1378	1158	2094	3398	2755	1418	1395	2144
cystine	804619	218	94	595	C01420	3201	10635	5167	22906	19190	1571	15042	5024	21082	7173	7299	12174	5802	17079	10911
cysteine	500158	220	65	5862	C00097	850	8229	11160	2603	12305	8204	3921	5870	6089	7680	5570	5269	20313	2305	7085
creatinine	502599	115	31	588	C00791	339216	220620	47762	127737	375390	296507	127243	95732	98494	147170	124253	125729	65067	163029	183797
conduritol-beta-epoxide	675635	318	2670	9989541		532	1312	2345	2529	1410	2919	6008	1139	1415	1586	1508	1932	2172	1371	1970
citrulline	621404	157	1712	9750	C00327	16142	30834	21921	44513	23440	30056	40588	50735	45894	35280	26669	35334	34586	33845	31923
citric acid	617342	273	288	311	C00158	67962	107719	306496	401031	162292	101712	340345	131869	472999	265351	165607	298651	372456	326384	334304
cis-gondoic acid	847372	367	87783	5282768	C16526	852	852	235	629	1249	846	859	769	931	1031	467	621	443	1178	387
cholic acid	1109517	253	110403	221493	C05463	639	552	476	509	678	2580	595	783	593	974	374	424	710	606	500
cholesterol	1078536	129	19	5997	C00187	454678	533915	380483	910706	284024	974234	522650	596767	1E+06	625757	339302	632566	547882	2E+06	845937
cellobiose	942758	361	120969	6255	C01971	176	1549	760	323	733	838	934	331	1313	707	20819	18649	613	1263	364
capric acid	451790	229	726	2969	C01571	5526	3689	2600	5189	3381	2906	4515	5379	4111	4503	4051	12673	4708	8116	5432
butyrolactam	277199	142	2047	12025		72670	52076	20814	36077	61280	40456	39939	32156	28795	35521	30823	33665	30516	35711	28743
butane-2,3-diol	205778	117	485	262	C03046	93484	166426	406990	236203	184174	271470	293507	111994	188403	135703	290932	224490	213224	113843	150645
beta-sitosterol	1128225	129	3174	222284	C01753	1885	2532	3360	1225	835	2002	2945	2401	6012	4287	1771	1777	2939	1103	1800
beta-glycerolphosphate	574470	243	22021	2526	C02979	2248	1522	1467	1541	931	1882	1779	1535	2549	1154	1094	1035	1728	1734	2126
beta-alanine	435564	248	148	239	C00099	3979	2111	2403	1884	3026	3459	8598	1889	3692	2334	1451	4857	1855	1988	1906
benzoic acid	339067	179	36	243	C00180	128445	114213	76918	134878	138233	209563	243137	165907	187660	154936	193055	154018	128036	171432	192852
azelaic acid	610551	317	329430	19347555	C08261	1044	1110	839	1439	1188	981	1693	1278	871	2012	2013	1629	908	2153	4272
aspartic acid	480387	232	79	5960	C00049	10955	14713	25392	22241	22407	20356	17181	36383	18353	28087	26597	27105	20774	20416	21541
asparagine	553743	231	369588	6267	C00152	16672	22652	39724	22748	18865	17311	28980	37196	35767	28146	23511	28910	42385	31574	25926
arachidonic acid	837115	91	64589	444899	C00219	15135	19537	7703	27118	14935	31124	11386	25318	23933	18238	17418	25311	8325	33875	25217
arachidic acid	856421	117	291	10467	C06425	14106	6788	3426	5882	6716	7274	7987	6816	8474	5542	6284	6032	5791	8268	25680
arabitol	572730	103	372446	94154	C01904	3783	7133	5991	8472	6108	7563	22759	6897	12437	13813	8003	7210	14307	9207	6747
aminomalonate	455754	218	413	100714	C00872	13871	11026	16626	36375	17898	44200	75461	40985	45093	33926	19881	34673	21659	29848	14242
alpha-ketoglutarate	507392	198	294	51	C00026	327	580	1076	427	2166	808	530	403	412	802	277	468	3772	375	332
alpha-aminoadipic acid	573295	260	125502	92136	C00956	1894	2679	3229	3662	2263	2911	2551	3253	2477	2495	3549	3100	2090	2280	2660
allantoic acid	726050	259	117021	203	C00499	40890	43406	24535	44862	49157	57097	33771	25965	73767	24083	52337	49578	30838	31433	37883
alanine	243971	116	34178	5950	C00041	386939	977720	3E+06	1E+06	719406	1E+06	1E+06	3E+06	2E+06	2E+06	3E+06	2E+06	2E+06	937838	2E+06
adipic acid	474435	111	125	196	C06104	4453	3287	1731	2528	4041	2560	3985	3081	2993	2450	10998	3280	4078	3044	24457
aconitic acid	586815	229	29	643757	C00417	1221	1845	1428	1875	862	2430	2504	4758	3412	1991	4851	5455	813	2731	3054
5-methoxytryptamine	864466	174	284	1833	C05659	227114	96969	77096	185452	197255	141596	22831	94645	129623	26060	56928	103833	59019	82881	75039
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	563	5466	1841	11503	867	3478	2237	978	1617	1803	16268	34830	1018	1798	4285
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	1317	4490	2445	1897	1791	734	712	1022	617	723	2192	769	3610	1028	7107
5-aminovaleric acid	536657	174	1698	138	C00431	62485	13246	8208	25230	13194	42475	100283	3823	19613	35034	17449	10705	16249	8181	37135
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	2159	3141	2850	6762	2637	4739	13442	834	3367	4908	1101	1557	2056	2812	2350
4-hydroxymandelic acid	601658	267	131944	328	C11527	814	1197	1277	1487	974	1477	1687	1469	1496	1568	937	1054	1333	1017	1008
4-hydroxyhippuric acid	784581	294	12284	151012		1806	377	873	524	203	145	428	190	509	364	199	430	370	423	238
3-ureidopropionate	554966	161	107897	111	C02642	1030	897	629	2242	1298	1256	873	987	1391	835	1337	594	2205	1830	1367
3-phosphoglycerate	610734	227	1667	724	C00597	312	442	541	451	1860	1359	469	794	1192	971	956	1249	536	631	892
3-phenyllactic acid	516011	193	113643	3848		612	1372	1714	3259	2900	1624	38846	773	4063	1778	2204	3632	5305	2142	1906
3-hydroxybutyric acid	278632	191	145501	92135	C01089	8E+06	4E+06	118193	253213	4E+06	228555	116693	601104	89542	47111	41138	154224	84345	258166	434764
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	8163	1352	550	954	836	645	1277	436	596	230	251	1183	578	815	1020
3-aminoisobutyric acid	452655	248	12265	64956	C05145	2512	3695	24079	2829	3905	3169	21088	4293	2668	3651	3773	17063	3706	2894	47219
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	35798	1590	1730	1418	1113	1250	2647	1473	1752	1476	1207	1572	1100	3889	1277
2-picolinic acid	381532	180	389051	1018	C10164	2681	1992	1458	4672	3535	1905	2570	1611	1448	1914	3437	4006	1726	1078	5248
2-monopalmitin	890356	129	2080	123409		1709	26373	21450	2109	1240	25817	2745	2753	1609	2397	1471	2754	412	2487	1751
2-ketoisocaproic acid	310761	89	208	70	C00233	1773	10771	7922	1640	23072	10026	3314	2187	3353	10559	1042	5200	23900	1187	1623
2-hydroxyvaleric acid	309587	131	25922	98009		70422	15532	12615	13602	31431	21004	24105	11916	7865	13002	12831	40288	9407	14701	21174
2-hydroxyglutaric acid	506306	247	2000	43	C02630	3027	6688	7574	6157	4402	8202	20345	5059	9414	12574	13847	13550	10956	9248	11882
2-hydroxybutanoic acid	258161	131	40	440864	C05984	738306	373027	128609	103991	273901	213425	133072	109587	101988	72403	87955	168265	115839	120671	163832
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		28134	28410	6674	7144	16553	13199	5579	9792	5151	7583	9826	10646	9469	10313	15846
2-deoxytetronic acid	433456	189	1208	150929		4010	7138	2840	7130	6645	7259	4506	5206	5040	4510	106519	149525	2589	6569	7342
2-deoxypentitol	521785	231	21714	249377		2218	3646	1547	1307	1503	2067	1949	1357	1060	1204	15587	18333	1541	1227	2400
2-aminobutyric acid	285825	130	160842	6657	C02721	53875	220764	58170	78449	64494	45690	61881	281815	56740	62860	59462	70810	51439	55396	89491
2,5-dihydroxypyrazine	397526	241	2254	23368901		884	3313	3420	2406	4140	5244	2903	2436	3936	4311	3164	5954	3857	3210	4121
2,3-dihydroxybutanoic acid	384796	292	31743	250402		5997	3262	716	2373	2329	5058	1183	1571	1137	3632	5404	9983	906	2721	4736
1-monostearin	959214	203	648	24699	D01947	3186	4009	2941	4416	6528	5791	8679	5298	5089	3551	2184	3236	4070	5256	3679
1-monopalmitin	901749	371	2070	14900	C01885	2334	2334	1671	2593	2236	3481	6521	3657	5719	3619	2337	3171	2329	4175	3179
1-kestose	1123027	361	14692	440080	C03661	191	2593	1728	286	1187	327	1849	256	1338	307	447	314	1198	953	999

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						Day 20 - AMC														
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BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
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xylose	543267	103	169	135191	C00181	5793	13582	9186	11772	9892	8090	9821	15695	7522	8903	10264	8150	10961	14047	11734
xylitol	567437	217	5857	6912	C00379	2160	3292	4147	4046	2713	3074	4099	3728	2798	3341	2843	3782	2899	2801	4099
xanthine	701688	353	1669	1188	C00385	1648	771	1604	512	2429	531	758	456	747	394	763	438	470	798	879
valine	313502	144	3	6287	C00183	1E+06	741382	564590	974693	820548	1E+06	856814	806893	1E+06	980635	1E+06	1E+06	1E+06	667322	1E+06
uric acid	730691	441	23	1175	C00366	4697	6165	5284	3293	7095	5113	8412	3682	6894	1029	3557	4232	6218	3357	2691
urea	329351	189	145496	1176	C00086	579180	928949	752152	4E+06	3E+06	3E+06	3E+06	3E+06	3E+06	4E+06	3E+06	2E+06	3E+06	3E+06	3E+06
uracil	385735	241	1664	1174	C00106	4176	6325	9251	4246	11137	3558	4058	7804	3612	3465	7801	5065	11632	7114	3464
tyrosine	671252	218	16	6057	C00082	291436	474566	326548	418112	450557	549651	343104	383763	304223	346271	284838	389714	482262	412558	378221
tryptophan	780482	202	14	6305	C00078	261678	440902	260997	430735	341309	482502	403403	463481	350611	354910	436425	374606	397027	393755	449142
trans-4-hydroxyproline	484934	140	97	5810	C01157	415191	329778	446133	561050	393807	411711	373917	367510	689160	547913	355440	460783	344975	587957	615086
tocopherol gamma-	1026121	223	4545	92729	C02483	814	859	676	1721	916	1778	1119	2366	999	1279	680	736	559	788	1111
tocopherol alpha-	1067809	237	100	14985	C02477	19475	28618	11024	16970	17178	18149	11383	27885	27117	43733	16618	22820	19761	24071	29393
thymine	420133	255	1692	1135	C00178	320	883	820	579	1093	479	610	961	679	559	946	1358	1208	634	615
thymidine	349402	170	87703	5789	C00214	23777	25588	30717	44539	42559	50648	29873	50951	34719	38029	17337	31338	37075	37530	46171
threonine	409568	218	26	6288	C00188	311101	204460	124705	221973	172599	276700	274618	330382	256465	262752	1E+06	517601	214021	161009	257351
threonic acid	497572	292	172	5460407	C01620	28211	19193	16134	12788	24763	6051	6116	11543	13849	20538	16886	20796	13244	19587	25776
threitol	467595	217	770	169019	C16884	1378	2544	2268	1995	2379	1026	997	1654	1306	1852	1955	1411	1107	1917	1378
taurine	556690	326	411	1123	C00245	1953	11466	13483	3599	45402	20394	11025	66254	40853	124	37755	40407	39112	50648	60761
tartaric acid	534291	292	33985	444305	C00898	244	295	296	447	245	398	241	388	374	477	681	652	235	386	353
tagatose	631835	307	33981	439312	C00795	1459	1436	2647	1105	2263	888	584	492	823	1375	1430	1393	1240	692	791
sucrose	915139	271	173	5988	C00089	4207	1015	1214	1550	2711	903	4862	1190	1280	1774	1441	3413	2685	4134	1493
succinic acid	370608	247	161	1110	C00042	6734	8210	7911	5273	7581	7796	10977	7975	6464	13268	5814	8970	5569	15489	5498
sophorose	962064	307	132242	441432	C08250	356	286	99	279	623	386	89	554	246	485	240	320	594	154	236
shikimic acid	611100	204	286	8742	C00493	1215	4007	2037	4880	1805	2208	3216	10351	1608	5192	3072	3196	4632	3228	4370
serotonin	863824	174	364413	5202	C00780	108539	85725	92158	76528	131212	84860	32748	127629	71962	134355	74380	86479	119097	43380	127610
serine	395020	204	25	5951	C00065	683553	510208	607560	900947	807948	782489	1E+06	699316	922938	804161	720350	665973	564919	1E+06	831910
salicylic acid	480699	267	3063	338	C00805	804	2214	1513	3174	2060	7507	4506	5137	1886	2344	16193	2053	2977	4452	4402
saccharic acid	699211	333	11214	33037	C00818	633	976	1263	520	1059	968	1002	1172	844	1316	1510	486	969	793	2750
ribose	553071	217	384948	10975657		36221	35468	44170	24598	51123	23123	42795	39261	15400	19335	63946	47155	25312	41226	5092
ribonic acid	599680	292	1683	5460677	C01685	4044	1756	3251	7484	4302	3683	1824	9622	7014	7460	2871	7308	4495	13359	8491
ribitol	575497	217	7362	827	C00474	1730	1413	2450	1288	1576	1758	1685	2807	1660	2377	4415	1902	1440	2119	1796
raffinose	1120886	361	3190	439242	C00492	2631	1832	845	1441	5380	1485	2948	359	1534	1406	688	2237	1158	3318	1692
pyrophosphate	547021	451	88522	1023	C00013	2212	2752	1760	3857	3556	2604	1143	3556	3283	1829	2583	3142	3315	3050	5837
putrescine	588119	174	21703	1045	C00138	5012	3625	2271	4890	5107	12038	7639	5888	7818	9035	11014	9088	3825	7359	10406
pseudo uridine	813899	217	1688	15047	C02067	9888	19920	17902	16489	15378	10289	10771	23245	9977	8681	11586	14754	13909	14847	16510
proline	364716	142	8	145742	C00148	1E+06	380907	307635	972418	605284	687065	997668	453627	1E+06	636318	899959	829878	713787	725426	1E+06
piperidone	275603	156	34023	12665		1486	4640	3386	12988	6279	3163	4265	1374	20227	4759	2061	6488	16260	5837	23784
pipecolinic acid	404121	156	2448	6931662		2668	2554	2462	4557	2404	2742	20073	1500	3225	2115	2004	2851	3175	3281	3939
pimelic acid	523205	155	33429	385	C02656	949	1609	1593	1708	1819	711	2556	2512	1583	1348	1412	511	862	1078	1814
phthalic acid	567345	147	46142	1017	C01606	5131	7140	15980	9016	6530	10079	14780	14844	7758	25659	9770	10258	10336	8291	11130
phosphoethanolamine	603912	299	1723	1015	C00346	2772	1337	3338	1728	4311	6078	1453	9182	3405	5033	2951	5138	10285	3766	14042
phosphate	345365	314	4	1004	C00009	610654	741817	804437	711014	630464	767165	616293	589889	765645	956557	1E+06	688240	597044	578337	764097
phenylethylamine	510327	174	2005	1001	C05332	12257	10743	8958	25206	10471	12006	36779	17936	29647	19960	27459	20062	13472	21342	32420
phenylalanine	537804	192	33	6140	C00079	189455	199875	144398	232218	164053	286766	184748	194135	164383	243397	152950	200894	216502	218080	213359
pentose	540818	103	360841	229		2004	4096	14253	3684	12477	14797	2591	2598	1853	2350	2831	2965	3147	3280	3381
pelargonic acid	399229	215	50	8158	C01601	14499	21961	18266	15441	17682	20146	23788	25004	25934	30111	19417	23591	20165	21092	17872
palmitoleic acid	706508	311	96	445638	C08362	936	4485	1512	2925	1267	2613	2750	4153	1884	1371	2522	1787	2716	2469	2643
palmitic acid	713809	313	11	985	C00249	59427	171858	99054	131190	86680	131916	118185	188965	90952	104482	94531	118605	141748	124789	116782
oxoproline	485935	156	10	7405	C01879	641172	809423	756888	873037	661060	828277	729198	951246	605114	754033	929872	742432	930356	946533	1E+06
oxalic acid	260513	190	4923	971	C00209	4087	2985	3534	1821	1999	5727	5398	7268	5055	2389	5012	3291	4011	4317	2519
ornithine 3TMS	527113	142	1821	6262	C00077	259889	125593	116436	236572	266808	604503	234038	160130	295295	297692	398897	383903	246922	199324	221366
oleic acid	779120	339	43	445639	C00712	13985	66385	26942	42241	1649	54065	4138	67624	28323	1047	1603	1682	42623	42248	1513
oleamide	849710	144	20961	5283387	C19670	18818	21650	29401	15833	28337	21106	28608	41133	18490	4326	25134	22080	21460	21773	3135
nonadecanoic acid	822782	117	46258	12591	C16535	3759	4945	3789	2764	4509	5311	4337	6133	2341	3455	21085	7450	3422	4992	4470
nicotinic acid	353428	180	327312	938	C00253	643876	186332	739207	85234	781013	4031	3779	9710	2160	4074	71290	3966	347791	3062	7695
N-acetylglycine	356109	174	97747	10972		1380	1523	1038	2046	1037	447	543	750	1201	1623	1279	917	1157	879	684
myristic acid	634414	285	127	11005	C06424	1788	5213	3254	3561	2272	3758	3930	5693	2844	10907	3632	3458	5073	3599	3528
myo-inositol	730022	305	1741	892	C00137	207561	234363	402658	166921	479257	237046	331927	559197	326798	292732	255057	356059	560470	496326	513484
mevalonic acid	498785	247	127978	439230		1304	898	2107	852	1203	585	1396	833	676	788	1372	1776	609	1074	1130
methionine sulfoxide	637588	128	1678	158980	C02989	82833	36000	22813	61343	63610	160466	109933	67982	99410	114741	164862	158667	43913	103942	155088
methionine	483560	176	45	6137	C00073	193939	134099	113407	317634	165500	118058	168793	67825	169242	139876	114051	127538	187037	110077	102325
methanolphosphate	289520	241	5393	13130		21556	17395	17631	21997	24871	24886	22805	26152	24549	53767	19233	24535	20190	28038	28841
mannose	645856	205	70	18950	C00159	107468	219024	160727	213046	127600	155812	127204	222760	123608	170979	270480	156620	157896	167486	188260
maltose	946601	204	1979	439186	C00208	10398	6630	23770	6426	37271	9517	7988	17429	12132	10001	31120	11917	12735	23642	38620
malonic acid	305372	233	16918	867	C00383	103	564	445	159	173	148	28	342	192	284	283	474	624	705	340
malic acid	463180	233	1391	525	C00711	2770	4270	8495	2877	6391	4330	3900	6308	4290	3996	4622	5637	7379	8492	7278
maleimide	245118	154	1743	10935	C07272	8077	9506	8576	12683	7965	10346	11413	14717	11227	13839	11126	11508	15176	10083	10665
lyxitol	573587	217	233	439255	C00532	14135	10903	11460	16536	18228	12306	12109	14321	16362	17457	15570	15426	12055	19460	15747
lysine	663483	317	12	5962	C00047	34513	40758	30821	28608	36080	63134	38605	57418	39984	25897	39748	62164	46918	36642	52521
linoleic acid	777285	337	471765	5280450	C01595	9721	27097	12022	21423	13276	23714	17503	27114	15476	16009	11790	16893	19344	20334	17773
levoglucosan	569637	204	3169	2724705		786	780	1155	1137	1052	848	2256	1063	766	1491	1149	1106	962	746	1105
leucine	346101	158	9	6106	C00123	2E+06	999519	811691	2E+06	1E+06	2E+06	1E+06	830455	1E+06	1E+06	1E+06	1E+06	1E+06	1E+06	1E+06
lauric acid	547906	117	49	3893	C02679	9076	13321	9786	13413	10220	9875	12007	17265	10200	265407	10252	10552	12937	11951	10575
lanosterol	1129573	393	133475	246983	C01724	319	208	382	205	374	293	372	192	174	246	301	339	216	266	280
lactose	936998	204	217651	6134	C01970	1376	1336	1687	1307	2177	1216	1274	6414	1318	1584	1931	1732	3077	3139	2115
lactic acid	217657	191	80	612	C01432	4E+06	4E+06	4E+06	1E+06	4E+06	2E+06	3E+06	3E+06	3E+06	3E+06	346626	3E+06	4E+06	3E+06	2E+06
lactamide	265698	232	415	94220		4326	5956	4022	1392	4384	1874	3537	3229	4695	2480	2644	2784	4089	1937	2735
kynurenine	769709	218	210712	25245862	C01718	13878	10953	7453	9586	14562	4747	9230	11972	5445	4121	16612	7134	4739	5492	10818
isothreonic acid	489385	292	1679	151152	C00639	7954	10706	8808	13630	8906	8253	6771	10882	7388	8668	8313	10937	9329	11129	11438
isomaltose	983199	160	127715	439193	C00252	651	527	177	548	822	672	415	320	475	325	554	463	529	609	388
isoleucine	359251	158	15	6306	C00407	596980	472284	389054	513010	456313	730752	416498	419274	530136	545482	507166	477787	512394	462301	516362
isocitric acid	616323	245	12267	5318532	C00451	4324	10203	8462	7755	5316	4998	4419	6897	6977	5607	6162	7115	5948	7095	8310
inositol-4-monophosphate	845976	315	4759	440043	C03546	1231	987	758	2012	1241	1703	1245	1286	988	406	1130	2110	1756	1549	946
inosine	897434	230	84524	6021	C00294	18253	18706	14953	17527	28739	46785	13611	39696	23918	35478	32110	39553	20691	32062	39025
indoxyl sulfate	577333	277	31543	10258		624	1578	2533	2167	726	1421	731	1588	1966	6119	1204	2031	1076	2086	5120
indole-3-propionic acid	732249	202	112556	3744		398	3432	1839	1174	871	1360	1425	2088	6715	13528	1748	1452	795	709	1826
indole-3-lactate	764079	202	390397	92904		3625	3438	4878	6874	6181	4299	5292	5536	7542	9413	8151	4699	6459	6937	10133
indole-3-acetate	684929	202	69	802	C00954	3165	3106	3609	8467	5160	6721	6279	2111	3246	8557	5755	6825	4357	6290	7471
hypoxanthine	619128	265	1663	790	C00262	66735	73600	91534	55792	119691	43278	22179	109406	44837	60542	133837	92302	139606	97162	112243
hydroxycarbamate	325318	278	130396	16639161		8099	7582	5205	3416	7485	8371	3089	8995	3652	8522	5755	9813	10287	4834	11053
homoserine	443878	218	2849	12647	C00263	1125	963	819	1462	1454	1485	1224	1407	816	659	1600	1421	961	776	1429

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						Day 20 - AMC														
						579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855	579855
						579900	579897	579894	579891	579888	579885	579882	579879	579876	579873	579870	579867	579903	579864	579861
						FMO13	FMO18	FMO20	FMO22	FMO24	FMO29	FMO32	FMO34	FMO56	FMO58	FMO67	FMO68	FMO7	FMO70	FMO74
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
homocystine	874865	128	2786	10010	C01817	961	773	1459	1632	1259	727	764	1309	863	1137	1195	1032	873	797	1325
histidine	663790	154	150	6274	C00135	93430	108493	105253	147760	99064	80508	60930	78199	55771	9439	79565	76326	92629	57075	77325
heptadecanoic acid	751309	117	727	10465		6595	19607	10741	12620	10148	13178	14529	22156	10530	12975	9599	15968	13632	12522	13225
guanosine	954962	324	1966	6802	C00387	2113	1946	1550	1777	2765	4224	1272	3562	1862	497	3935	3295	2593	3598	4064
guanine	744307	352	2519	764	C00242	1996	3314	3315	2242	2623	1105	1659	7108	1292	1080	4814	2239	6817	3245	2628
glycyl proline	691357	174	18496	3013625		1163	865	1779	1711	1014	1179	933	510	1567	2082	1411	1175	1156	922	1909
glycolic acid	227636	177	1971	757	C00160	13833	14542	14479	15952	15552	16951	12806	14846	16404	24137	16634	13642	17996	17770	16318
glycine	368707	248	6	750	C00037	858307	616494	717271	1E+06	886821	600561	2E+06	608864	1E+06	788484	863812	665594	543768	1E+06	828379
glycerol-alpha-phosphate	590747	357	1687	754	C03189	30997	31005	17439	30185	20213	30245	15168	29620	26822	44120	32584	42721	33274	33808	24652
glycerol-3-galactoside	800205	204	100875	16048618	C05401	4086	4354	2928	3006	3335	3513	3696	7437	3609	3978	4646	3116	2731	2995	4429
glycerol	344466	205	30	753	C00116	258546	669191	417361	313287	349696	676317	263400	363869	316726	301003	394088	323457	422870	246302	207120
glyceric acid	377308	189	394878	752	C00258	19749	16496	17970	21845	20842	13918	12755	20253	16755	18459	17548	18238	28025	28239	24244
glutaric acid	421260	261	1727	743	C00489	603	634	658	660	845	550	961	568	825	878	966	540	730	801	708
glutamine	600315	156	18	5961	C00064	536851	785939	947472	1E+06	387651	653582	661484	683142	284021	331595	616529	556793	625139	512338	609318
glutamic acid	529100	246	28	33032	C00025	55801	49973	76483	55073	70289	41874	72617	68977	42448	43075	64686	69414	81143	64195	69662
glucuronic acid	665901	333	344793	94715	C00191	5201	7175	10971	9102	6858	6998	6531	8243	7827	6909	5899	8047	8046	9297	7132
glucose-6-phosphate	808788	387	360626	5958	C00092	2784	3095	2985	1694	3260	2136	1004	1582	2086	1381	3324	1243	2456	2126	1719
glucose-1-phosphate	594647	217	3167	65533	C00103	2150	2374	7284	4756	4272	2079	1905	3048	3121	3923	2913	2924	4709	3498	3653
glucose	659798	319	22	64689	C00221	2E+06	3E+06	4E+06	4E+06	3E+06	3E+06	3E+06	3E+06	3E+06	4E+06	4E+06	3E+06	3E+06	3E+06	3E+06
gluconic acid lactone	645815	220	3502	7027	C00198	3431	10436	27638	4390	17565	10830	4155	6073	17723	11960	18832	18547	11559	15267	12973
gluconic acid	693148	333	7501	6857417	C00800	17671	50720	185975	28302	108678	61452	21488	35674	101207	93045	96232	115104	70793	83888	76536
galactinol	1017580	204	1975	11727586	C01235	2460	1772	1690	1870	4096	1943	1922	1347	1369	2200	1776	2054	1988	3273	1684
fumaric acid	390775	245	1718	444972	C00122	1006	1506	1903	1119	1494	1895	2499	2381	2856	2927	1398	2916	2013	4622	2655
fucose	578299	160	3009	439650	C02095	5436	6598	8499	6300	8025	6032	6461	7832	6251	8501	10026	6897	6951	6655	9709
fructose	639442	307	21	439709	C02336	183393	280634	102010	352093	207952	253991	209076	207044	229612	284574	361602	307131	235149	215291	245554
ethanolamine	342561	174	342038	700	C00189	37244	35551	58981	16373	69049	46527	23930	46536	32406	39707	50845	57636	34917	47464	63375
erythritol	471922	217	92	222285	C00503	9171	14818	10489	10215	10253	9021	9075	14256	7853	10466	16058	12363	9248	10393	11012
epsilon-caprolactam	353069	170	3101	7768	C06593	10822	8307	13466	11148	12714	4615	6442	15097	7607	3510	17435	8517	14012	4989	13244
docosahexaenoic acid	902819	91	87709	445580	C06429	1785	2345	1350	1887	1650	2271	1813	3078	1762	1861	1708	1237	2139	2998	1960
dihydrocholesterol	1082070	215	42937	66066	C12978	3787	3617	2960	3349	2817	4874	2557	6214	4696	10080	3046	4024	4830	4592	5699
dihydro-3-coumaric acid	582960	192	384891	91	C11457	668	1124	1086	1204	798	1037	888	1353	2153	1680	1095	1160	1298	1152	1220
cytosine	486724	254	2186	597	C00380	905	1386	1656	3012	2166	1076	1826	1817	1938	2254	3145	1640	1588	1428	1352
cystine	804619	218	94	595	C01420	15681	36098	16124	39575	24739	8020	12403	14903	15057	1626	8148	16616	20770	23192	27103
cysteine	500158	220	65	5862	C00097	7304	12957	14675	20511	12024	3742	5623	8194	8563	1031	6549	12855	19861	7559	13099
creatinine	502599	115	31	588	C00791	71419	79128	109629	99187	68608	96715	93818	90217	173978	183130	105688	191023	82194	109636	99126
conduritol-beta-epoxide	675635	318	2670	9989541		1985	1839	2278	2183	1880	1837	872	1366	1626	1962	2436	2811	1869	1637	11031
citrulline	621404	157	1712	9750	C00327	35688	27859	31975	33085	32478	56367	31430	36580	36644	40939	37197	44242	40643	35291	53802
citric acid	617342	273	288	311	C00158	208238	466413	388526	410052	258549	262829	208768	358262	274582	297787	288837	336123	282078	350118	420940
cis-gondoic acid	847372	367	87783	5282768	C16526	424	422	238	398	327	573	371	929	382	561	551	482	619	444	683
cholic acid	1109517	253	110403	221493	C05463	506	406	792	1606	633	522	682	859	381	860	584	552	571	456	1123
cholesterol	1078536	129	19	5997	C00187	462037	498670	436103	569212	468347	533152	545091	733934	533741	1E+06	478277	518119	548497	609025	731861
cellobiose	942758	361	120969	6255	C01971	527	548	235	493	618	504	535	845	561	650	1076	569	746	1132	1090
capric acid	451790	229	726	2969	C01571	3022	4568	3514	4424	3719	4429	4319	5032	3457	12887	4563	3988	3745	3627	3749
butyrolactam	277199	142	2047	12025		19577	35284	18614	31837	23229	34172	17246	21723	18487	34421	17248	31933	28482	35045	26638
butane-2,3-diol	205778	117	485	262	C03046	232245	254452	309346	92663	309255	107257	240501	171240	175313	248660	153058	170446	238503	126056	78087
beta-sitosterol	1128225	129	3174	222284	C01753	5615	5171	2895	2117	4007	4721	7035	15527	2329	4552	6604	8047	5020	7244	5752
beta-glycerolphosphate	574470	243	22021	2526	C02979	801	1098	1254	1310	1041	1127	1170	1336	1099	2123	1258	1729	1369	1519	929
beta-alanine	435564	248	148	239	C00099	3382	2812	2779	2573	2291	3408	2407	2519	4833	2670	6046	4399	4414	2325	3634
benzoic acid	339067	179	36	243	C00180	113475	133402	102780	147975	104762	187077	158156	200242	146508	204641	252891	178730	111073	146831	145798
azelaic acid	610551	317	329430	19347555	C08261	858	1001	1219	1452	1238	1433	2375	1949	1034	1689	1294	1126	603	969	1747
aspartic acid	480387	232	79	5960	C00049	22516	22502	25236	24470	31540	23282	29588	39350	19775	21018	35382	22452	30992	33770	34732
asparagine	553743	231	369588	6267	C00152	30132	34505	38802	46953	35942	41229	46045	44179	25964	18426	42575	28012	30566	27898	39140
arachidonic acid	837115	91	64589	444899	C00219	8382	13302	6160	10925	9120	14716	9311	20147	14654	22181	11205	14574	9986	12260	15030
arachidic acid	856421	117	291	10467	C06425	4047	6135	4921	5319	4899	7122	8038	8748	5684	6046	4926	5788	5543	5634	5572
arabitol	572730	103	372446	94154	C01904	11756	14330	7595	10569	11330	9953	7366	8229	14746	16429	12179	18819	15044	14015	12361
aminomalonate	455754	218	413	100714	C00872	59846	24054	30164	26419	50155	34833	24148	28976	33750	40942	30579	36269	35643	35935	51290
alpha-ketoglutarate	507392	198	294	51	C00026	466	1836	2846	2873	660	260	80	486	323	431	424	425	3108	388	562
alpha-aminoadipic acid	573295	260	125502	92136	C00956	2225	3004	2777	2481	2771	1865	3845	3196	3094	2438	2966	3847	2565	2393	2615
allantoic acid	726050	259	117021	203	C00499	24557	36177	27979	42519	31532	31286	29105	24642	40345	66431	30201	42439	25548	32711	76364
alanine	243971	116	34178	5950	C00041	2E+06	2E+06	2E+06	2E+06	2E+06	1E+06	3E+06	3E+06	2E+06	967079	2E+06	2E+06	1E+06	2E+06	2E+06
adipic acid	474435	111	125	196	C06104	1710	3350	4836	2214	3981	2673	11781	5722	3070	4080	4354	2628	3200	3199	2016
aconitic acid	586815	229	29	643757	C00417	421	1488	434	1377	534	2011	1674	2950	1623	2216	1463	2476	436	2237	2577
5-methoxytryptamine	864466	174	284	1833	C05659	87643	71179	74622	62283	105079	102478	26083	101458	57413	108443	61123	70205	97810	34418	101240
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	717	1261	898	1325	756	783	954	747	756	1250	788	1174	1208	826	1462
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	873	2655	1544	3400	914	753	1940	1456	1313	597	1484	857	1466	1191	966
5-aminovaleric acid	536657	174	1698	138	C00431	7402	6940	34968	19927	6465	7445	6259	2909	12957	10405	3768	8694	13398	7459	36622
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	1173	1130	862	1002	1192	1573	2324	804	1058	2873	2336	2888	898	1435	1104
4-hydroxymandelic acid	601658	267	131944	328	C11527	1066	1330	1710	1807	855	1378	1290	1272	852	1575	1740	1285	1256	727	623
4-hydroxyhippuric acid	784581	294	12284	151012		266	317	439	340	366	322	342	319	273	342	217	218	342	431	371
3-ureidopropionate	554966	161	107897	111	C02642	1878	1956	1666	2560	3981	1665	1024	3132	663	1324	4115	2738	2273	1083	1839
3-phosphoglycerate	610734	227	1667	724	C00597	421	527	1123	551	1099	878	389	1970	1554	1134	1322	452	3694	2247	1850
3-phenyllactic acid	516011	193	113643	3848		3352	753	825	4122	2753	4236	5988	3248	1744	1372	4314	2645	4245	2077	1984
3-hydroxybutyric acid	278632	191	145501	92135	C01089	53196	68440	50784	49686	36745	105233	49674	54796	32309	71162	15600	98972	65237	70185	40677
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	256	782	289	545	936	387	336	1058	455	416	402	665	464	558	655
3-aminoisobutyric acid	452655	248	12265	64956	C05145	11375	3038	18517	3953	11160	3072	3361	4637	4449	2876	3445	13342	8906	8120	43549
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	716	1164	795	909	999	1282	1309	1344	1086	1932	1233	1167	1174	1158	1450
2-picolinic acid	381532	180	389051	1018	C10164	2415	2237	3686	2366	3512	1594	2414	3005	1610	1684	1787	2129	2546	1475	1700
2-monopalmitin	890356	129	2080	123409		3547	3039	2197	3954	2453	31759	4191	2631	2066	2048	3015	1994	1546	1981	4265
2-ketoisocaproic acid	310761	89	208	70	C00233	4005	18957	14042	16322	5999	1464	3487	1064	2598	567	1894	2390	13888	1737	1520
2-hydroxyvaleric acid	309587	131	25922	98009		8837	9369	6862	14706	13767	7446	7218	6887	5492	5251	10203	14550	6831	7466	15447
2-hydroxyglutaric acid	506306	247	2000	43	C02630	9726	11477	7532	15671	7661	17089	13167	10492	7116	10401	10107	18209	10259	15198	18991
2-hydroxybutanoic acid	258161	131	40	440864	C05984	62920	115450	41806	51119	71982	75104	80078	104012	71103	63475	64268	90425	59734	51336	111915
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		4982	9227	8925	6778	6007	8254	5497	8861	3940	4799	5046	7308	6932	6394	8112
2-deoxytetronic acid	433456	189	1208	150929		829	4316	3389	3703	3369	3146	3416	5471	3179	4356	5159	4553	2392	4773	3216
2-deoxypentitol	521785	231	21714	249377		1235	1273	1263	700	1178	1029	1875	1254	1026	973	854	919	825	1340	2035
2-aminobutyric acid	285825	130	160842	6657	C02721	22612	33767	32352	45756	27992	27899	41976	66109	44203	31940	29678	38086	31977	32390	57340
2,5-dihydroxypyrazine	397526	241	2254	23368901		2787	5295	5284	3781	3872	2514	3788	4316	4077	1768	2488	3801	5603	4724	4652
2,3-dihydroxybutanoic acid	384796	292	31743	250402		1960	2902	1467	1733	1251	2028	2134	3240	1174	2015	8145	5700	1080	2019	2605
1-monostearin	959214	203	648	24699	D01947	2194	4805	4867	3841	5198	4043	3710	4754	2574	4949	1849	3610	3963	3959	3608
1-monopalmitin	901749	371	2070	14900	C01885	1813	2459	2478	2480	2344	2882	3373	3441	2721	5240	2586	2897	2515	2493	2264
1-kestose	1123027	361	14692	440080	C03661	1207	734	703	1152	1516	1046	1328	484	1811	1069	800	1355	1166	1617	1514

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						Day 300 - AMC														
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						579875	579872	579869	579866	579863	579856	579899	579896	579893	579890	579887	579884	579881	579878	579902
						FMFO56	FMFO58	FMFO67	FMFO68	FMFO70	FMFO74	FMO13	FMO18	FMO20	FMO22	FMO24	FMO29	FMO32	FMO34	FMO7
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	1954	1300	1436	1454	1714	1909	1822	2064	1988	1452	3388	1194	1411	2538	3025
xylose	543267	103	169	135191	C00181	14013	18140	10704	8084	10708	9280	8918	7207	10287	8392	8454	9320	8452	7265	7393
xylitol	567437	217	5857	6912	C00379	3930	4958	4594	4140	7219	7656	2193	2737	5173	12331	4127	4559	2987	2898	10168
xanthine	701688	353	1669	1188	C00385	1501	814	507	699	519	834	929	491	796	379	843	616	320	495	485
valine	313502	144	3	6287	C00183	683545	1129263	942012	1213775	900795	622427	853298	828137	615977	725485	932980	999318	813566	929498	750122
uric acid	730691	441	23	1175	C00366	3537	6451	3040	5820	3776	4797	4850	4419	5624	4658	7449	3135	3641	9996	4850
urea	329351	189	145496	1176	C00086	3513298	3134049	3921551	2450157	3221977	2918158	2511088	2919809	3804424	2956108	3360562	2932285	3214095	3173142	3750499
uracil	385735	241	1664	1174	C00106	10684	4612	3481	4013	1910	3711	3897	2515	2404	2549	6123	3158	4398	5289	5541
tyrosine	671252	218	16	6057	C00082	382956	452126	370944	510876	440063	449889	305488	340647	403604	469838	427845	618072	447918	367857	408347
tryptophan	780482	202	14	6305	C00078	398392	445973	590886	425463	568637	597386	312460	425876	419755	534761	525663	428126	440616	676074	508660
trans-4-hydroxyproline	484934	140	97	5810	C01157	394119	77068	440319	123327	336072	215635	186537	416557	282029	260912	187831	300900	199899	424588	519418
tocopherol gamma-	1026121	223	4545	92729	C02483	1524	843	865	583	1399	726	989	631	1145	860	1065	1105	1024	818	1609
tocopherol alpha-	1067809	237	100	14985	C02477	18214	21677	23078	13830	25341	26128	9331	31303	16073	14179	15926	14612	52497	22596	19660
thymine	420133	255	1692	1135	C00178	1322	1763	707	765	576	499	413	534	629	1193	1106	703	756	858	579
thymidine	349402	170	87703	5789	C00214	29062	32384	39816	29000	45494	30699	31453	27024	33379	37653	51740	34986	26361	45980	38530
threonine	409568	218	26	6288	C00188	200642	383004	441607	482570	252660	202441	179942	183639	176617	219864	207890	245855	366428	425560	186983
threonic acid	497572	292	172	5460407	C01620	27274	5896	10907	12181	21773	9158	6507	16653	27117	12338	15647	13593	42054	28355	51489
threitol	467595	217	770	169019	C16884	2335	1793	2245	936	2438	848	1582	1610	1936	1368	1118	1286	1204	2247	1349
taurine	556690	326	411	1123	C00245	100720	25104	22545	5630	30570	268	1855	3194	241	2165	79234	29034	29547	54087	8856
tartaric acid	534291	292	33985	444305	C00898	278	278	2134	1759	2335	1860	273	1139	1257	1187	1189	376	504	574	1487
tagatose	631835	307	33981	439312	C00795	1177	1742	3343	1096	1250	2088	1198	1972	5072	3554	3718	384	714	504	2069
sucrose	915139	271	173	5988	C00089	372	215	1489	22633	1780	755	765	1500	5173	1057	698	1344	1102	2154	1721
succinic acid	370608	247	161	1110	C00042	8093	6545	11968	14467	23297	8392	10143	14580	10557	14292	7672	10960	12032	15222	14207
sophorose	962064	307	132242	441432	C08250	679	386	370	346	320	329	450	390	411	252	487	162	266	484	300
shikimic acid	611100	204	286	8742	C00493	4290	4995	6974	6291	4236	6558	7682	4929	9742	5695	11413	6952	9682	12675	3885
serotonin	863824	174	364413	5202	C00780	99819	25027	99631	71675	70304	68008	96777	85044	104266	121884	56079	74581	54505	26285	60415
serine	395020	204	25	5951	C00065	654612	517983	582015	449092	819102	660438	454380	484350	642057	648948	663325	614662	720863	757292	802304
salicylic acid	480699	267	3063	338	C00805	3097	3037	9859	2625	4945	4734	3295	1603	2463	2563	2701	2516	5533	5026	3466
saccharic acid	699211	333	11214	33037	C00818	1798	978	1713	938	1305	995	568	325	1784	1088	1109	823	1048	955	972
ribose	553071	217	384948	10975657		21217	35360	44459	37599	22769	38058	33610	17324	21682	13407	22483	38112	14039	15216	17036
ribonic acid	599680	292	1683	5460677	C01685	10343	22098	9758	6807	5001	7117	5532	7497	3342	5279	6085	3096	4384	6680	3566
ribitol	575497	217	7362	827	C00474	2696	2116	1729	2043	2018	1705	1989	2407	3323	1367	1448	1411	3695	3310	2421
raffinose	1120886	361	3190	439242	C00492	329	233	2230	183	6807	233	529	1681	5054	1489	1931	186	456	807	1584
pyrophosphate	547021	451	88522	1023	C00013	3486	2792	1839	536	4056	659	282	1417	1142	1658	1994	1526	2513	2899	2019
putrescine	588119	174	21703	1045	C00138	6388	4848	9970	5929	8332	5008	2910	5828	3942	5860	4486	3774	11035	11316	6407
pseudo uridine	813899	217	1688	15047	C02067	11065	14120	12344	11029	11289	10257	15992	11775	15064	17006	12822	13696	8608	14320	10505
proline	364716	142	8	145742	C00148	636666	394783	905429	558230	870415	403537	487494	696009	390187	573090	463164	441287	695806	839162	757517
piperidone	275603	156	34023	12665		2324	5130	12726	3834	3635	1633	2094	2011	5371	6935	12103	2262	7959	1653	4680
pipecolinic acid	404121	156	2448	6931662		1735	3012	2571	14176	3292	1977	1981	3993	1876	4357	2471	3206	3793	4934	4118
pimelic acid	523205	155	33429	385	C02656	2504	3201	1658	998	1565	1468	1710	1952	2026	650	1949	2699	2946	1589	2015
phthalic acid	567345	147	46142	1017	C01606	30461	10953	12520	7714	14195	11466	6249	8122	20705	19743	9979	9877	9660	10548	17693
phosphoethanolamine	603912	299	1723	1015	C00346	14492	3116	5269	2473	2055	1888	1408	2578	3961	2612	1691	3830	6980	4951	1836
phosphate	345365	314	4	1004	C00009	719353	508431	521573	366085	565984	463581	278025	520638	350807	299978	432804	427464	534440	495227	436786
phenylethylamine	510327	174	2005	1001	C05332	14812	4766	18238	6315	19036	10755	7901	35409	5199	129988	6482	5651	13407	48687	41821
phenylalanine	537804	192	33	6140	C00079	169839	254981	198995	221919	189965	224246	145433	119806	159150	211291	213135	239960	233617	219417	235672
pentose	540818	103	360841	229		3383	2348	2832	2029	10896	2319	10285	1693	2990	2840	9555	2256	10420	2116	8209
pelargonic acid	399229	215	50	8158	C01601	24678	22342	94297	17551	25793	21434	21638	17349	24241	22581	15780	17687	26138	31427	22406
palmitoleic acid	706508	311	96	445638	C08362	1010	1325	1135	1514	2584	1749	7009	729	1357	1902	3380	2944	4894	273	2264
palmitic acid	713809	313	11	985	C00249	78672	117246	99797	111470	136065	121494	205474	79554	107402	131105	228014	157182	172549	166969	144927
oxoproline	485935	156	10	7405	C01879	971978	1052064	1214410	762571	1046181	1131050	711644	627614	1096103	926451	1309144	912010	1012373	892682	1060599
oxalic acid	260513	190	4923	971	C00209	3532	4687	3853	4810	7985	5794	8776	6603	5590	5564	3401	2644	4052	3106	4034
ornithine 3TMS	527113	142	1821	6262	C00077	109779	343994	156076	144446	113352	147131	122600	188605	121816	147804	112192	143406	156490	291957	151765
oleic acid	779120	339	43	445639	C00712	1459	1652	1463	2471	1758	4181	88804	2432	3604	1707	67939	2342	5649	39019	2109
oleamide	849710	144	20961	5283387	C19670	13598	40946	14891	29776	23066	22165	31696	36882	13946	37512	30224	38249	41988	41340	36403
nonadecanoic acid	822782	117	46258	12591	C16535	3934	7980	3334	2988	4625	4370	4653	5455	4667	5568	3320	4691	3560	4511	6324
nicotinic acid	353428	180	327312	938	C00253	3204	5855	29507	3743	4620	5405	318541	854904	809256	593635	287450	2114	10484	3124	156718
N-acetylglycine	356109	174	97747	10972		435	1325	824	753	1615	282	1001	715	630	621	1107	553	787	1387	836
myristic acid	634414	285	127	11005	C06424	8682	3473	4197	3048	3833	3256	6629	3881	10737	3993	4847	4294	4725	6070	4433
myo-inositol	730022	305	1741	892	C00137	548941	255666	200293	219483	254127	213103	182639	196568	239444	205673	435721	387987	208293	666800	451473
mevalonic acid	498785	247	127978	439230		1139	3032	1458	1029	1827	1455	949	940	1685	1108	2715	1074	960	1459	919
methionine sulfoxide	637588	128	1678	158980	C02989	69738	49835	138792	67667	112695	73238	37234	55314	32423	81852	62622	48043	145254	159807	97704
methionine	483560	176	45	6137	C00073	73260	70171	105909	84548	85703	55250	77166	113275	121782	107267	102626	78749	154638	161320	161591
methanolphosphate	289520	241	5393	13130		29414	31530	21948	14596	39691	44137	15622	43777	22795	14098	12699	25011	47569	34276	16364
mannose	645856	205	70	18950	C00159	227496	226797	150530	144680	172156	202871	162351	156880	245329	289648	303915	182946	159501	164103	161274
maltose	946601	204	1979	439186	C00208	38494	6599	5877	3976	4699	6663	1661	8086	9932	6794	27022	7180	5164	14861	6469
malonic acid	305372	233	16918	867	C00383	239	511	621	259	694	36	218	225	456	210	148	169	399	353	500
malic acid	463180	233	1391	525	C00711	12781	9122	6592	8684	16488	9436	4882	6000	4651	4687	6500	5847	7042	4539	7756
maleimide	245118	154	1743	10935	C07272	12410	11463	7983	5996	11198	12380	8113	12685	11270	19172	12540	10053	13055	9148	8300
lyxitol	573587	217	233	439255	C00532	13957	9064	18198	8820	18816	7831	10139	15718	16978	13011	9797	10972	8216	34119	20122
lysine	663483	317	12	5962	C00047	25104	67254	34295	61452	33176	39667	43578	46010	48229	68813	35964	65863	37451	60255	22013
linoleic acid	777285	337	471765	5280450	C01595	11801	15327	12739	10695	25843	17790	39230	12441	14556	19078	31434	25017	28306	22189	21703
levoglucosan	569637	204	3169	2724705		2163	1338	1185	968	1123	1088	1103	989	1570	1430	5405	2110	988	1600	5524
leucine	346101	158	9	6106	C00123	888246	1076122	1117124	1169559	1098859	851100	1089390	720361	817287	809317	1109395	986723	1328177	1037291	1132987
lauric acid	547906	117	49	3893	C02679	222821	16026	28691	10547	12420	14478	14093	10083	213212	15656	14197	10653	20597	18348	11024
lanosterol	1129573	393	133475	246983	C01724	240	332	263	211	463	250	234	223	370	207	168	175	414	280	292
lactose	936998	204	217651	6134	C01970	2174	1980	2984	1957	1765	1760	1694	2064	2730	1820	3271	52196	2495	5017	1605
lactic acid	217657	191	80	612	C01432	3132773	722669	1333638	3343843	2159237	1970096	4284889	2608563	1058649	1597742	1746847	3947871	3639434	2814141	2767481
lactamide	265698	232	415	94220		2723	1154	1642	3110	2173	2108	3864	2323	1176	1301	1677	3891	3942	2212	3225
kynurenine	769709	218	210712	25245862	C01718	3796	8866	9197	7010	7111	10272	8016	6503	9772	8434	7075	7352	5639	10148	6609
isothreonic acid	489385	292	1679	151152	C00639	9138	10972	8234	6691	8466	6627	8022	7024	9712	7919	8316	7835	6827	7562	7446
isomaltose	983199	160	127715	439193	C00252	307	434	483	370	545	693	578	440	1192	588	546	579	446	153	273
isoleucine	359251	158	15	6306	C00407	322246	490265	414884	520306	417519	313855	459714	385309	327432	303920	464735	496813	369939	433364	343163
isocitric acid	616323	245	12267	5318532	C00451	10818	5568	7832	4814	7813	7587	4925	4394	6677	7249	6062	5325	4955	4588	5744
inositol-4-monophosphate	845976	315	4759	440043	C03546	2229	1656	2350	990	2067	2280	919	1628	1881	553	1289	1074	2208	1962	797
inosine	897434	230	84524	6021	C00294	34125	21938	49948	33030	23984	24599	20570	26646	24025	25158	32655	41338	23263	47659	32059
indoxyl sulfate	577333	277	31543	10258		3617	4830	4982	2342	3802	1926	1236	888	826	1379	2210	2104	4833	1407	785
indole-3-propionic acid	732249	202	112556	3744		8850	4079	6153	4702	13117	6292	5812	6007	17027	28402	10312	3291	7140	4213	5201
indole-3-lactate	764079	202	390397	92904		6668	5051	10744	6707	8999	12017	6053	5843	10833	7942	7905	4016	6829	6668	19312
indole-3-acetate	684929	202	69	802	C00954	4502	4171	11980	6405	12889	6186	2209	3811	8331	13261	4838	3746	9142	5416	4606
hypoxanthine	619128	265	1663	790	C00262	156151	60148	96616	89435	50849	76017	67025	40362	46845	57844	72426	76586	96213	77306	78371
hydroxycarbamate	325318	278	130396	16639161		7194	10825	15719	6653	7829	3973	8233	8011	12498	10052	3028	6342	9909	6444	2867
homoserine	443878	218	2849	12647	C00263	926	1558	824	1141	1240	966	1191	642	510	1287	1179	890	1047	1162	1232

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BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
homocystine	874865	128	2786	10010	C01817	1167	999	701	905	915	762	576	745	693	1345	1186	1253	843	1324	1042
histidine	663790	154	150	6274	C00135	39680	79114	57838	91053	70722	90779	88667	99934	42444	125161	117466	82667	89146	77946	114633
heptadecanoic acid	751309	117	727	10465		11552	16323	12387	16294	16970	14812	24417	11402	15011	16105	28259	18779	14284	17344	19707
guanosine	954962	324	1966	6802	C00387	3146	1619	5361	3081	2454	2443	2110	2453	1735	2752	3061	4145	2195	4359	3271
guanine	744307	352	2519	764	C00242	6840	3483	3328	2415	1654	3224	2601	1329	2267	2115	2661	3165	2940	2593	3626
glycyl proline	691357	174	18496	3013625		1147	1062	919	717	2045	520	608	1815	1140	1094	1524	432	1265	2607	1213
glycolic acid	227636	177	1971	757	C00160	16665	15743	13880	11019	16057	10394	15159	13651	16266	15134	14016	12668	13098	20407	21899
glycine	368707	248	6	750	C00037	639443	407416	564233	346488	581800	558175	458437	640397	516089	823148	727766	546885	609612	886053	956515
glycerol-alpha-phosphate	590747	357	1687	754	C03189	32770	29004	33888	24780	43150	21495	30773	38768	27447	23567	26631	15798	49654	33472	38342
glycerol-3-galactoside	800205	204	100875	16048618	C05401	4216	2762	7370	9615	3949	4780	8311	6991	6643	3672	10245	5522	11955	15011	3648
glycerol	344466	205	30	753	C00116	255491	389882	383585	586833	414579	376466	1168567	379576	292793	241298	356732	447530	543030	539098	316545
glyceric acid	377308	189	394878	752	C00258	30768	21128	19413	9741	20478	13861	14313	15362	17762	15746	16361	14809	20703	17471	19027
glutaric acid	421260	261	1727	743	C00489	1191	940	966	1042	1150	687	754	702	1061	917	1529	321	865	652	1470
glutamine	600315	156	18	5961	C00064	450968	1578340	816135	1186643	1007891	1606283	1220481	673030	628122	1141935	931738	1103831	865725	532532	798313
glutamic acid	529100	246	28	33032	C00025	118147	94829	65453	74194	69394	73485	51254	47224	34253	85606	79250	65672	71346	67856	74996
glucuronic acid	665901	333	344793	94715	C00191	8070	10103	11352	6466	9711	11341	5286	8009	14356	11262	12438	6316	13051	9373	6958
glucose-6-phosphate	808788	387	360626	5958	C00092	5085	2026	1671	2100	1521	2160	1832	2796	2796	2387	4591	1655	1004	1365	2822
glucose-1-phosphate	594647	217	3167	65533	C00103	4074	5791	2777	2686	3695	6018	3898	5052	4947	3649	4217	3171	2772	3084	3037
glucose	659798	319	22	64689	C00221	4405469	4919942	5326719	3379634	4003403	4681103	3120015	4511505	7004888	5003452	4781652	2546181	3016475	2896951	4179164
gluconic acid lactone	645815	220	3502	7027	C00198	12960	17442	9222	15506	8770	15453	3024	15185	9904	4484	13002	8891	4371	10266	8888
gluconic acid	693148	333	7501	6857417	C00800	91883	105883	62694	102872	45470	77880	7218	93584	66836	7773	73295	56761	25071	70831	47817
galactinol	1017580	204	1975	11727586	C01235	1606	810	4487	607	5516	1103	1054	2073	4541	2457	2099	688	1100	1783	1983
fumaric acid	390775	245	1718	444972	C00122	7521	3527	2575	3419	6114	4110	1545	1585	1135	1529	1494	3530	2281	3073	2308
fucose	578299	160	3009	439650	C02095	10424	12328	11035	6920	9611	10283	8587	9895	14816	10843	7352	6717	6793	7360	7604
fructose	639442	307	21	439709	C02336	394863	482232	691416	298005	378840	484255	278872	478643	969680	695439	675988	176625	228038	232091	449631
ethanolamine	342561	174	342038	700	C00189	45386	40601	48705	42683	48743	35234	29886	29248	51102	34617	29741	33912	48955	34900	18958
erythritol	471922	217	92	222285	C00503	11583	11792	12467	12072	12662	9023	10162	16123	12465	9144	8457	10604	12111	13740	13421
epsilon-caprolactam	353069	170	3101	7768	C06593	9857	13393	10763	13293	11996	6061	16780	8322	6889	12094	17722	14696	11520	8545	10496
docosahexaenoic acid	902819	91	87709	445580	C06429	1595	1614	2144	1566	2987	1728	2673	2294	2972	1913	1611	2495	2506	2246	1494
dihydrocholesterol	1082070	215	42937	66066	C12978	4456	5427	2630	2390	4466	6339	3353	7170	3720	2527	2767	3878	6446	4576	3165
dihydro-3-coumaric acid	582960	192	384891	91	C11457	790	1487	3202	948	2516	2804	1128	1086	2166	2091	1457	1128	1330	1135	1426
cytosine	486724	254	2186	597	C00380	1036	776	1926	1098	744	902	1523	1747	855	1831	1200	1716	1449	1869	2246
cystine	804619	218	94	595	C01420	4209	5880	2301	17199	19518	14518	13397	21701	11043	38380	16938	15936	19609	12805	21849
cysteine	500158	220	65	5862	C00097	6975	8018	5375	14395	10993	5650	6450	8269	7137	15479	16536	11340	12430	4540	13267
creatinine	502599	115	31	588	C00791	131858	232381	127407	164691	216004	167537	175813	226436	130068	136560	144935	158196	153524	343377	211752
conduritol-beta-epoxide	675635	318	2670	9989541		2247	1687	2971	1504	1902	1759	1543	2018	3511	2428	2588	1319	862	2085	4245
citrulline	621404	157	1712	9750	C00327	20458	19558	30941	36131	33037	30754	38460	36316	32827	36357	26776	32930	30618	43076	29769
citric acid	617342	273	288	311	C00158	433230	318165	374976	252452	446983	388323	280448	230554	348303	404011	294865	253824	225427	195154	230126
cis-gondoic acid	847372	367	87783	5282768	C16526	280	700	649	315	1078	663	529	544	711	727	718	664	851	477	492
cholic acid	1109517	253	110403	221493	C05463	1500	753	753	508	587	581	505	982	629	661	798	672	851	874	719
cholesterol	1078536	129	19	5997	C00187	703586	708514	413406	371159	720424	918878	382573	739223	598767	394375	452048	444385	885665	724180	568350
cellobiose	942758	361	120969	6255	C01971	807	332	810	532	627	706	549	513	501	469	1473	576	537	1009	630
capric acid	451790	229	726	2969	C01571	7267	4896	10276	3682	5330	3124	4937	3548	6750	5414	4353	3912	5171	6084	5479
butyrolactam	277199	142	2047	12025		32042	32198	34596	16629	35101	29017	19019	23771	25951	18691	28089	39906	30567	21623	16088
butane-2,3-diol	205778	117	485	262	C03046	140902	49113	117283	105903	114177	117061	216111	144392	107652	88795	99341	197627	190724	149535	152425
beta-sitosterol	1128225	129	3174	222284	C01753	7849	10933	4999	7353	7119	12751	3727	6062	4009	1976	3848	3907	10746	7422	2434
beta-glycerolphosphate	574470	243	22021	2526	C02979	1708	1058	1698	1009	1694	1488	1268	1460	2095	1867	2141	1019	1573	2043	2671
beta-alanine	435564	248	148	239	C00099	5574	5287	7692	1589	4754	3201	2218	3908	5183	3505	4690	2826	4765	4937	6193
benzoic acid	339067	179	36	243	C00180	157935	198073	229075	157365	179984	154733	146206	137691	163177	140124	143294	152526	211549	220074	164518
azelaic acid	610551	317	329430	19347555	C08261	2513	1780	1967	1784	955	1340	1177	1759	2380	1152	3925	1836	1699	2576	2964
aspartic acid	480387	232	79	5960	C00049	51356	24839	33048	18687	20052	17786	22033	11871	11340	23624	23105	23917	29634	28651	26277
asparagine	553743	231	369588	6267	C00152	29674	28931	27082	28109	27840	38392	26412	17593	24674	35081	39579	28079	36378	28583	30591
arachidonic acid	837115	91	64589	444899	C00219	11969	27817	15699	8435	21301	25781	15684	23342	23186	15719	25577	16234	21072	19770	14460
arachidic acid	856421	117	291	10467	C06425	4865	6227	5829	5483	6670	5647	5887	4900	6381	6383	14864	5427	7266	7591	13290
arabitol	572730	103	372446	94154	C01904	9052	7383	15349	7424	13356	7305	7125	11291	11668	9610	6747	6623	6569	25817	14622
aminomalonate	455754	218	413	100714	C00872	24166	18749	25536	13251	25138	15834	20547	39418	44726	46363	9121	17144	35652	31202	12164
alpha-ketoglutarate	507392	198	294	51	C00026	288	573	660	323	416	457	471	541	524	444	418	776	318	518	433
alpha-aminoadipic acid	573295	260	125502	92136	C00956	2289	3145	2158	2994	3571	2644	3196	3071	2574	2804	1977	2472	2112	3900	2371
allantoic acid	726050	259	117021	203	C00499	72987	33368	85408	25330	30664	24163	27181	24839	74528	32053	28802	24202	16943	49894	24245
alanine	243971	116	34178	5950	C00041	1979188	2896544	1646833	3157473	2113457	2479484	2482233	2677507	1439337	2341580	1762690	3098940	2013506	2009902	1551591
adipic acid	474435	111	125	196	C06104	3556	5881	4454	7977	3927	4224	7067	4056	4013	6372	17324	7753	6307	10379	18545
aconitic acid	586815	229	29	643757	C00417	2460	1701	2090	1940	3547	1844	778	388	697	488	884	2417	1877	2049	1056
5-methoxytryptamine	864466	174	284	1833	C05659	80244	32257	82495	58932	57776	54505	79487	68824	85079	99461	46672	59478	44303	20580	49951
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	1408	1455	1614	1378	2521	1350	979	1386	2036	1241	1403	1426	1622	2134	1618
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	904	587	633	686	803	2435	926	1109	621	2148	5099	1215	760	850	5236
5-aminovaleric acid	536657	174	1698	138	C00431	3229	4173	3922	3749	2879	2735	4417	3015	2941	5156	2866	5592	14380	3767	7051
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	1578	2858	1440	849	1187	1020	988	769	1344	988	751	1012	2967	1561	1044
4-hydroxymandelic acid	601658	267	131944	328	C11527	1208	1181	1011	991	1626	698	948	718	1827	1074	1314	967	1714	1582	1799
4-hydroxyhippuric acid	784581	294	12284	151012		241	390	622	228	329	346	231	285	528	384	233	382	280	380	329
3-ureidopropionate	554966	161	107897	111	C02642	1218	1226	2743	2780	2242	919	1068	1283	1418	1659	1500	1070	1356	1278	958
3-phosphoglycerate	610734	227	1667	724	C00597	5333	801	442	526	685	587	441	480	484	621	2356	802	1228	1512	2233
3-phenyllactic acid	516011	193	113643	3848		2284	1416	2463	845	2158	1743	1286	940	2202	1652	668	1433	2917	2923	8986
3-hydroxybutyric acid	278632	191	145501	92135	C01089	26700	55491	24238	29502	78686	88818	136470	59079	55739	39514	87325	94353	53968	11652	62405
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	1158	668	1275	661	837	404	717	660	994	900	870	312	944	1171	1436
3-aminoisobutyric acid	452655	248	12265	64956	C05145	5529	2784	2763	9320	3485	7547	3892	10231	8483	11655	5110	3447	4567	2730	3288
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1036	1605	1926	1011	1720	1305	1036	1119	1574	1381	1715	1312	1415	1579	1535
2-picolinic acid	381532	180	389051	1018	C10164	1284	2400	2210	2228	1969	1441	2809	4595	3146	5763	3863	2840	2503	2988	4035
2-monopalmitin	890356	129	2080	123409		1945	3022	1374	2330	2146	1912	2886	2479	5966	2769	1841	1812	3555	1379	3100
2-ketoisocaproic acid	310761	89	208	70	C00233	2474	3576	2215	3665	786	571	5785	7429	8999	2704	2722	4997	2067	2395	3902
2-hydroxyvaleric acid	309587	131	25922	98009		6348	8064	12495	8735	11988	9487	9296	5316	9190	16811	7269	5946	8164	5626	8147
2-hydroxyglutaric acid	506306	247	2000	43	C02630	2928	4541	5577	4004	5520	2337	3432	4868	5228	4584	2737	4596	4929	3623	4757
2-hydroxybutanoic acid	258161	131	40	440864	C05984	56506	69793	51307	64608	103892	88373	109007	98752	80336	78203	105642	72308	57427	87663	63233
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		4842	8746	5899	6582	5446	5150	8419	8938	5480	6594	5145	8897	5365	7388	6004
2-deoxytetronic acid	433456	189	1208	150929		1989	3180	3512	1704	2976	1814	2558	2781	2776	2856	2324	2288	2183	4250	2163
2-deoxypentitol	521785	231	21714	249377		2229	872	1138	644	1165	1192	1357	893	1404	999	743	1333	1954	1222	1644
2-aminobutyric acid	285825	130	160842	6657	C02721	26557	126681	44091	33208	41094	52875	58521	38231	40083	100097	54883	69887	42049	59035	29976
2,5-dihydroxypyrazine	397526	241	2254	23368901		2141	2296	1272	3768	3429	3002	2563	5260	2787	3510	4012	3778	4621	3564	6026
2,3-dihydroxybutanoic acid	384796	292	31743	250402		1140	4341	3364	3734	2112	1266	1779	1921	2048	1198	1637	1817	1657	2514	967
1-monostearin	959214	203	648	24699	D01947	3295	3789	2940	2005	3014	2727	3355	3017	3712	3200	3306	3140	3817	5077	3104
1-monopalmitin	901749	371	2070	14900	C01885	2463	3168	3166	2349	2864	2606	3819	2904	3407	2969	3081	2644	3035	3180	3018
1-kestose	1123027	361	14692	440080	C03661	525	304	1312	327	1627	384	529	944	3071	1423	1370	379	314	1171	1234

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						Day 0 - CON														
						FMO23	FMO26	FMO31	FMO36	FMO38	FMO4	FMO43	FMO47	FMO48	FMO49	FMO59	FMO6	FMO61	FMO62	FMO64
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	1020	1768	3426	1458	1145	1053	2315	2467	1944	1570	1959	1393	6379	1515	1733
xylose	543267	103	169	135191	C00181	7626	16781	11865	9988	8613	11746	21537	17459	13882	15380	13090	10233	12390	10504	8891
xylitol	567437	217	5857	6912	C00379	2568	3417	5754	6690	3187	4949	11534	3749	2666	3120	2787	3643	2249	3048	4239
xanthine	701688	353	1669	1188	C00385	457	589	542	508	230	798	470	575	250	418	236	1988	358	504	394
valine	313502	144	3	6287	C00183	1262283	1035678	1063744	1076900	1249435	670345	427725	907530	934802	878543	1091805	782017	1216505	1059776	991128
uric acid	730691	441	23	1175	C00366	2693	8376	11121	1867	4212	8219	3171	3648	2458	3436	3750	8827	5221	4181	2519
urea	329351	189	145496	1176	C00086	2758043	1070139	3794371	4280460	2978791	2855007	3118989	3938522	1223657	2814202	3055306	3150531	2560485	3463312	2846349
uracil	385735	241	1664	1174	C00106	6350	5199	3511	3220	3621	7468	5181	2769	1669	3539	4329	4921	5000	4791	5543
tyrosine	671252	218	16	6057	C00082	420225	347266	442296	390381	290090	258617	325073	379272	302210	401522	364185	296791	338955	392534	336262
tryptophan	780482	202	14	6305	C00078	425353	331904	247329	194782	252871	215441	137122	191669	178037	318233	340447	184402	202737	160770	453358
trans-4-hydroxyproline	484934	140	97	5810	C01157	197104	189402	318467	351733	174770	584861	456275	311893	234472	332203	818075	570858	195894	298295	397192
tocopherol gamma-	1026121	223	4545	92729	C02483	813	1922	1788	668	692	1063	886	1582	703	860	742	707	875	1108	813
tocopherol alpha-	1067809	237	100	14985	C02477	16310	34050	28529	41447	33801	24054	61789	99533	55334	36714	20327	10644	22297	45580	43486
thymine	420133	255	1692	1135	C00178	985	369	956	593	694	567	1277	657	465	989	506	972	628	504	550
thymidine	349402	170	87703	5789	C00214	15760	27186	32742	48282	27791	17549	24760	35530	25958	32337	31410	30249	14651	32435	40062
threonine	409568	218	26	6288	C00188	278353	185556	249984	207553	121223	137605	45157	179132	230966	184143	215544	118728	206594	189417	246880
threonic acid	497572	292	172	5460407	C01620	16382	42529	19001	62890	33607	5154	76623	44887	32590	26415	13090	3923	39224	48529	13487
threitol	467595	217	770	169019	C16884	1827	2061	1658	1702	901	2305	3155	2590	1536	1465	1532	1576	1155	2261	1300
taurine	556690	326	411	1123	C00245	170	6440	16336	4942	24558	2636	88428	21693	19322	34266	5378	1817	13403	39318	11188
tartaric acid	534291	292	33985	444305	C00898	630	287	374	415	461	251	359	191	274	434	344	273	245	222	738
tagatose	631835	307	33981	439312	C00795	1725	1699	880	2286	505	2328	1259	970	358	913	954	1746	322	607	684
sucrose	915139	271	173	5988	C00089	367	5905	1365	1675	927	129426	1490	2396	1506	1093	3203	2684	1995	1288	544
succinic acid	370608	247	161	1110	C00042	5334	5430	10288	7544	9426	13843	7844	16328	7084	42377	23694	23015	4760	8665	10964
sophorose	962064	307	132242	441432	C08250	278	429	567	390	338	505	485	701	418	211	328	503	202	368	273
shikimic acid	611100	204	286	8742	C00493	8075	14202	8383	3910	3060	1798	6104	2617	3908	4981	5453	2241	5937	2627	3526
serotonin	863824	174	364413	5202	C00780	96663	62062	51137	52197	82034	192507	104833	73735	77505	78625	68482	100871	70723	103193	35930
serine	395020	204	25	5951	C00065	709813	736988	1239501	1217877	704447	902394	739409	912603	752023	1381137	1056156	941646	1129919	884943	706742
salicylic acid	480699	267	3063	338	C00805	1830	2776	2952	28661	3875	3565	5023	12507	4487	3185	7072	1514	3315	3341	2991
saccharic acid	699211	333	11214	33037	C00818	1237	1638	1683	1573	1194	1378	2802	1357	1106	761	627	983	538	814	1226
ribose	553071	217	384948	10975657		13981	11164	11407	10526	30727	48178	18802	21872	3985	4933	27055	24579	32713	31880	23615
ribonic acid	599680	292	1683	5460677	C01685	4826	5524	8127	4895	1191	5346	1185	13231	6607	3601	17378	4159	4212	3816	5187
ribitol	575497	217	7362	827	C00474	1278	2082	2015	2257	1292	2882	3370	2983	2508	1763	2384	2978	2139	1589	1930
raffinose	1120886	361	3190	439242	C00492	215	1079	1407	626	221	978	343	2230	1331	252	1721	819	445	543	683
pyrophosphate	547021	451	88522	1023	C00013	2472	4236	4327	3600	2793	1843	1866	7145	3841	4354	1298	2361	343	5853	2334
putrescine	588119	174	21703	1045	C00138	5454	8865	13411	7558	5071	5447	10316	10896	13289	7097	7582	5472	7427	7302	7831
pseudo uridine	813899	217	1688	15047	C02067	12429	34860	14203	15418	12076	14547	20659	15100	11865	18706	13444	14484	9166	10968	12744
proline	364716	142	8	145742	C00148	599422	518083	948912	579722	409699	615419	346745	927098	1606824	668533	1172206	626400	1610373	1264585	744923
piperidone	275603	156	34023	12665		8111	1906	13920	9048	4622	3147	2669	2593	1597	4766	3868	16964	3263	3471	110736
pipecolinic acid	404121	156	2448	6931662		1860	3256	9936	3852	2656	3393	2239	1928	2246	2711	5617	1781	2409	2020	4086
pimelic acid	523205	155	33429	385	C02656	1361	1403	1697	2488	1233	1640	2187	1400	1598	1398	1992	354	2323	595	2382
phthalic acid	567345	147	46142	1017	C01606	7850	11643	94058	65473	9412	10058	20183	9029	6562	9512	8052	17587	7221	6810	9779
phosphoethanolamine	603912	299	1723	1015	C00346	2499	3124	9123	8879	2717	2801	5366	8798	3200	3484	3633	3791	1717	8118	3759
phosphate	345365	314	4	1004	C00009	526745	674199	604698	621757	328753	770063	767736	785779	556627	445661	780315	884011	725391	827683	571846
phenylethylamine	510327	174	2005	1001	C05332	156056	9871	196885	42479	44854	11247	20692	7343	9096	17552	27488	9954	124582	43143	23264
phenylalanine	537804	192	33	6140	C00079	240277	209709	329349	250429	121624	166058	159712	225022	153043	229889	289478	192866	169664	201711	238240
pentose	540818	103	360841	229		2693	4097	1863	13629	2725	3145	3224	16178	3232	3063	2331	2960	2569	3936	2475
pelargonic acid	399229	215	50	8158	C01601	35148	29005	26340	34163	28148	15905	24692	24054	21352	31220	18530	22848	14738	26253	20805
palmitoleic acid	706508	311	96	445638	C08362	1608	4404	3569	1332	2108	1178	1681	3780	1790	2677	2749	1464	3646	1670	3573
palmitic acid	713809	313	11	985	C00249	125051	215566	158515	102638	103771	88623	104730	148782	75338	138892	133816	101996	102463	91421	174787
oxoproline	485935	156	10	7405	C01879	726456	951673	684763	823825	471660	582379	1047406	1200069	918227	809842	814776	638991	726007	951568	806982
oxalic acid	260513	190	4923	971	C00209	5390	7401	7990	3383	1428	4382	9012	2841	4218	3302	10121	1865	1812	5974	5388
ornithine 3TMS	527113	142	1821	6262	C00077	248088	155308	382243	286832	110577	198974	105526	126268	95712	227097	386563	231913	148274	210937	245984
oleic acid	779120	339	43	445639	C00712	1567	111314	55989	1459	1150	23739	27165	1936	976	1851	55015	1342	3059	962	62693
oleamide	849710	144	20961	5283387	C19670	18596	37613	13047	18428	13888	20404	34761	16325	32309	23741	19168	20736	30149	15825	34194
nonadecanoic acid	822782	117	46258	12591	C16535	5373	5823	1339	5091	3403	3251	4151	1357	2562	3547	4866	3970	2083	3419	5823
nicotinic acid	353428	180	327312	938	C00253	172041	247061	5030	170339	2306	657433	7186	9467	8381	3606	5125	752788	3326	7769	3058
N-acetylglycine	356109	174	97747	10972		660	2687	791	620	790	1843	940	677	528	1883	1201	1963	907	749	1001
myristic acid	634414	285	127	11005	C06424	6968	6759	14679	21028	6194	3483	3915	6717	3633	4428	4168	7119	3368	3210	4596
myo-inositol	730022	305	1741	892	C00137	297037	122312	227577	217095	248675	212900	248748	218025	159363	240714	380926	233106	157886	256526	257650
mevalonic acid	498785	247	127978	439230		1779	2815	2134	4606	1229	885	1491	1737	821	867	2032	944	12082	1384	674
methionine sulfoxide	637588	128	1678	158980	C02989	39994	83904	173654	105040	47368	36184	140246	149674	204129	98763	141870	30962	128994	98631	128213
methionine	483560	176	45	6137	C00073	264582	432508	208564	52128	89340	60510	207559	327218	376136	129799	193704	48582	70182	65028	90135
methanolphosphate	289520	241	5393	13130		22359	20001	42514	27161	26772	24012	30500	47968	22088	21791	24505	30335	20631	39322	30540
mannose	645856	205	70	18950	C00159	242629	373801	204819	269661	167233	177224	219035	242439	128849	277701	203387	151480	167113	162782	222986
maltose	946601	204	1979	439186	C00208	9521	25063	16221	8246	10686	12212	37854	18603	16641	12184	11162	7019	15979	16057	14923
malonic acid	305372	233	16918	867	C00383	191	471	409	166	298	177	248	308	190	380	369	433	267	479	340
malic acid	463180	233	1391	525	C00711	3643	1462	2848	4540	6006	7933	6724	3605	3799	3677	4797	8630	3430	6254	4496
maleimide	245118	154	1743	10935	C07272	11539	37509	21214	13348	9362	11590	13637	18923	11431	12514	12716	10895	14351	8745	9487
lyxitol	573587	217	233	439255	C00532	8590	11397	18335	12463	7921	14402	11887	17203	10754	9441	18999	16338	7780	10444	8345
lysine	663483	317	12	5962	C00047	109452	138740	43918	48488	57861	29150	15831	22811	13575	104557	66438	25722	29054	38331	81398
linoleic acid	777285	337	471765	5280450	C01595	18269	31583	25907	10740	9490	9699	15306	23523	10530	17587	22398	12202	15519	14567	27688
levoglucosan	569637	204	3169	2724705		1448	1236	1032	2253	712	1295	863	1458	730	520	1084	1494	2167	958	1567
leucine	346101	158	9	6106	C00123	1370312	1115810	1385342	1148930	1226766	670805	654776	1145456	1136291	1012241	1071129	849935	1597900	1109513	926112
lauric acid	547906	117	49	3893	C02679	180083	16627	348926	418181	180837	15066	15578	16073	12545	17885	15599	189869	12534	16453	11933
lanosterol	1129573	393	133475	246983	C01724	389	288	542	251	283	170	553	311	195	256	329	223	1350	554	346
lactose	936998	204	217651	6134	C01970	3467	2317	2513	2627	1469	87593	2689	2610	2783	1250	2333	1269	2597	1253	1391
lactic acid	217657	191	80	612	C01432	2053498	1152436	746641	2735950	4490958	4550634	4514499	1870834	3020132	2805510	747213	4233814	2519982	3298089	2945008
lactamide	265698	232	415	94220		1929	1766	2597	1901	3744	4865	4451	2313	3298	2094	2857	5295	1150	3113	2629
kynurenine	769709	218	210712	25245862	C01718	11676	14230	10700	7540	9947	5930	4972	9625	7208	6572	8356	7942	7926	10794	8820
isothreonic acid	489385	292	1679	151152	C00639	10886	16210	11849	13070	8249	10823	15668	12233	9068	14645	16843	11591	6110	9827	6207
isomaltose	983199	160	127715	439193	C00252	408	1353	394	510	296	227	1185	381	383	300	694	412	529	356	366
isoleucine	359251	158	15	6306	C00407	797322	571888	527024	468518	519729	335255	260321	473458	427647	420946	539653	395491	642396	520964	465157
isocitric acid	616323	245	12267	5318532	C00451	5561	6173	5951	5888	5592	9557	12028	6117	5199	5574	6315	10894	3500	6063	4552
inositol-4-monophosphate	845976	315	4759	440043	C03546	2090	1775	3281	2657	1584	1374	1388	3036	1732	1321	2190	1676	1561	2120	1054
inosine	897434	230	84524	6021	C00294	23916	16004	18124	41331	26648	25817	37338	35328	25420	21844	39914	19776	31182	35573	21420
indoxyl sulfate	577333	277	31543	10258		632	1101	5660	3544	5255	3242	849	1523	1432	2802	3209	1335	2743	6372	1442
indole-3-propionic acid	732249	202	112556	3744		3903	1112	29037	9476	2983	3523	946	1992	6268	10338	12216	18622	3758	3969	7356
indole-3-lactate	764079	202	390397	92904		3792	2826	6908	5060	2845	5402	9059	19425	19391	3849	8190	4718	3458	4390	5338
indole-3-acetate	684929	202	69	802	C00954	9560	4174	16501	4586	2450	4724	22817	11016	4171	8601	6729	4341	6759	6630	32990
hypoxanthine	619128	265	1663	790	C00262	55267	29163	61551	70596	75391	65744	50300	30132	33414	25080	70917	79912	66846	59024	50455
hydroxycarbamate	325318	278	130396	16639161		5372	10918	13167	12034	4394	6699	9626	13489	8940	7208	5822	9279	3663	11166	5924
homoserine	443878	218	2849	12647	C00263	1236	1722	1523	1786	573	794	1658	1030	1379	2017	1503	834	1448	1394	1427
homocystine	874865	128	2786	10010	C01817	1331	3468	1107	783	989	1649	4289	1783	1270	1582	1240	899	768	987	665

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BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	203563	182014	54852	53285	66330	73450	64756	62914	108395	97710	71414	49197	96680	72544	87704
heptadecanoic acid	751309	117	727	10465		15135	22228	17223	15700	10846	10397	12762	14016	11084	13771	15949	11233	9679	8912	18016
guanosine	954962	324	1966	6802	C00387	2576	1644	1584	2466	2683	2214	2900	1527	1155	2035	3721	1916	1750	2998	2306
guanine	744307	352	2519	764	C00242	2477	1177	1739	1228	1461	3735	1461	1011	844	1486	3195	1818	1386	1575	2091
glycyl proline	691357	174	18496	3013625		825	1395	1355	1741	909	1335	1349	1711	622	2764	2247	1375	512	1361	1095
glycolic acid	227636	177	1971	757	C00160	13368	10720	23134	29946	10974	30010	15171	18926	10160	15308	21550	24631	10746	15746	13313
glycine	368707	248	6	750	C00037	546140	813060	1050103	760964	718897	1109956	470795	567551	535367	1846148	1485759	845444	1054772	704584	743777
glycerol-alpha-phosphate	590747	357	1687	754	C03189	21692	23403	30193	25505	13451	24608	21904	33561	15988	25252	31864	26353	15411	25019	35960
glycerol-3-galactoside	800205	204	100875	16048618	C05401	7153	8651	3500	4627	3054	2757	5092	7073	5857	5893	5526	2103	9103	16214	2639
glycerol	344466	205	30	753	C00116	555227	578954	483417	496135	350618	429948	337366	540072	396010	518023	545189	352490	175431	367776	494022
glyceric acid	377308	189	394878	752	C00258	23501	22571	18648	25573	10583	29547	19376	18167	10920	17256	20451	21110	15511	16429	12315
glutaric acid	421260	261	1727	743	C00489	431	983	761	1032	1066	574	627	1141	734	647	835	1041	1227	824	1312
glutamine	600315	156	18	5961	C00064	1406138	1167758	447131	632269	564747	660318	767634	1014386	1477460	651386	702034	523263	1087463	708182	1283939
glutamic acid	529100	246	28	33032	C00025	64244	96072	74447	39195	55230	76311	61169	50258	61477	53547	59568	53757	57515	49271	54134
glucuronic acid	665901	333	344793	94715	C00191	6219	10560	7250	15432	9444	9749	18156	13236	8604	8487	5853	7220	4877	6483	8490
glucose-6-phosphate	808788	387	360626	5958	C00092	5124	2515	1690	2582	3870	2013	1301	1780	1608	1509	2425	1623	1736	1951	1731
glucose-1-phosphate	594647	217	3167	65533	C00103	3776	4659	3127	4049	3211	3810	4156	1908	2035	639	4892	3734	2344	3151	2667
glucose	659798	319	22	64689	C00221	2796666	4070435	3712511	3665107	3780012	3112959	3644662	3865745	2642940	3205727	3169130	2761872	2622890	3075457	3237135
gluconic acid lactone	645815	220	3502	7027	C00198	12383	8840	16236	9715	14503	15932	25466	13097	2471	12637	23553	15431	4913	11556	8985
gluconic acid	693148	333	7501	6857417	C00800	70709	39966	132619	62776	121638	94385	154294	73866	11877	60750	129686	93773	17160	72206	47616
galactinol	1017580	204	1975	11727586	C01235	800	1032	2220	1600	707	1571	6516	4530	2968	1474	1823	1536	2457	2347	1269
fumaric acid	390775	245	1718	444972	C00122	1175	1910	4398	1731	3553	1285	2952	2263	2054	2410	2654	1645	2981	2231	2431
fucose	578299	160	3009	439650	C02095	6675	10533	9658	8883	10080	5396	7821	8410	7081	7823	8349	6828	13168	8077	7040
fructose	639442	307	21	439709	C02336	203215	342183	261871	300989	152577	287044	239809	332684	128365	268177	273919	205894	144162	204879	242399
ethanolamine	342561	174	342038	700	C00189	28690	31779	45162	39705	37312	37331	37921	34008	28710	39224	41918	60922	34896	52363	49451
erythritol	471922	217	92	222285	C00503	9898	18125	12897	13256	7886	13378	18975	16644	13723	9952	10737	18126	7192	9379	7503
epsilon-caprolactam	353069	170	3101	7768	C06593	6415	15679	5682	13820	6391	7353	9253	6412	13595	7179	5176	5191	9748	7331	11898
docosahexaenoic acid	902819	91	87709	445580	C06429	1721	4846	1906	2160	1502	2249	2975	1986	2015	1921	2743	2361	3181	2799	3239
dihydrocholesterol	1082070	215	42937	66066	C12978	2327	4555	3112	7185	3901	7952	6174	4715	1878	4491	3301	14287	1418	4839	5211
dihydro-3-coumaric acid	582960	192	384891	91	C11457	988	1168	1595	1399	876	1090	998	1310	755	1345	1591	917	787	1292	2039
cytosine	486724	254	2186	597	C00380	1031	1997	2823	2244	936	1023	950	1422	821	1804	1796	1667	1422	460	1969
cystine	804619	218	94	595	C01420	14056	37940	14002	25712	17940	11858	16967	8022	7619	25416	9515	6270	6838	6394	9586
cysteine	500158	220	65	5862	C00097	8331	15415	3622	4653	10268	4935	16919	4475	10817	10229	7253	4669	3055	6042	6803
creatinine	502599	115	31	588	C00791	189153	56530	113255	121676	58849	109753	67804	60510	62044	150355	225376	77654	79346	85568	159716
conduritol-beta-epoxide	675635	318	2670	9989541		1394	1705	2730	1559	2080	1653	1624	1783	1396	2108	2503	1347	881	1075	1844
citrulline	621404	157	1712	9750	C00327	37697	41269	46134	64683	20673	45503	28677	38093	26047	48363	62044	40279	25879	36560	42339
citric acid	617342	273	288	311	C00158	213890	300560	327558	296738	285772	437757	604988	306127	266870	301242	321816	532385	195393	351911	249606
cis-gondoic acid	847372	367	87783	5282768	C16526	325	949	832	998	219	385	383	752	391	696	570	495	510	414	402
cholic acid	1109517	253	110403	221493	C05463	438	948	629	983	1207	828	3987	1793	817	532	523	656	592	1190	558
cholesterol	1078536	129	19	5997	C00187	638002	812459	666304	482130	498247	514740	898652	877088	414743	563982	622039	702651	504420	823664	799505
cellobiose	942758	361	120969	6255	C01971	640	1300	689	394	240	631	1379	501	445	538	793	329	620	570	679
capric acid	451790	229	726	2969	C01571	13944	5416	9068	10575	12090	3982	5001	5251	3812	5306	4601	7040	3629	4724	4667
butyrolactam	277199	142	2047	12025		31955	29087	37100	35380	29568	24108	23710	32364	20248	22747	29686	28189	11418	29097	17285
butane-2,3-diol	205778	117	485	262	C03046	129026	72178	287806	176255	320385	299614	274648	132126	145314	87262	114789	468971	137298	196048	167715
beta-sitosterol	1128225	129	3174	222284	C01753	4731	7875	5199	3276	1987	2190	5824	9163	3988	4960	3323	4020	2416	6171	1765
beta-glycerolphosphate	574470	243	22021	2526	C02979	1385	1051	1999	1801	868	1635	1008	536	816	909	1498	1919	732	1317	1257
beta-alanine	435564	248	148	239	C00099	1418	2722	7369	3579	1306	4434	1723	5310	903	4517	2726	4544	1429	3870	2815
benzoic acid	339067	179	36	243	C00180	111174	153453	171475	406884	125761	147179	164090	232042	154564	180661	207789	127483	147447	205055	170841
azelaic acid	610551	317	329430	19347555	C08261	1483	1536	2760	2413	1114	1156	1597	1415	1084	1212	1467	1645	2178	1039	1995
aspartic acid	480387	232	79	5960	C00049	30815	32165	24682	21925	22591	20358	20559	21971	21211	22454	22404	14993	26262	20561	21354
asparagine	553743	231	369588	6267	C00152	70920	65136	36061	28422	24734	24356	31631	44581	56792	43049	35552	20565	43168	29973	42369
arachidonic acid	837115	91	64589	444899	C00219	10963	12200	13835	13698	15956	9957	13917	19691	8273	22323	15827	8254	9952	18857	36272
arachidic acid	856421	117	291	10467	C06425	6026	9107	7499	6417	3590	4673	6746	7586	4259	8090	7281	5826	7030	5975	6306
arabitol	572730	103	372446	94154	C01904	4130	7961	13740	9514	5630	9976	9717	13408	8961	7934	17631	12052	5569	7125	8454
aminomalonate	455754	218	413	100714	C00872	21225	40532	76150	49588	20173	75725	20661	26562	24552	76232	51402	70735	21477	44072	23114
alpha-ketoglutarate	507392	198	294	51	C00026	1198	1599	637	562	354	977	666	639	388	390	413	7836	379	483	550
alpha-aminoadipic acid	573295	260	125502	92136	C00956	3798	3025	3419	2585	2816	2562	2155	1459	1287	4203	3035	2442	1660	2166	1944
allantoic acid	726050	259	117021	203	C00499	26221	48646	26855	28903	27454	28469	36471	30663	21592	53789	41366	29322	23547	24247	26804
alanine	243971	116	34178	5950	C00041	2441249	1879558	2186152	1578688	2485068	1397617	1575401	1939545	3188572	1920473	2042105	1735470	2697925	1907344	2180926
adipic acid	474435	111	125	196	C06104	3328	3527	4259	4313	2886	3325	5476	3076	2835	2851	3766	3149	10695	2432	6397
aconitic acid	586815	229	29	643757	C00417	631	2706	2496	1894	2186	565	3632	5986	4035	3592	2220	586	1652	1933	1867
5-methoxytryptamine	864466	174	284	1833	C05659	116882	77592	41490	65315	101835	156641	129882	60454	62976	62085	54216	83003	56811	83590	28487
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	1034	714	1053	2336	679	1600	791	1390	838	962	2011	1405	944	1563	1018
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	2555	1423	838	503	1066	1914	1700	968	1715	842	1540	484	2863	706	900
5-aminovaleric acid	536657	174	1698	138	C00431	6119	9582	30230	9173	10947	2787	38905	14737	11682	10803	30000	12795	55077	52986	10525
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	2153	4159	3808	1864	1825	2467	5280	6042	4090	1421	1612	1438	3388	4785	894
4-hydroxymandelic acid	601658	267	131944	328	C11527	1563	1376	993	1226	710	1594	1171	2143	1258	1228	1422	1091	1557	1292	814
4-hydroxyhippuric acid	784581	294	12284	151012		1223	357	693	806	242	455	429	294	310	223	195	277	348	294	315
3-ureidopropionate	554966	161	107897	111	C02642	2207	2067	1549	1460	1785	2812	1069	1500	1819	1914	1506	550	1765	1758	1180
3-phosphoglycerate	610734	227	1667	724	C00597	728	901	674	697	292	742	802	717	449	665	1343	1253	875	1315	799
3-phenyllactic acid	516011	193	113643	3848		858	2110	9397	1843	464	1688	3392	3084	3128	811	2038	1432	4005	2959	659
3-hydroxybutyric acid	278632	191	145501	92135	C01089	106052	319328	94760	68218	244790	64084	214466	89605	78797	67348	69161	81655	32933	70882	83793
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	743	523	584	603	772	369	871	681	351	173	666	676	356	509	301
3-aminoisobutyric acid	452655	248	12265	64956	C05145	12753	39399	3795	20444	2526	16700	2438	2409	2113	3743	2938	12709	5512	10926	4968
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1038	969	2663	2038	930	822	1040	1838	1198	1467	983	1280	1589	2350	1711
2-picolinic acid	381532	180	389051	1018	C10164	2400	2506	1878	3322	1677	3417	2080	2411	2317	1782	1851	2776	2475	1750	2064
2-monopalmitin	890356	129	2080	123409		26613	2931	2867	2234	1941	2907	1764	2224	2357	1811	2195	2023	1645	1814	1734
2-ketoisocaproic acid	310761	89	208	70	C00233	16365	12901	2852	1256	4738	9630	2396	5890	4221	2909	3148	28487	4416	4565	1911
2-hydroxyvaleric acid	309587	131	25922	98009		18244	13401	15670	16557	6574	11889	8155	10016	6051	6060	8274	9100	12887	9119	7186
2-hydroxyglutaric acid	506306	247	2000	43	C02630	9119	13338	15268	28797	6283	12384	9944	13144	9537	6183	16598	12093	14101	14460	10054
2-hydroxybutanoic acid	258161	131	40	440864	C05984	81458	111026	107184	42087	67226	67062	291863	92932	109815	55096	143667	69968	54713	44717	70793
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		13148	16399	7281	9809	7377	7889	7766	14125	26284	11579	16236	6490	6642	9181	17570
2-deoxytetronic acid	433456	189	1208	150929		6907	8353	3938	7829	2382	4034	4777	5677	2366	5084	6268	3943	4214	5658	4935
2-deoxypentitol	521785	231	21714	249377		691	1501	1413	1088	1174	1163	1918	1262	1141	1012	890	1393	1029	1213	929
2-aminobutyric acid	285825	130	160842	6657	C02721	63538	123610	62537	35787	70470	18699	81553	60026	89046	46716	70316	13694	61608	38073	47331
2,5-dihydroxypyrazine	397526	241	2254	23368901		5092	6447	3395	4885	2553	2043	9512	3091	3119	5285	4283	2768	2963	3422	2800
2,3-dihydroxybutanoic acid	384796	292	31743	250402		3115	3336	1962	2466	1285	1948	1930	2233	2453	1596	3393	2009	867	1893	2665
1-monostearin	959214	203	648	24699	D01947	4929	4378	4782	6144	4309	7511	4149	3558	4047	4218	3090	5668	2440	4529	3569
1-monopalmitin	901749	371	2070	14900	C01885	1905	2981	3781	7179	2773	4910	3031	3961	4828	2807	3314	4075	3021	5365	3712
1-kestose	1123027	361	14692	440080	C03661	215	482	1055	327	232	827	559	1987	1682	196	1449	828	1041	1030	426

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						FMO23	FMO26	FMO31	FMO36	FMO38	FMO4	FMO43	FMO47	FMO48	FMO49	FMO59	FMO6	FMO61	FMO62	FMO64
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	2581	1990	1888	1869	1871	1224	1909	1771	2439	1859	2345	4014	4341	2163	1938
xylose	543267	103	169	135191	C00181	7570	11173	8335	11515	7202	10392	13020	10300	12383	10496	14370	15496	13117	12744	11867
xylitol	567437	217	5857	6912	C00379	2962	3097	3606	4565	2804	3416	4213	2661	5147	3633	5351	3210	2560	2890	5291
xanthine	701688	353	1669	1188	C00385	990	379	914	782	508	655	486	395	702	309	643	876	423	949	618
valine	313502	144	3	6287	C00183	789647	1179394	942008	918012	1363557	670741	748309	990733	764667	1022356	695730	843262	716866	824129	819236
uric acid	730691	441	23	1175	C00366	5825	3093	8055	2534	5902	6376	3028	2768	7320	4127	3092	3509	6773	8336	5340
urea	329351	189	145496	1176	C00086	3576059	225497	3310528	403202	2533209	2675249	4567136	374706	2130026	3230149	4504981	3071063	3019249	2893420	4430031
uracil	385735	241	1664	1174	C00106	5884	3529	2808	2031	2993	6364	4268	3638	3881	2250	5087	7590	4744	5514	6302
tyrosine	671252	218	16	6057	C00082	282115	351664	373744	464702	331563	303092	545423	353530	325603	429977	594671	399218	205181	234277	488589
tryptophan	780482	202	14	6305	C00078	218503	76794	398899	347283	434522	286578	570571	351942	302162	434314	415933	314653	200741	212803	598198
trans-4-hydroxyproline	484934	140	97	5810	C01157	374302	311227	412144	397866	451565	549624	475102	397093	290611	284177	447977	631059	528007	503797	898318
tocopherol gamma-	1026121	223	4545	92729	C02483	968	1277	1791	1665	2096	1042	2064	1425	1012	1113	841	2097	858	729	829
tocopherol alpha-	1067809	237	100	14985	C02477	13470	6920	15698	26184	26126	32809	27742	20523	14816	19165	25119	36954	9014	20921	44508
thymine	420133	255	1692	1135	C00178	1103	1097	947	472	604	802	417	491	589	541	669	780	552	578	1045
thymidine	349402	170	87703	5789	C00214	22118	24671	40559	43576	37274	33214	53930	40165	56894	33711	30303	33796	29579	40646	57017
threonine	409568	218	26	6288	C00188	178753	47443	261918	245448	332564	174366	267338	208300	189933	279016	212373	414809	154559	161209	185477
threonic acid	497572	292	172	5460407	C01620	11106	36700	12887	10401	20397	9738	25885	8749	9728	13928	17684	7630	25832	27486	6325
threitol	467595	217	770	169019	C16884	2282	1677	1487	2362	1208	1260	1511	2033	1443	2560	1573	1462	2138	1648	1277
taurine	556690	326	411	1123	C00245	3994	23943	62564	3300	28745	15410	7981	10320	5601	5919	43412	21905	179	24295	12537
tartaric acid	534291	292	33985	444305	C00898	603	367	271	433	280	336	882	453	377	269	370	449	264	225	385
tagatose	631835	307	33981	439312	C00795	1333	1884	931	838	786	1546	898	842	550	1331	617	6588	807	882	1295
sucrose	915139	271	173	5988	C00089	1800	1022	2884	2435	3342	2590	4115	3354	900	1084	673	1499	3354	2691	1852
succinic acid	370608	247	161	1110	C00042	6369	6289	11773	8410	9998	10158	21339	8612	12430	7244	10540	7235	9118	7924	14103
sophorose	962064	307	132242	441432	C08250	132	441	254	452	72	363	328	672	338	478	411	495	205	295	384
shikimic acid	611100	204	286	8742	C00493	12819	2624	5377	8561	2305	1372	13817	2984	2381	9470	4700	2978	4423	2851	7402
serotonin	863824	174	364413	5202	C00780	63220	127389	74271	100736	82807	133292	166414	28253	72075	48772	105840	125733	61315	68573	27895
serine	395020	204	25	5951	C00065	625924	1411639	899159	852005	668432	683711	884774	747756	655226	853215	869654	1060881	1310570	710429	1060706
salicylic acid	480699	267	3063	338	C00805	2766	2318	4782	14779	2818	2946	4849	5201	6152	4442	9109	1944	2864	5750	14065
saccharic acid	699211	333	11214	33037	C00818	865	1130	1175	909	1494	908	1433	3500	1242	920	914	1066	1267	676	1109
ribose	553071	217	384948	10975657		10501	15705	5323	15198	36051	18712	25328	22544	54945	15805	36004	21078	32422	4049	50409
ribonic acid	599680	292	1683	5460677	C01685	3279	3218	7667	9183	2813	3541	3989	3725	4682	5718	6774	1687	4433	3254	3113
ribitol	575497	217	7362	827	C00474	1463	2603	1896	1569	2175	1531	1903	2030	2341	1853	1580	1610	2748	1667	2076
raffinose	1120886	361	3190	439242	C00492	1570	1327	5000	6214	3829	2819	1699	3620	551	1373	522	1203	1406	1427	1420
pyrophosphate	547021	451	88522	1023	C00013	1091	7214	5352	1870	4371	2757	5383	3586	3747	1655	5903	4563	1249	1660	4647
putrescine	588119	174	21703	1045	C00138	4652	13252	10945	1870	8938	4505	10273	5505	4019	9299	7625	4893	7179	9790	7752
pseudo uridine	813899	217	1688	15047	C02067	13676	16733	19203	18914	12819	17514	16471	16570	19920	19355	20741	17228	15936	21945	18306
proline	364716	142	8	145742	C00148	800927	1032583	900463	652149	1125341	740201	364678	690779	254305	683689	232398	1379300	689502	991025	832403
piperidone	275603	156	34023	12665		9061	41618	5855	5511	8570	3325	4335	7023	3194	1880	14704	7711	2125	6212	8674
pipecolinic acid	404121	156	2448	6931662		4108	5189	4525	5045	13279	2917	1306	2001	2476	2874	1460	3361	2032	5473	3674
pimelic acid	523205	155	33429	385	C02656	1486	1320	670	691	1571	1444	1165	1791	2184	1412	1344	1508	1932	1184	2668
phthalic acid	567345	147	46142	1017	C01606	9783	7103	20645	7938	10661	8127	62955	14301	37427	9628	12130	7348	5382	11210	9380
phosphoethanolamine	603912	299	1723	1015	C00346	979	3668	9438	771	3068	2645	10210	3289	4292	2915	15699	1763	6216	3564	9110
phosphate	345365	314	4	1004	C00009	590696	715217	525434	710542	585771	719891	1285367	730593	718768	470124	1196172	840221	796964	540000	684271
phenylethylamine	510327	174	2005	1001	C05332	24929	58145	38655	16161	20904	18545	15796	25092	10536	18417	17865	30557	73147	69033	34673
phenylalanine	537804	192	33	6140	C00079	198806	162408	256911	202607	162943	188258	295484	175734	163842	234601	312865	184159	182092	170458	301753
pentose	540818	103	360841	229		2253	2321	3101	2475	2098	2871	1973	2535	3619	3792	2872	2427	3769	3624	2336
pelargonic acid	399229	215	50	8158	C01601	13653	18342	36702	30636	22051	15583	31374	22850	22523	29998	24644	16357	23831	19792	34142
palmitoleic acid	706508	311	96	445638	C08362	4289	3258	2775	8397	1273	1589	4465	1037	2053	1741	2380	2228	2135	3178	1920
palmitic acid	713809	313	11	985	C00249	161745	107027	124804	245799	77196	104252	194331	80392	105653	137714	154876	115563	91123	158019	161251
oxoproline	485935	156	10	7405	C01879	696873	778608	905203	952612	681663	1006570	1096938	904525	831765	804199	927016	917944	715860	894524	1198070
oxalic acid	260513	190	4923	971	C00209	7067	8589	5129	6162	6267	6119	4699	3683	5412	3502	10002	4225	7594	6540	5692
ornithine 3TMS	527113	142	1821	6262	C00077	204695	312341	299682	162226	172276	150605	313514	154924	107719	205093	281951	270866	179850	188650	251054
oleic acid	779120	339	43	445639	C00712	53296	1399	38703	107448	15631	26624	2737	19679	1329	1585	45075	3725	1765	73335	2822
oleamide	849710	144	20961	5283387	C19670	33830	19741	27732	27404	19648	35804	18127	23571	15251	25549	19170	24641	10325	35790	17020
nonadecanoic acid	822782	117	46258	12591	C16535	4766	3681	3375	7614	2360	5732	8571	4356	3658	4439	5149	6429	4492	6007	5134
nicotinic acid	353428	180	327312	938	C00253	144006	287352	3901	27127	3623	172643	6799	7933	6172	2773	7997	258031	4779	3096	30804
N-acetylglycine	356109	174	97747	10972		1512	1929	607	647	1243	1098	2208	1115	1107	578	1394	1406	1579	961	1122
myristic acid	634414	285	127	11005	C06424	4729	3206	8271	7253	2677	3130	16328	2409	11309	3957	4831	3087	3504	4972	5712
myo-inositol	730022	305	1741	892	C00137	218313	254029	437016	195652	338640	378325	338701	207995	422348	171831	522413	171671	397203	500830	330737
mevalonic acid	498785	247	127978	439230		1010	3575	1019	616	806	899	3596	748	4534	588	1502	1399	5648	1631	1066
methionine sulfoxide	637588	128	1678	158980	C02989	55983	61056	144784	137607	117470	60094	145662	64739	36171	121432	97766	66781	83489	115624	94396
methionine	483560	176	45	6137	C00073	238621	213432	142034	95522	151776	145348	100556	84097	100906	85361	63163	214300	146277	114632	168642
methanolphosphate	289520	241	5393	13130		28247	27502	28916	26491	34292	36458	34694	26681	17682	21161	31464	42960	20497	24643	38911
mannose	645856	205	70	18950	C00159	183341	199547	156922	249828	102738	195844	211803	177149	179207	338199	220193	134449	169413	153041	205015
maltose	946601	204	1979	439186	C00208	10849	10763	5215	3830	15157	8255	19107	19946	12080	5249	12934	7220	8405	5567	10627
malonic acid	305372	233	16918	867	C00383	529	427	588	118	527	459	744	587	280	571	603	226	312	36	483
malic acid	463180	233	1391	525	C00711	7237	3210	4565	4786	5693	5410	4489	3725	6600	2372	6718	1744	3094	4942	5872
maleimide	245118	154	1743	10935	C07272	8967	10666	11943	13471	11960	7110	11889	10784	15792	18541	7647	17251	14180	10038	13881
lyxitol	573587	217	233	439255	C00532	22240	10672	16819	10999	28744	16027	25721	11351	14639	14038	12959	14064	17456	14504	15058
lysine	663483	317	12	5962	C00047	15981	59077	64960	51489	28950	25797	51413	44454	47945	64978	67709	38204	34233	45835	62880
linoleic acid	777285	337	471765	5280450	C01595	29166	23580	20884	38450	14332	15494	38874	12369	15548	16835	18332	19993	14898	25892	17555
levoglucosan	569637	204	3169	2724705		3670	843	747	1140	649	804	984	1327	2439	902	884	1219	1017	1949	1383
leucine	346101	158	9	6106	C00123	1255799	1510936	1400579	1090692	1816764	863536	1265335	983052	874236	1185061	1005195	1069444	925160	812274	917404
lauric acid	547906	117	49	3893	C02679	11788	8276	231507	23286	9575	10556	342164	13686	256237	15707	17848	14569	17013	12864	21043
lanosterol	1129573	393	133475	246983	C01724	364	344	274	329	207	201	297	342	291	388	208	279	680	308	559
lactose	936998	204	217651	6134	C01970	3060	1209	1192	1703	1496	1457	3845	3237	1517	1921	1786	1544	1599	1102	3309
lactic acid	217657	191	80	612	C01432	4085249	547097	2874900	2276629	3280831	4288842	1616782	4061924	4285045	2042716	2846214	2118875	3215684	3437735	782762
lactamide	265698	232	415	94220		3709	2267	3134	2424	2552	3845	2612	3581	4250	2251	2556	2584	2391	3557	3961
kynurenine	769709	218	210712	25245862	C01718	6981	9386	10252	6923	8528	7790	9883	10899	9807	14703	10237	7136	10983	10474	12649
isothreonic acid	489385	292	1679	151152	C00639	9142	12360	10087	8608	8711	8998	11787	10692	13277	10020	12598	9596	9567	12126	10783
isomaltose	983199	160	127715	439193	C00252	296	668	369	496	460	154	1011	507	601	537	455	316	329	322	659
isoleucine	359251	158	15	6306	C00407	427093	479174	460818	346708	540296	369933	588496	497485	440119	464306	554576	415178	446186	390750	397641
isocitric acid	616323	245	12267	5318532	C00451	6719	4351	7546	8961	6812	7035	8157	5932	8817	3856	9031	6374	6042	7675	6900
inositol-4-monophosphate	845976	315	4759	440043	C03546	1309	1906	2022	2152	2177	1852	3806	1748	2148	1663	2256	3080	1919	1114	1930
inosine	897434	230	84524	6021	C00294	40724	36482	33134	45056	29657	27545	39162	13204	22384	14604	48602	16463	22115	35226	20351
indoxyl sulfate	577333	277	31543	10258		2185	3411	2399	3083	1666	2277	4313	6014	7674	1227	12465	1629	7803	3023	3146
indole-3-propionic acid	732249	202	112556	3744		11994	10132	6392	9640	11202	9943	11145	6991	15386	5280	9889	8493	4591	4632	6516
indole-3-lactate	764079	202	390397	92904		5174	6805	5552	8287	10545	6352	8769	4557	4297	5480	8115	7377	4431	3508	8847
indole-3-acetate	684929	202	69	802	C00954	6602	3353	7553	5300	11418	4251	8809	7809	16277	7525	5362	6219	11763	4471	42625
hypoxanthine	619128	265	1663	790	C00262	83846	47379	65485	55916	47508	53162	51643	28569	59723	19438	106435	61076	32244	80936	88876
hydroxycarbamate	325318	278	130396	16639161		2035	6700	15197	4446	7889	3582	7550	9755	5545	9920	9938	6149	8685	5232	12851
homoserine	443878	218	2849	12647	C00263	1179	1725	979	1293	775	1479	832	822	1144	1734	1056	1096	1606	1011	1586
homocystine	874865	128	2786	10010	C01817	1513	1649	1824	882	1094	816	1228	1175	1392	1532	1191	1517	1006	935	1430

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						Day 28 - CON														
						FMO23	FMO26	FMO31	FMO36	FMO38	FMO4	FMO43	FMO47	FMO48	FMO49	FMO59	FMO6	FMO61	FMO62	FMO64
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	107350	124524	74789	91970	57739	105256	81808	67303	90859	93589	70100	151094	34365	72131	66523
heptadecanoic acid	751309	117	727	10465		21138	13704	12505	27082	9019	11907	20604	9485	13843	13811	22200	11441	17128	20666	16707
guanosine	954962	324	1966	6802	C00387	2633	2704	2246	4385	3124	2828	3889	1159	2022	1353	6179	1654	2246	2488	2125
guanine	744307	352	2519	764	C00242	2288	1045	1335	1078	1628	3218	1408	1857	2300	1249	3749	2236	1879	1686	4111
glycyl proline	691357	174	18496	3013625		1416	1626	1338	1011	1241	893	1648	1288	695	708	1333	1437	2191	1357	1287
glycolic acid	227636	177	1971	757	C00160	18522	12276	18170	12362	13418	16080	30514	15704	15483	14624	17180	20552	18435	15403	25551
glycine	368707	248	6	750	C00037	891461	1219071	802657	876854	640679	1132302	736764	600167	529794	726201	686665	1121913	1121793	1193391	1033497
glycerol-alpha-phosphate	590747	357	1687	754	C03189	32796	23781	20634	30822	41547	29937	48544	19929	12746	25267	29994	39595	19541	25677	39050
glycerol-3-galactoside	800205	204	100875	16048618	C05401	14092	3384	4439	4033	4573	2159	5745	2737	3990	8726	3409	3884	3240	3137	5663
glycerol	344466	205	30	753	C00116	531334	327212	384680	595837	335522	383381	706200	405184	538402	403364	417665	391778	238058	280315	342765
glyceric acid	377308	189	394878	752	C00258	18115	24295	16377	12658	15335	16337	20124	10747	13392	12962	22584	24318	13695	14594	18245
glutaric acid	421260	261	1727	743	C00489	2126	1046	775	1764	306	515	726	759	741	595	970	424	587	930	883
glutamine	600315	156	18	5961	C00064	655901	686550	514614	1344711	509234	908251	626636	1188740	1257057	1171166	467620	738076	434950	727133	934972
glutamic acid	529100	246	28	33032	C00025	42327	69008	70341	51275	59797	69531	31473	50662	64955	41761	38337	57640	33869	59207	77434
glucuronic acid	665901	333	344793	94715	C00191	6012	5254	7012	9457	9038	6368	8118	8414	10068	8263	9606	9365	8655	7262	9300
glucose-6-phosphate	808788	387	360626	5958	C00092	2146	2279	1406	1285	1264	1764	1805	1410	1485	1780	1561	2427	1175	1443	1260
glucose-1-phosphate	594647	217	3167	65533	C00103	4353	3457	2598	4960	1955	2297	3523	2693	2795	5518	5337	2444	1995	3228	4458
glucose	659798	319	22	64689	C00221	2987176	3733427	2998324	3360611	2812386	2508815	3746734	2948434	3493751	4271792	3119811	2893008	2972307	2785112	3246263
gluconic acid lactone	645815	220	3502	7027	C00198	27341	12014	7857	5490	7882	12822	8573	11250	5047	6607	21352	5118	4988	14226	6100
gluconic acid	693148	333	7501	6857417	C00800	205535	88951	46663	22278	46859	62817	58905	65385	19600	11829	143769	24797	22108	84643	34174
galactinol	1017580	204	1975	11727586	C01235	1532	1399	5353	4273	2979	2364	3017	3173	2041	1931	1957	1677	1931	1740	2073
fumaric acid	390775	245	1718	444972	C00122	1412	1184	2531	2201	2398	1592	2622	1504	2928	2121	2980	1438	4043	3340	710
fucose	578299	160	3009	439650	C02095	5761	9359	8326	7182	4997	7073	9059	9244	10101	8793	8729	6808	16407	6829	7536
fructose	639442	307	21	439709	C02336	233538	234419	261487	249782	234093	193446	303022	194815	211944	434630	286457	215996	211881	232314	299045
ethanolamine	342561	174	342038	700	C00189	17201	34998	41110	37512	47498	35720	88227	27728	53770	30350	53985	51447	56030	23604	53957
erythritol	471922	217	92	222285	C00503	12637	15242	11706	11131	12124	10668	16550	12262	14433	12925	14000	12200	11491	12380	11714
epsilon-caprolactam	353069	170	3101	7768	C06593	6440	9844	9416	14983	8780	8294	2355	9412	5485	8978	2220	11442	2960	10853	9990
docosahexaenoic acid	902819	91	87709	445580	C06429	2844	3002	2550	2527	2241	1930	1727	2775	2087	3064	2957	2185	2827	1437	2429
dihydrocholesterol	1082070	215	42937	66066	C12978	2126	1583	3474	6634	8216	5842	6510	6156	1781	8932	5323	6742	968	3108	5675
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1245	1160	1229	1507	1382	905	1680	1450	2875	1626	1457	1075	1516	1400	2387
cytosine	486724	254	2186	597	C00380	2256	2078	2334	1223	1709	1486	835	888	1078	2391	1453	2499	2092	2340	2054
cystine	804619	218	94	595	C01420	13042	15979	7233	24815	10599	16449	32151	7066	10324	21221	28618	22997	3389	9903	23538
cysteine	500158	220	65	5862	C00097	10756	6934	7557	6090	9456	8717	1590	6926	8026	5246	3829	13267	2721	8030	10572
creatinine	502599	115	31	588	C00791	168165	55738	116206	161788	141890	129152	96384	68244	77260	122940	81772	133613	116548	128586	200690
conduritol-beta-epoxide	675635	318	2670	9989541		2252	3942	1607	1374	3274	2119	2312	2890	1861	1639	1061	2017	1284	995	2304
citrulline	621404	157	1712	9750	C00327	24730	38653	63475	47862	28657	38863	52790	43902	35971	52970	55704	49470	45721	37501	65854
citric acid	617342	273	288	311	C00158	340867	207336	324184	389255	329598	319319	426454	296944	429300	208153	446206	200999	305763	440629	337988
cis-gondoic acid	847372	367	87783	5282768	C16526	724	755	417	312	204	474	880	375	468	630	456	591	561	965	617
cholic acid	1109517	253	110403	221493	C05463	552	1088	753	1179	668	683	1242	980	629	974	601	964	793	441	615
cholesterol	1078536	129	19	5997	C00187	516568	465865	589580	633111	1013210	711563	826828	721176	397851	748886	670056	957465	470237	547378	856781
cellobiose	942758	361	120969	6255	C01971	905	477	606	540	872	467	1433	947	520	796	782	421	421	406	721
capric acid	451790	229	726	2969	C01571	4374	4637	10528	5349	3840	3720	8605	4687	7315	5170	5980	2976	4830	5239	7235
butyrolactam	277199	142	2047	12025		18630	35084	34043	39515	29000	25928	48863	31327	33441	37362	39676	25169	34623	31991	35759
butane-2,3-diol	205778	117	485	262	C03046	310917	196497	152414	135783	188837	270361	122875	197779	216813	130087	209711	126323	219303	191686	254547
beta-sitosterol	1128225	129	3174	222284	C01753	4581	2627	4720	7195	9539	5295	5562	10061	5760	13429	4012	9191	1617	2172	3536
beta-glycerolphosphate	574470	243	22021	2526	C02979	1630	1112	1495	1559	1311	1566	1540	901	1051	1034	1082	1248	1955	1576	1796
beta-alanine	435564	248	148	239	C00099	944	2735	4532	2711	4004	2468	5287	4575	4117	4371	5886	2172	6990	2842	3622
benzoic acid	339067	179	36	243	C00180	128087	141115	196586	229627	141877	124133	218136	201502	198533	205935	212423	142895	148707	195208	268214
azelaic acid	610551	317	329430	19347555	C08261	2567	1114	1951	1714	978	1118	1690	1382	1455	1248	913	1731	1339	2621	2254
aspartic acid	480387	232	79	5960	C00049	10704	20486	28925	20064	22370	26804	25012	27876	24176	19735	24149	25528	18989	25753	32458
asparagine	553743	231	369588	6267	C00152	29077	22872	42372	43423	29075	36097	29040	42269	45608	54366	34953	49077	33614	40355	38643
arachidonic acid	837115	91	64589	444899	C00219	11900	12532	14155	15511	13923	16387	20714	12172	7815	15919	19789	18588	8987	21935	22615
arachidic acid	856421	117	291	10467	C06425	10251	4384	5899	8109	4307	5771	8927	4891	4157	5824	6392	5926	4419	9415	6781
arabitol	572730	103	372446	94154	C01904	13848	8415	12132	12189	18896	14467	20286	13328	12947	12486	12351	16127	17554	10513	11095
aminomalonate	455754	218	413	100714	C00872	17025	57503	57621	24954	32911	27395	33844	32000	19074	30538	25666	44330	44722	24325	56877
alpha-ketoglutarate	507392	198	294	51	C00026	6603	744	381	556	396	488	572	722	607	712	394	1262	508	646	538
alpha-aminoadipic acid	573295	260	125502	92136	C00956	2500	3374	3736	2990	4025	1672	3317	2717	3512	3836	2512	3381	2193	2999	2779
allantoic acid	726050	259	117021	203	C00499	43088	24484	41415	45579	42268	35469	41925	40372	60922	45134	81800	36497	61178	52554	35752
alanine	243971	116	34178	5950	C00041	2063777	2925183	2091317	1942496	1701267	1975134	772127	2353125	2111429	2361264	1970300	1842075	3511457	2752728	2342811
adipic acid	474435	111	125	196	C06104	13563	2136	3454	4567	1929	3458	3175	4014	2822	3282	3557	4077	3041	10628	4365
aconitic acid	586815	229	29	643757	C00417	1214	1240	2390	3448	2268	1337	2821	3101	3540	2208	2494	776	2202	2814	2256
5-methoxytryptamine	864466	174	284	1833	C05659	50174	158849	60708	80033	67233	107949	206788	22616	57509	40101	86550	101942	49757	56153	22445
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	1873	901	998	1480	1002	1128	1266	945	956	1124	1494	1093	1083	1169	944
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	5700	1084	584	3345	1198	4558	1005	610	633	698	677	2672	597	2656	614
5-aminovaleric acid	536657	174	1698	138	C00431	5420	57026	24926	9520	20309	3527	30004	7156	3435	6266	15531	12830	29392	17778	37618
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	1639	8067	3569	1233	86	3562	1939	1143	2270	1072	3753	1962	4358	5589	2200
4-hydroxymandelic acid	601658	267	131944	328	C11527	1393	1522	1021	2127	1843	1263	1295	1307	1447	1472	1829	1839	1291	1598	1126
4-hydroxyhippuric acid	784581	294	12284	151012		469	624	518	617	331	525	886	223	392	294	455	401	302	241	754
3-ureidopropionate	554966	161	107897	111	C02642	1619	1009	1200	1134	2105	1268	1627	973	3547	1032	1553	1438	901	2359	734
3-phosphoglycerate	610734	227	1667	724	C00597	1083	1229	1197	610	350	1039	1512	416	794	531	2574	634	599	1139	701
3-phenyllactic acid	516011	193	113643	3848		5091	6123	7201	2132	7455	1539	7366	1345	616	1888	1272	5979	3454	1650	1866
3-hydroxybutyric acid	278632	191	145501	92135	C01089	141095	146415	60330	121094	74787	63645	106079	49951	94934	47990	110066	44842	74524	76865	79840
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	499	707	1363	742	414	680	1052	377	971	233	793	605	801	575	217
3-aminoisobutyric acid	452655	248	12265	64956	C05145	13017	21425	11977	35686	6884	16970	2593	3434	2967	4960	1912	34973	3299	11912	4304
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1703	1043	2209	1602	1182	1153	1954	1028	1933	1687	1917	986	1690	1091	2183
2-picolinic acid	381532	180	389051	1018	C10164	3090	2897	1711	1935	1410	1969	1456	1807	1586	2146	2239	2856	1615	2740	2488
2-monopalmitin	890356	129	2080	123409		2209	34211	2553	2384	1770	2208	3544	2265	1926	2181	42008	33885	3075	2260	2274
2-ketoisocaproic acid	310761	89	208	70	C00233	23831	12831	1710	3303	4701	7305	2269	2869	14615	742	2059	7355	7120	1206	6637
2-hydroxyvaleric acid	309587	131	25922	98009		22421	29801	10175	16160	11513	9931	6188	5839	6707	5941	12047	13470	11439	9935	8054
2-hydroxyglutaric acid	506306	247	2000	43	C02630	8513	6854	13171	11583	8173	8463	11050	7394	8117	4681	16047	9577	11238	12883	16784
2-hydroxybutanoic acid	258161	131	40	440864	C05984	99550	127430	76191	84532	89157	93279	74115	52806	80966	41699	125192	60827	102584	99241	82042
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		9422	11383	9571	8345	4638	8860	5541	8348	17412	8186	10723	7674	6323	7150	17862
2-deoxytetronic acid	433456	189	1208	150929		4633	3689	3994	4050	3330	3873	4317	4327	4014	5038	3881	3825	5036	5751	4590
2-deoxypentitol	521785	231	21714	249377		1295	1122	1161	1287	980	1005	1510	728	994	1088	993	764	1267	1293	1561
2-aminobutyric acid	285825	130	160842	6657	C02721	41785	106470	61615	68529	37853	43430	16882	45093	45493	37051	31982	38655	41813	52853	43158
2,5-dihydroxypyrazine	397526	241	2254	23368901		7223	4705	2777	2634	3128	3661	2955	1912	3108	2022	4077	3851	3052	4204	4563
2,3-dihydroxybutanoic acid	384796	292	31743	250402		2123	604	1674	1578	3036	1385	3050	2842	3623	2457	2512	2470	1521	1478	1973
1-monostearin	959214	203	648	24699	D01947	3740	3516	4332	3954	3099	4164	4520	3240	2902	3922	4758	4184	3119	2587	5637
1-monopalmitin	901749	371	2070	14900	C01885	2695	2650	3724	4401	2703	2565	3977	3078	2720	3361	4989	2921	2960	3326	6603
1-kestose	1123027	361	14692	440080	C03661	1000	482	1027	2305	1928	1665	1074	1227	673	1560	463	688	1682	1674	879

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						Day 300 - CON														
						FMO49	FMO23	FMO26	FMO31	FMO36	FMO38	FMO4	FMO43	FMO47	FMO48	FMO59	FMO6	FMO61	FMO62	FMO64
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	3251	2485	3150	2300	1466	1317	1300	3690	1053	2341	1650	3089	1872	1745	1560
xylose	543267	103	169	135191	C00181	139780	5956	12923	7980	8649	6855	9598	8822	7017	8158	8038	6620	13338	16355	9490
xylitol	567437	217	5857	6912	C00379	5135	2092	2786	5138	3305	5109	3443	3302	2793	6197	6328	3850	6663	7557	9079
xanthine	701688	353	1669	1188	C00385	693	288	620	682	535	481	485	521	631	463	306	592	429	894	514
valine	313502	144	3	6287	C00183	965583	609121	918329	869166	802077	696628	850399	990122	1190462	604974	786686	1114010	976953	627903	688616
uric acid	730691	441	23	1175	C00366	6691	3716	2616	10063	6507	4559	5562	1927	3215	3592	3828	3756	4182	4269	4834
urea	329351	189	145496	1176	C00086	3460378	3134631	4967545	1878472	2204970	2426870	3416475	3253746	2620318	3108635	2504930	5225573	244083	5028633	2451642
uracil	385735	241	1664	1174	C00106	5822	2027	4577	2199	1738	4225	4777	3305	4843	4845	3843	4466	3190	8513	3393
tyrosine	671252	218	16	6057	C00082	624008	465432	365454	445649	395367	354821	309742	438584	396341	359462	432318	380784	352176	337404	483806
tryptophan	780482	202	14	6305	C00078	778239	376287	232707	434215	397153	317818	415873	625648	585009	377037	499069	479958	312456	399404	385930
trans-4-hydroxyproline	484934	140	97	5810	C01157	170887	217915	353790	129642	288933	190829	284145	258378	219023	457755	80309	418332	121976	127432	120769
tocopherol gamma-	1026121	223	4545	92729	C02483	1537	811	1104	765	798	704	1204	1076	1201	1578	973	2089	894	690	1049
tocopherol alpha-	1067809	237	100	14985	C02477	25659	8529	3060	24920	20723	26340	34475	18825	26148	24139	19133	35971	26383	7998	22674
thymine	420133	255	1692	1135	C00178	1847	370	889	448	546	658	414	638	1068	944	511	703	1129	1320	579
thymidine	349402	170	87703	5789	C00214	53020	26707	51731	31411	39569	32885	43441	40633	49534	47270	23411	35392	24207	64548	28180
threonine	409568	218	26	6288	C00188	284386	199629	220793	352477	213256	178203	234256	329413	235775	153853	184973	416759	203746	132660	180357
threonic acid	497572	292	172	5460407	C01620	11988	24198	22433	8188	19331	6424	11629	22232	14713	19493	3608	8647	19543	5175	6239
threitol	467595	217	770	169019	C16884	3479	1551	1993	937	1788	1302	1163	2135	1634	1867	1216	1611	1780	2460	1210
taurine	556690	326	411	1123	C00245	36514	1937	4904	2202	1806	24092	3632	35142	69190	40996	13227	6235	23455	6858	27163
tartaric acid	534291	292	33985	444305	C00898	317	978	1928	246	241	5416	836	295	273	1471	1170	350	924	378	1598
tagatose	631835	307	33981	439312	C00795	1192	6785	7256	1102	847	701	2076	1083	562	2167	1588	1314	1607	1351	26759
sucrose	915139	271	173	5988	C00089	2146	977	2547	1815	1208	489	798	1683	669	2344	369	1187	568	953	742
succinic acid	370608	247	161	1110	C00042	25999	7087	6828	15065	14106	16757	20155	7683	12316	12081	12422	8802	14901	10072	9830
sophorose	962064	307	132242	441432	C08250	318	241	620	312	474	240	373	160	324	314	193	380	303	712	353
shikimic acid	611100	204	286	8742	C00493	6121	5014	3340	3797	7476	2727	1702	15836	5538	4059	5428	3087	5646	12959	17370
serotonin	863824	174	364413	5202	C00780	29440	74104	8027	48393	50086	35653	149015	67058	51356	80035	66606	63805	32607	36498	25189
serine	395020	204	25	5951	C00065	808576	670738	1041104	590645	662092	486510	696105	863531	602873	820825	346616	890024	548425	687345	507473
salicylic acid	480699	267	3063	338	C00805	13703	2334	1722	2973	8585	3080	2542	8108	3684	13167	2680	2809	3834	6650	10644
saccharic acid	699211	333	11214	33037	C00818	1703	1083	968	810	1007	836	1176	1043	1021	1101	604	652	1009	1062	924
ribose	553071	217	384948	10975657		18403	8221	13041	21383	12531	37674	23467	21813	33637	26489	8703	27026	18316	38834	17271
ribonic acid	599680	292	1683	5460677	C01685	15596	3108	5358	5010	12015	3840	2207	4348	5111	7392	6846	9376	9546	3307	6421
ribitol	575497	217	7362	827	C00474	2294	1227	2098	1822	1555	2010	1670	2619	2806	3173	1617	1186	1008	2078	1628
raffinose	1120886	361	3190	439242	C00492	379	721	733	362	777	287	1974	1150	988	1566	380	1508	278	299	366
pyrophosphate	547021	451	88522	1023	C00013	5144	1308	3179	917	986	2095	5317	1008	3033	2798	1530	4555	2156	1761	1879
putrescine	588119	174	21703	1045	C00138	5585	3871	3706	8107	7010	2150	4965	7567	7053	5283	4845	5042	4344	5567	3787
pseudo uridine	813899	217	1688	15047	C02067	18066	10856	15245	11430	10672	12948	14711	11095	10477	10487	9086	11657	12132	20794	9977
proline	364716	142	8	145742	C00148	425358	384683	494826	476775	734472	490738	600191	630654	672323	597307	337914	1216979	431775	132959	303449
piperidone	275603	156	34023	12665		2818	3104	2921	1759	5960	1153	12047	6163	2241	1307	3113	19099	4513	2742	1115
pipecolinic acid	404121	156	2448	6931662		2494	2030	13800	3697	7002	2312	2321	10586	2597	2859	1647	3407	2942	1229	1882
pimelic acid	523205	155	33429	385	C02656	868	1737	1789	2360	1886	1608	2113	2126	669	2404	1824	294	1887	1258	2107
phthalic acid	567345	147	46142	1017	C01606	11346	8066	8314	16090	8029	12646	14547	13313	8815	13017	11264	11479	13453	18209	15108
phosphoethanolamine	603912	299	1723	1015	C00346	9117	2106	8671	1878	1186	2973	8564	2581	7433	3578	5135	2369	3709	1791	3042
phosphate	345365	314	4	1004	C00009	589811	284568	586850	332648	326346	428414	557997	514654	517381	560307	360616	625766	394105	691876	342973
phenylethylamine	510327	174	2005	1001	C05332	6997	11400	34415	9533	6497	22027	7670	8569	3709	14043	3897	16666	4158	3849	11638
phenylalanine	537804	192	33	6140	C00079	385424	137624	221784	220829	201455	154961	223231	266318	228279	227229	190243	226028	154380	273536	248405
pentose	540818	103	360841	229		26454	1544	12193	2342	1951	1967	2270	1861	3292	1422	2055	2378	2881	3622	2842
pelargonic acid	399229	215	50	8158	C01601	43004	23188	23993	21029	31306	16040	34790	30385	19129	31349	21671	22117	27445	29145	22322
palmitoleic acid	706508	311	96	445638	C08362	3185	1772	1142	1004	698	1582	1603	5457	4766	1197	2248	5691	2435	3273	1708
palmitic acid	713809	313	11	985	C00249	169548	109702	102375	129522	96839	111687	124663	292754	184101	111779	131667	188823	138860	221957	114166
oxoproline	485935	156	10	7405	C01879	1122181	634448	1259165	802412	824358	711582	1235432	1085477	1070137	1089374	845131	892886	1043802	1259438	788150
oxalic acid	260513	190	4923	971	C00209	2245	5423	3164	4195	3902	6697	5321	4954	323	4588	10608	3724	9265	6855	2159
ornithine 3TMS	527113	142	1821	6262	C00077	195849	110960	153656	115666	149451	104723	147748	166299	177587	165740	99772	197008	110491	171149	98813
oleic acid	779120	339	43	445639	C00712	2185	1355	1122	2236	1060	28356	1557	72877	61799	3056	46253	75508	5682	53901	36639
oleamide	849710	144	20961	5283387	C19670	18371	15191	25100	34283	37526	27100	17454	33538	31709	49701	21158	20788	34874	14709	34286
nonadecanoic acid	822782	117	46258	12591	C16535	3523	4127	5015	5819	5225	3815	4672	5216	5284	6666	4638	5536	6327	4942	4270
nicotinic acid	353428	180	327312	938	C00253	38566	626443	587716	3555	28638	2547	491919	2049	4530	48376	3011	79518	6223	10706	34740
N-acetylglycine	356109	174	97747	10972		1765	1039	1757	258	1021	398	1603	437	610	1054	501	1474	1176	1541	1050
myristic acid	634414	285	127	11005	C06424	6188	7999	3782	3536	2826	2909	10840	7515	5309	3708	3501	7056	4392	8683	4065
myo-inositol	730022	305	1741	892	C00137	272506	147863	197938	172388	191891	413934	277176	257218	383316	205835	217632	172050	209593	328863	163429
mevalonic acid	498785	247	127978	439230		1314	2469	1788	702	926	792	772	3822	769	1088	770	1094	2662	1959	851
methionine sulfoxide	637588	128	1678	158980	C02989	38862	37243	35441	124831	86133	23108	46538	117759	98440	76234	48640	51758	36910	19365	56585
methionine	483560	176	45	6137	C00073	141373	108495	141169	88216	84872	57833	103910	95815	102063	104145	35391	156125	92643	89244	31787
methanolphosphate	289520	241	5393	13130		39681	14365	29146	28930	17877	34059	44645	17151	35487	60485	27989	49541	34524	34169	22914
mannose	645856	205	70	18950	C00159	270133	226462	294504	176050	187637	151417	220644	221617	132954	190983	229585	145755	207576	260373	470024
maltose	946601	204	1979	439186	C00208	10328	6944	3251	3179	3112	2920	8730	10572	7859	6997	9378	5031	4276	9973	5186
malonic acid	305372	233	16918	867	C00383	449	424	639	334	345	448	530	257	630	141	271	613	77	568	656
malic acid	463180	233	1391	525	C00711	6736	3086	2185	5718	5352	10848	8926	6313	7625	6131	7132	3203	8265	13738	4341
maleimide	245118	154	1743	10935	C07272	13542	7134	7163	9166	6881	12857	11121	16825	10699	7246	7803	12852	9600	10358	16328
lyxitol	573587	217	233	439255	C00532	10493	9482	10359	13587	13190	9769	12964	9866	10139	19295	6669	16615	10801	13136	5133
lysine	663483	317	12	5962	C00047	86289	46224	50730	56250	67245	35982	46377	51576	57592	29062	58151	46040	49709	48321	50901
linoleic acid	777285	337	471765	5280450	C01595	19697	15318	11237	11940	9592	15657	18015	34986	31722	15795	19434	38946	20737	25468	15095
levoglucosan	569637	204	3169	2724705		2740	1322	1560	1524	1674	1248	1403	4067	1420	2024	1047	1067	1336	1226	2293
leucine	346101	158	9	6106	C00123	856456	764157	858790	996822	975678	812378	1112794	1279710	1624538	831289	749539	1444016	1040589	1010254	842165
lauric acid	547906	117	49	3893	C02679	23356	176939	20285	13355	16535	9303	319946	23123	14391	19407	12323	20790	16144	21750	16978
lanosterol	1129573	393	133475	246983	C01724	444	455	463	196	244	119	326	277	236	383	257	447	447	404	272
lactose	936998	204	217651	6134	C01970	1798	2915	2343	1455	1948	780	1345	3412	1846	1890	1663	1541	19533	3983	2828
lactic acid	217657	191	80	612	C01432	2691053	1585004	1445528	1865986	3879079	3499835	1631947	2483689	3653704	3560271	3311275	1160764	2248974	1877898	2075994
lactamide	265698	232	415	94220		2832	1404	1881	1796	3404	3185	1526	2495	3971	2950	2335	1065	1919	2912	1911
kynurenine	769709	218	210712	25245862	C01718	13675	7251	13629	9979	7299	5436	5343	8184	6965	10607	7343	5116	5424	17785	6824
isothreonic acid	489385	292	1679	151152	C00639	15588	6719	12517	5481	7269	5987	7417	6734	6094	8916	5588	7533	10123	19266	6273
isomaltose	983199	160	127715	439193	C00252	486	394	431	488	468	260	664	269	110	1234	736	506	408	596	608
isoleucine	359251	158	15	6306	C00407	437177	328461	477906	416543	352861	412059	395354	549639	656221	230481	369046	526138	444588	562626	413719
isocitric acid	616323	245	12267	5318532	C00451	6360	3775	3326	7266	6881	6445	7644	4656	7644	6594	4486	3949	7418	8853	2855
inositol-4-monophosphate	845976	315	4759	440043	C03546	2607	1555	1488	1223	924	954	2277	1583	1279	2082	1182	3249	1234	2845	1574
inosine	897434	230	84524	6021	C00294	39881	16288	7759	36789	26105	20678	36979	35196	28645	25322	28252	25150	25157	24717	30361
indoxyl sulfate	577333	277	31543	10258		3127	732	1792	3095	2357	1430	1398	3001	2599	5296	2835	933	7603	8084	1389
indole-3-propionic acid	732249	202	112556	3744		5585	1768	4189	6094	10879	5434	11020	10249	9008	12560	4392	5231	6855	9102	3152
indole-3-lactate	764079	202	390397	92904		24022	7303	3192	9742	15067	5019	12834	7207	11006	8340	10526	14501	8876	13708	5073
indole-3-acetate	684929	202	69	802	C00954	5403	4555	3644	5908	5230	3622	9200	7584	7424	26238	4921	7932	3566	6225	8577
hypoxanthine	619128	265	1663	790	C00262	88922	15388	58203	47546	48354	64098	47464	31095	86802	91565	54610	50782	42417	95822	54658
hydroxycarbamate	325318	278	130396	16639161		14745	7133	15011	8986	7010	3747	12004	2799	6818	8248	10810	8624	10060	9398	4074
homoserine	443878	218	2849	12647	C00263	1493	647	1493	1035	1029	818	1016	1185	795	1413	1403	801	1349	852	1375
homocystine	874865	128	2786	10010	C01817	1017	1339	1748	687	1175	790	915	1048	570	1213	618	1246	868	1092	769

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						Day 300 - CON														
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BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	90015	125466	108564	104421	105242	68807	74385	100050	92117	66627	57863	155695	65739	33898	51583
heptadecanoic acid	751309	117	727	10465		16690	15851	11643	15317	10766	15609	15860	30879	22091	14956	17002	20024	19433	24255	15982
guanosine	954962	324	1966	6802	C00387	3435	1682	603	2935	2670	2212	3256	3898	2631	1922	3581	2597	2276	2024	2981
guanine	744307	352	2519	764	C00242	3149	758	2936	1301	1531	3289	1539	2721	3655	3820	1788	2059	1959	4498	1949
glycyl proline	691357	174	18496	3013625		909	1286	1216	961	816	618	695	316	964	1587	1588	1214	1103	1292	656
glycolic acid	227636	177	1971	757	C00160	25290	14770	22107	9109	13326	7885	19974	19452	10897	34755	10067	11939	13734	26258	10399
glycine	368707	248	6	750	C00037	909627	490348	662697	476851	623072	553198	491764	759035	500201	668902	270770	616039	345432	387966	436882
glycerol-alpha-phosphate	590747	357	1687	754	C03189	33640	21742	18941	22824	17103	32964	38344	38459	35619	30677	28648	57939	18359	18306	24365
glycerol-3-galactoside	800205	204	100875	16048618	C05401	3053	3163	2748	2013	6331	1706	2381	10790	7970	4513	2007	5318	5446	7436	7127
glycerol	344466	205	30	753	C00116	593591	495601	297676	641314	555803	822170	705720	570341	482579	309076	542713	604289	601608	709873	938865
glyceric acid	377308	189	394878	752	C00258	24824	13466	23236	13670	14486	12672	9602	20936	21209	16182	11227	13430	18509	46535	9566
glutaric acid	421260	261	1727	743	C00489	642	928	968	998	727	1070	772	1663	1093	871	638	1034	619	966	897
glutamine	600315	156	18	5961	C00064	794063	1147663	1441022	1438559	1522881	750325	880040	982460	726029	1173569	1015222	1299976	1111662	710052	1112276
glutamic acid	529100	246	28	33032	C00025	65352	31738	92718	73514	52808	73954	79139	71852	88575	65028	56323	57340	63571	68570	67688
glucuronic acid	665901	333	344793	94715	C00191	12937	9657	6109	9372	6786	5986	11278	7875	8205	8632	8329	8542	10784	11073	10317
glucose-6-phosphate	808788	387	360626	5958	C00092	1283	2414	3384	1536	1103	477	1691	1759	1699	1003	2057	2132	1772	1902	2665
glucose-1-phosphate	594647	217	3167	65533	C00103	6735	6724	6181	6412	4003	2658	2545	3222	1961	3316	4032	3139	4528	8498	7145
glucose	659798	319	22	64689	C00221	3083648	6724057	3916926	4488355	3521652	3181670	3559555	3111536	2413066	3846536	4574046	3633786	4162460	5464290	5478912
gluconic acid lactone	645815	220	3502	7027	C00198	12245	4907	7891	3910	4342	11498	9750	11487	3936	4605	25998	4544	4313	11815	11491
gluconic acid	693148	333	7501	6857417	C00800	79179	16986	25763	13194	9644	72561	67823	78861	22159	19748	160985	16740	16825	89801	52904
galactinol	1017580	204	1975	11727586	C01235	1471	1042	1859	905	1473	708	2746	2187	1802	2112	829	2510	1535	1166	1030
fumaric acid	390775	245	1718	444972	C00122	2408	1064	2032	2783	1550	4255	1632	4118	3180	1883	2965	1503	3009	5007	1611
fucose	578299	160	3009	439650	C02095	6595	12415	9171	9725	7826	6351	6529	5352	6271	8848	9050	7278	14466	12775	11490
fructose	639442	307	21	439709	C02336	285960	736813	340676	384539	325214	248028	353567	232753	195113	416863	420188	317544	458788	433690	1408954
ethanolamine	342561	174	342038	700	C00189	46730	26285	30184	39760	30170	29366	44612	24372	39587	39621	31875	28933	40220	74602	37509
erythritol	471922	217	92	222285	C00503	12923	8408	9495	9607	12459	9615	10117	10508	8904	12934	9024	10778	10250	13190	9072
epsilon-caprolactam	353069	170	3101	7768	C06593	10510	7094	14139	9903	20801	8668	11928	11887	13326	16338	6598	9958	14062	2263	14116
docosahexaenoic acid	902819	91	87709	445580	C06429	3329	2032	2688	1642	2610	2406	2797	1669	2497	2974	2717	3678	2655	3760	1827
dihydrocholesterol	1082070	215	42937	66066	C12978	9033	1757	5116	6962	3879	6432	7577	3544	3548	6604	3697	7934	4480	4803	6979
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1679	1055	1343	1380	1308	1633	1717	1883	1000	2115	1313	1213	2591	2173	1105
cytosine	486724	254	2186	597	C00380	1124	981	3439	1500	1599	598	1122	1191	1465	2644	815	913	1169	1555	961
cystine	804619	218	94	595	C01420	22486	25231	13627	5246	26709	11346	33381	7823	7726	17331	11297	27726	12641	2059	9945
cysteine	500158	220	65	5862	C00097	17917	11539	11162	4928	13721	10537	15077	6007	8546	11575	7539	17473	14085	1324	5433
creatinine	502599	115	31	588	C00791	264930	100273	109550	213203	230569	181964	187474	216423	189909	214395	188074	185715	166649	175963	202171
conduritol-beta-epoxide	675635	318	2670	9989541		1650	3454	1672	1973	1369	1322	1810	1974	1083	1998	1646	1195	2218	2558	2405
citrulline	621404	157	1712	9750	C00327	46774	26292	49230	30827	35937	23870	40895	35940	34754	40755	38849	30017	30218	39440	29491
citric acid	617342	273	288	311	C00158	370633	208591	166041	406358	355790	365649	372381	260583	311827	345020	258204	212302	421090	500426	172753
cis-gondoic acid	847372	367	87783	5282768	C16526	415	460	883	358	426	315	571	508	473	1116	716	571	734	437	768
cholic acid	1109517	253	110403	221493	C05463	831	1098	958	447	557	634	973	697	510	1358	665	823	665	662	1346
cholesterol	1078536	129	19	5997	C00187	906530	458551	749698	677296	389723	711396	1068853	552756	523262	794776	516302	1313058	746427	797054	708301
cellobiose	942758	361	120969	6255	C01971	833	577	239	310	443	129	571	525	644	517	662	506	403	877	382
capric acid	451790	229	726	2969	C01571	6504	7779	5585	4059	4811	3126	16407	5767	5078	6213	4573	5451	4604	5969	4454
butyrolactam	277199	142	2047	12025		33923	25055	29738	21327	25696	15269	27286	17305	20990	30002	28211	32192	22528	50848	33899
butane-2,3-diol	205778	117	485	262	C03046	102548	108254	103926	94952	214323	133525	123792	143324	215625	213303	193946	58553	126553	167095	127312
beta-sitosterol	1128225	129	3174	222284	C01753	10980	4950	9664	5936	5211	8416	7014	2360	7728	10647	3526	11821	8432	6933	9046
beta-glycerolphosphate	574470	243	22021	2526	C02979	1836	1224	1264	1218	1116	1504	1676	3055	1449	1593	1411	2123	1415	1846	1340
beta-alanine	435564	248	148	239	C00099	6453	205	4166	3805	6983	380	7826	5038	2351	4915	3228	4628	3853	8435	2650
benzoic acid	339067	179	36	243	C00180	336542	127140	178247	155126	213666	106710	131715	226925	192398	312343	128801	177793	189320	258924	213974
azelaic acid	610551	317	329430	19347555	C08261	1505	1245	1289	1688	1468	1351	1716	4347	1584	1862	1369	1193	2485	1532	3131
aspartic acid	480387	232	79	5960	C00049	31210	11003	42710	22563	17790	24408	22968	31148	36702	27650	15277	15413	17849	28266	21314
asparagine	553743	231	369588	6267	C00152	31053	29568	39694	37108	29267	37351	29841	40032	35594	26029	22561	34091	29173	29205	28077
arachidonic acid	837115	91	64589	444899	C00219	23736	11778	13395	13596	13433	17867	24575	28920	27090	19918	22695	30021	20867	28956	18296
arachidic acid	856421	117	291	10467	C06425	6953	3900	4895	6726	5718	5271	7826	20311	5802	7285	4651	8473	5033	6838	6674
arabitol	572730	103	372446	94154	C01904	10505	6316	10029	8708	9293	7725	9611	6376	9818	13514	6193	11681	10194	6992	5588
aminomalonate	455754	218	413	100714	C00872	47670	33282	48036	19205	20367	15161	39633	11013	20094	31525	15722	24302	17364	15537	12832
alpha-ketoglutarate	507392	198	294	51	C00026	2498	744	5066	363	444	1219	719	361	499	579	496	609	802	5821	332
alpha-aminoadipic acid	573295	260	125502	92136	C00956	4996	2579	3942	3986	2313	2611	2597	2806	2504	3246	2461	3530	2090	2723	2049
allantoic acid	726050	259	117021	203	C00499	37530	23167	26688	29075	44688	24076	70076	24276	24089	27683	17358	31543	15565	92333	31170
alanine	243971	116	34178	5950	C00041	1516274	2353496	2985242	3392201	2223907	4350787	2346753	2148088	2230930	1595609	3458111	1515099	3451544	1534677	1853692
adipic acid	474435	111	125	196	C06104	3414	4072	2560	7606	7924	6102	4702	20209	4741	7169	2022	3229	4893	3821	9882
aconitic acid	586815	229	29	643757	C00417	2626	547	638	2584	2067	3098	863	1793	2743	2115	1727	994	2654	2466	863
5-methoxytryptamine	864466	174	284	1833	C05659	23353	61187	6322	39187	40001	28898	184913	53221	41172	62870	51812	76758	26441	28021	20206
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	1596	1010	1538	1473	2867	1277	1856	1603	1518	1454	1064	1720	1796	1324	1356
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	1074	984	996	1203	942	969	1026	3403	1066	988	494	1181	666	1057	1318
5-aminovaleric acid	536657	174	1698	138	C00431	4343	8224	2835	3290	4309	2449	2812	4891	3719	4044	3486	9715	2507	3509	3387
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	951	958	1167	977	1302	723	1222	887	1307	1085	1947	1286	1586	2737	650
4-hydroxymandelic acid	601658	267	131944	328	C11527	1929	982	1424	1355	1334	892	1495	1292	1060	1992	652	1379	1263	1672	1042
4-hydroxyhippuric acid	784581	294	12284	151012		457	218	267	450	477	825	348	468	186	509	1579	522	260	276	192
3-ureidopropionate	554966	161	107897	111	C02642	1664	1530	1131	982	949	2767	1387	1536	2044	1503	862	1107	939	2059	726
3-phosphoglycerate	610734	227	1667	724	C00597	1224	286	1431	414	579	431	680	2636	2971	677	937	638	1193	1061	584
3-phenyllactic acid	516011	193	113643	3848		3022	1320	1044	1185	2202	874	2060	2006	1798	2137	1795	2519	1374	1670	860
3-hydroxybutyric acid	278632	191	145501	92135	C01089	44415	60273	44398	25482	39170	30931	46917	86982	64475	76713	59836	45171	100798	201174	103376
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	996	895	873	566	1013	724	634	1362	632	368	674	488	522	469	822
3-aminoisobutyric acid	452655	248	12265	64956	C05145	3573	13181	13360	3289	8229	5002	16684	2632	3331	3617	1902	14413	3415	5244	2419
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1774	951	1068	1116	1110	909	1395	1836	890	1424	1752	686	1654	1415	1281
2-picolinic acid	381532	180	389051	1018	C10164	4046	2145	4401	2384	3244	1856	2978	4319	2304	4244	1170	2123	2027	2652	3948
2-monopalmitin	890356	129	2080	123409		2410	1679	3923	2528	2153	1374	2463	2450	1712	3077	1457	2757	2943	12747	2380
2-ketoisocaproic acid	310761	89	208	70	C00233	12253	9728	13766	925	1964	16331	9999	1314	2140	3956	408	9008	14184	31111	781
2-hydroxyvaleric acid	309587	131	25922	98009		9029	9486	11494	5642	7735	6128	11374	5040	5940	9035	6833	10746	8899	10538	6999
2-hydroxyglutaric acid	506306	247	2000	43	C02630	3602	4713	5338	4779	5204	3426	4259	3964	4223	5817	3805	4220	4597	4874	2089
2-hydroxybutanoic acid	258161	131	40	440864	C05984	62922	75214	45913	52121	44018	96724	69000	62403	88061	100867	155838	45505	129884	100278	49706
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		7804	6061	8922	4880	5311	5024	5777	6788	8347	8666	6189	6364	7703	6778	5687
2-deoxytetronic acid	433456	189	1208	150929		5602	2281	4257	1994	3054	1659	2789	2455	2614	4101	1919	2401	8566	4119	2506
2-deoxypentitol	521785	231	21714	249377		1167	791	1403	1159	982	908	1414	919	1194	1558	846	1046	1938	1915	557
2-aminobutyric acid	285825	130	160842	6657	C02721	38437	56283	54913	36083	41405	70653	55258	41643	61006	31400	78194	39014	94353	32548	36963
2,5-dihydroxypyrazine	397526	241	2254	23368901		8174	4384	2997	1769	3089	2660	5405	3238	2501	3986	3063	3928	6158	1990	2642
2,3-dihydroxybutanoic acid	384796	292	31743	250402		2484	1907	1804	1782	1581	1459	3020	2261	2496	1349	2050	2473	1671	1983	871
1-monostearin	959214	203	648	24699	D01947	3412	2403	6039	4118	1995	2739	3804	5854	2989	4799	2565	4084	4692	27819	3354
1-monopalmitin	901749	371	2070	14900	C01885	2884	2315	5166	3000	3978	2181	3336	3006	2519	3855	2077	3797	2744	28153	4401
1-kestose	1123027	361	14692	440080	C03661	463	711	519	380	569	397	1172	462	967	912	380	1433	367	241	335

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BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	1538	1350	2468	1641	1207	2171	1500	1910	264	3722	2352	850	4049	1806	2614
xylose	543267	103	169	135191	C00181	7581	15904	12842	8656	10808	9627	12506	15332	7911	9573	17344	14610	23937	20283	13697
xylitol	567437	217	5857	6912	C00379	3237	4981	4273	2582	2742	4584	4409	6638	3475	3243	5032	3235	5192	3789	3129
xanthine	701688	353	1669	1188	C00385	737	534	505	519	728	521	1065	1093	985	1137	321	1281	975	473	306
valine	313502	144	3	6287	C00183	1019055	399761	899209	715522	696603	1509173	1336693	880996	837938	1064388	1351355	1014009	1568203	727308	777019
uric acid	730691	441	23	1175	C00366	7233	7075	5781	5585	4387	2492	5567	3471	6914	5485	3420	4727	13345	5447	2561
urea	329351	189	145496	1176	C00086	2667935	4523582	3363384	3452757	2497747	3149815	2384716	3101182	2411894	676717	3066397	2515057	3273264	2640799	3171563
uracil	385735	241	1664	1174	C00106	6676	6196	4578	3565	9594	5545	5108	5998	2843	12572	6338	4009	9665	15027	6037
tyrosine	671252	218	16	6057	C00082	237002	394563	408852	397618	294630	380363	264226	388620	327988	382841	183567	432825	389631	469396	189936
tryptophan	780482	202	14	6305	C00078	221077	285404	328702	182069	176622	234320	214189	229891	236257	176226	275621	427499	633698	255096	129679
trans-4-hydroxyproline	484934	140	97	5810	C01157	138298	273538	479494	225381	120194	152104	177710	498012	451069	279481	244783	178414	142797	179798	305817
tocopherol gamma-	1026121	223	4545	92729	C02483	876	1103	1252	1634	705	1243	687	976	755	1065	619	1417	1310	797	798
tocopherol alpha-	1067809	237	100	14985	C02477	35421	33311	41188	45525	34462	41190	40737	66848	40388	9920	93205	70612	32875	5852	23479
thymine	420133	255	1692	1135	C00178	400	780	619	505	964	566	657	983	605	750	623	635	1061	1156	208
thymidine	349402	170	87703	5789	C00214	15585	40104	36574	17697	35685	27784	24067	25968	25126	22050	51017	46393	46121	25346	17671
threonine	409568	218	26	6288	C00188	140438	109123	166801	85102	95287	317569	151142	83453	172877	146644	168524	121918	314602	102725	152995
threonic acid	497572	292	172	5460407	C01620	6787	11085	8094	20439	24033	23125	62585	53328	33200	19477	61472	41464	49226	10339	15195
threitol	467595	217	770	169019	C16884	2560	2846	2870	10514	1563	1655	1664	1571	1421	1363	1820	1916	7250	2975	1469
taurine	556690	326	411	1123	C00245	2442	7173	436	3504	6960	4211	41947	74878	42177	8709	24755	13325	50943	44220	224
tartaric acid	534291	292	33985	444305	C00898	282	318	716	1875	764	1069	187	300	440	260	322	258	424	237	332
tagatose	631835	307	33981	439312	C00795	1300	1875	2202	1662	1049	478	395	990	661	385	688	2089	3591	11890	1585
sucrose	915139	271	173	5988	C00089	1603	4805	3143	5650	817	134	1242	296	1994	2419	548	962	6118	1587	3449
succinic acid	370608	247	161	1110	C00042	5761	17840	9777	10072	5971	5726	5872	7975	6437	26360	7379	18083	7049	5702	7820
sophorose	962064	307	132242	441432	C08250	710	343	348	293	284	351	357	410	306	409	238	910	487	942	224
shikimic acid	611100	204	286	8742	C00493	2159	4916	6643	4579	13897	17767	6027	1115	5900	3227	6441	6214	1881	4648	2548
serotonin	863824	174	364413	5202	C00780	81815	164532	115351	67313	116348	138494	134022	39620	79588	92216	66605	202607	86280	307739	385815
serine	395020	204	25	5951	C00065	734302	690829	943379	718734	672302	1061329	746293	842044	638216	1348989	921574	976020	1117253	534239	661841
salicylic acid	480699	267	3063	338	C00805	2897	3402	4244	4413	3988	2813	3000	2682	15481	4711	8007	2446	3662	1880	2910
saccharic acid	699211	333	11214	33037	C00818	1212	1691	1533	4359	1104	756	2939	1069	959	1021	1021	982	1007	1151	1103
ribose	553071	217	384948	10975657		17269	47575	34690	23509	22974	35379	31503	29196	11547	30678	18716	23903	30685	80759	28462
ribonic acid	599680	292	1683	5460677	C01685	3261	7939	6109	7813	10156	2276	3837	2608	8514	746	3115	9174	10719	8026	5186
ribitol	575497	217	7362	827	C00474	1867	3385	1852	2392	2321	1718	1639	1890	1944	2382	1628	2195	2886	2384	1900
raffinose	1120886	361	3190	439242	C00492	564	1481	919	1606	353	203	239	509	3012	719	406	383	368	1052	1811
pyrophosphate	547021	451	88522	1023	C00013	2775	3097	919	3948	2619	1659	3405	6319	2021	4707	2866	3649	3341	2064	2636
putrescine	588119	174	21703	1045	C00138	5700	13057	7058	22082	5297	7706	5397	16064	6636	4693	9014	5872	11217	6194	7545
pseudo uridine	813899	217	1688	15047	C02067	11254	26986	24685	19642	16848	14471	18957	13777	14154	11716	21841	15605	26128	19694	17761
proline	364716	142	8	145742	C00148	516273	218935	598977	642261	250769	583346	430885	848181	921133	1004806	538443	542668	473935	731553	641703
piperidone	275603	156	34023	12665		7053	2271	2521	6368	2066	1827	1615	7445	8506	2292	1464	567	1333	1808	137645
pipecolinic acid	404121	156	2448	6931662		1562	1787	4127	4148	2306	2231	4340	1611	3649	1632	2926	1366	4474	2738	4023
pimelic acid	523205	155	33429	385	C02656	1487	2176	2229	3287	1214	1864	1721	1844	2000	721	1547	1550	1365	1872	1546
phthalic acid	567345	147	46142	1017	C01606	23547	8692	8844	14414	8155	10539	6023	17671	9567	9968	9745	6646	10614	10013	4919
phosphoethanolamine	603912	299	1723	1015	C00346	3013	2991	731	3061	4845	4045	5430	3213	1535	4866	5176	22946	4858	1647	7746
phosphate	345365	314	4	1004	C00009	655033	741884	634687	532730	398877	552130	563206	742654	557011	799726	676805	1133182	748045	342204	615240
phenylethylamine	510327	174	2005	1001	C05332	41496	35693	13043	16003	14826	41367	59139	19280	30750	93994	22671	11821	11153	5831	8195
phenylalanine	537804	192	33	6140	C00079	139212	261777	258073	169904	160082	165493	171248	221539	180871	208043	163082	256717	222249	198717	176517
pentose	540818	103	360841	229		1698	1488	3924	3766	2786	2565	2217	3942	2859	3732	3488	3013	5260	4995	3660
pelargonic acid	399229	215	50	8158	C01601	15064	20844	30523	32159	21415	19582	19329	17642	16560	32942	26111	15895	32027	24178	22404
palmitoleic acid	706508	311	96	445638	C08362	3220	2338	2006	3285	4517	3075	2771	1769	1681	2386	6062	6394	5292	1730	1837
palmitic acid	713809	313	11	985	C00249	105567	140153	192266	135938	246440	185079	169340	100764	116619	92346	232691	193743	129457	117515	106687
oxoproline	485935	156	10	7405	C01879	716119	1047818	841710	762765	695734	614299	747134	1106185	675869	674736	802310	976500	817522	1087501	905047
oxalic acid	260513	190	4923	971	C00209	4315	9729	6378	5656	12984	11146	9762	6273	5147	2331	14186	8407	4466	3366	3812
ornithine 3TMS	527113	142	1821	6262	C00077	144603	159861	329336	122527	113604	157808	141295	184521	207745	371837	196205	311374	415597	191173	140436
oleic acid	779120	339	43	445639	C00712	1256	1176	1776	1537	112852	82803	64924	1093	2950	1036	113908	81030	51454	1264	1948
oleamide	849710	144	20961	5283387	C19670	12416	20158	16220	15812	38256	23919	17556	23041	26283	15415	14624	11622	26543	25521	5337
nonadecanoic acid	822782	117	46258	12591	C16535	2868	4512	3840	2763	7003	3922	4577	3126	3800	2700	3529	3943	3258	4042	2689
nicotinic acid	353428	180	327312	938	C00253	445520	526108	133773	413393	5283	5564	1870	4970	40630	15929	8035	3558	3478	286468	548156
N-acetylglycine	356109	174	97747	10972		1808	1853	916	674	976	876	1261	975	803	1478	1942	3162	3054	2028	1352
myristic acid	634414	285	127	11005	C06424	12405	4453	5104	8759	8667	5118	4825	3561	3259	5546	9309	7259	5288	5039	3278
myo-inositol	730022	305	1741	892	C00137	164569	529456	248286	91200	391711	229238	416738	140672	184877	171656	574253	675659	649430	253053	200938
mevalonic acid	498785	247	127978	439230		920	840	872	1105	677	1072	908	1208	792	4573	1078	1629	5184	3180	2283
methionine sulfoxide	637588	128	1678	158980	C02989	40010	23644	34829	447435	56467	94696	82087	241701	95255	49111	130106	84683	185860	66261	49430
methionine	483560	176	45	6137	C00073	209816	84387	95783	1076728	36317	62888	76665	361633	205233	120005	103406	71964	185941	369944	124058
methanolphosphate	289520	241	5393	13130		19126	18897	29328	44354	33562	30446	20644	32558	26632	29391	28715	67680	41743	19843	21856
mannose	645856	205	70	18950	C00159	186911	234317	229815	212118	268841	245112	154582	170696	146494	184658	223690	217590	275093	215591	174486
maltose	946601	204	1979	439186	C00208	25429	14108	18805	28389	16643	15891	8987	29128	11343	78292	16103	28136	13723	58658	4606
malonic acid	305372	233	16918	867	C00383	505	317	349	721	379	401	259	270	397	424	445	423	283	582	267
malic acid	463180	233	1391	525	C00711	5398	6432	4382	1912	6166	3176	6243	6194	3468	5287	4272	10860	4088	8500	4380
maleimide	245118	154	1743	10935	C07272	12779	18406	25782	17992	7331	7604	12990	14098	11056	6724	15057	14637	9367	23598	18430
lyxitol	573587	217	233	439255	C00532	9840	12541	14786	13135	7261	8759	8767	10001	18213	8442	10030	8367	9655	14692	11354
lysine	663483	317	12	5962	C00047	30585	64368	76950	168445	75238	98320	48969	23838	27059	36736	81345	30702	92497	14854	25323
linoleic acid	777285	337	471765	5280450	C01595	14480	18772	19151	16400	25556	17478	18747	13580	16654	14041	31943	35617	28328	13642	16450
levoglucosan	569637	204	3169	2724705		1086	1132	1509	1278	1065	854	1899	557	2595	623	772	1176	645	1196	878
leucine	346101	158	9	6106	C00123	1110281	653746	815330	1247469	634965	1476810	1569950	1053163	1118398	1188967	1211957	1504747	1666661	1007859	985777
lauric acid	547906	117	49	3893	C02679	155994	15997	18485	205140	15009	12018	13294	10933	12794	168813	25494	25921	20240	17544	15308
lanosterol	1129573	393	133475	246983	C01724	233	225	225	645	208	310	202	341	207	679	251	682	471	423	486
lactose	936998	204	217651	6134	C01970	1634	2341	3089	3534	3076	3542	2142	1739	1662	4074	4462	2266	1666	5265	1275
lactic acid	217657	191	80	612	C01432	4152187	3458043	295412	1713945	3693140	1210797	3832689	3472858	4002868	3077979	1536530	1947619	1132469	1285000	3167209
lactamide	265698	232	415	94220		3314	3712	2122	1684	3229	1557	2959	2681	4474	3162	1700	1960	3081	5175	2598
kynurenine	769709	218	210712	25245862	C01718	9478	10239	10501	12707	6975	13098	7187	7244	2956	8379	11079	6358	26578	10599	14176
isothreonic acid	489385	292	1679	151152	C00639	9446	18622	14148	18332	8369	7829	10608	11768	11132	9244	11216	12010	16305	16693	11903
isomaltose	983199	160	127715	439193	C00252	496	507	632	1851	421	521	450	480	163	558	379	362	516	1797	559
isoleucine	359251	158	15	6306	C00407	477215	348012	405312	302181	363756	587633	686709	370883	403551	596711	629758	651104	891047	364285	448961
isocitric acid	616323	245	12267	5318532	C00451	4433	8937	7896	11583	4524	3960	8780	10630	7434	5342	8289	6262	6354	8105	7150
inositol-4-monophosphate	845976	315	4759	440043	C03546	1263	1454	2601	3705	1157	1541	2041	1821	1341	2208	1792	4233	2344	2309	1723
inosine	897434	230	84524	6021	C00294	13796	37279	28722	10993	71224	30587	31899	13679	28710	14414	19367	39928	64842	63786	70097
indoxyl sulfate	577333	277	31543	10258		1541	2936	2123	1180	2581	5649	5616	2562	1866	2912	1089	1608	1406	1420	2827
indole-3-propionic acid	732249	202	112556	3744		11819	2630	5981	14607	3048	3104	3234	5780	9086	10288	2353	5207	6033	755	22938
indole-3-lactate	764079	202	390397	92904		4166	1924	2563	10408	1765	4961	1715	6734	3521	3645	1772	6310	8442	30185	2664
indole-3-acetate	684929	202	69	802	C00954	27511	5235	4402	14330	1970	4736	2945	6020	10816	8402	6351	12532	9759	26543	10477
hypoxanthine	619128	265	1663	790	C00262	63848	69260	54397	23636	83640	65201	98568	58009	77949	78307	80015	112254	74014	123413	62054
hydroxycarbamate	325318	278	130396	16639161		6398	8756	4982	14526	9339	10178	3522	12181	3298	8925	7862	6369	5404	4349	13221
homoserine	443878	218	2849	12647	C00263	641	576	785	2066	850	1153	1039	1366	934	1160	1468	1002	2362	999	1328
homocystine	874865	128	2786	10010	C01817	1613	1590	1146	1430	758	986	1166	1568	1077	680	2502	921	2063	3416	637

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						FMO14	FMO15	FMO16	FMO19	FMO33	FMO35	FMO37	FMO41	FMO55	FMO63	FMO66	FMO71	FMO75	FMO8	FMO9
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	103728	60905	108186	107816	62540	167724	85962	61833	50882	79726	89384	26028	41572	136656	19614
heptadecanoic acid	751309	117	727	10465		10283	18171	16945	13710	34998	24046	17260	10099	13073	12218	23660	16603	10932	10703	12612
guanosine	954962	324	1966	6802	C00387	1695	3598	3016	1175	5561	2993	3381	1654	883	2059	2568	2928	4925	6088	1650
guanine	744307	352	2519	764	C00242	1655	2892	2495	1514	1889	3684	2601	1474	1112	3420	3040	3062	1483	6022	863
glycyl proline	691357	174	18496	3013625		977	2296	1710	1604	1523	1327	1428	956	1671	835	973	1052	1974	1446	1398
glycolic acid	227636	177	1971	757	C00160	14462	21385	23961	23245	16897	10791	11664	17986	17082	21941	7988	12590	19000	16572	9938
glycine	368707	248	6	750	C00037	590169	686463	1370230	505942	565114	694466	818630	600120	1206985	917429	820406	670852	1013781	816310	704054
glycerol-alpha-phosphate	590747	357	1687	754	C03189	23726	35807	40582	37472	18172	17107	15694	24220	20309	22719	20136	43689	17403	26564	23983
glycerol-3-galactoside	800205	204	100875	16048618	C05401	6713	2358	5057	4030	12216	26159	3376	4196	5843	16513	1622	9913	3011	6406	3122
glycerol	344466	205	30	753	C00116	589410	647781	722957	412445	443457	414498	443236	336986	472353	281019	354554	356193	430688	483074	2397154
glyceric acid	377308	189	394878	752	C00258	33697	57026	57412	47794	16913	10335	15165	18207	14245	28198	22701	26555	31112	52976	42229
glutaric acid	421260	261	1727	743	C00489	647	688	1107	876	735	569	753	584	1017	1405	546	600	861	1148	1302
glutamine	600315	156	18	5961	C00064	991036	645658	1194353	1006168	883110	917714	661159	771213	413438	528730	834802	393703	335085	1162716	293270
glutamic acid	529100	246	28	33032	C00025	58657	43459	77051	55117	59536	60207	70180	47872	60648	58333	71897	58575	76750	122995	52447
glucuronic acid	665901	333	344793	94715	C00191	7673	8966	9074	18394	5810	6067	9118	17899	7240	7971	5747	6468	9086	15985	8610
glucose-6-phosphate	808788	387	360626	5958	C00092	2959	2136	1719	1930	2246	789	1183	1416	2045	2622	2050	490	2668	1052	1667
glucose-1-phosphate	594647	217	3167	65533	C00103	3343	3265	6058	3039	4765	2784	3470	1640	3116	6279	2611	4382	5625	6987	2982
glucose	659798	319	22	64689	C00221	3592288	4345326	4173792	3570363	4061504	3175959	2150527	3326336	3158042	3189547	3136595	3099942	3256990	4175509	2946099
gluconic acid lactone	645815	220	3502	7027	C00198	17892	14035	9508	5958	27109	5340	18599	6389	12173	15073	7590	13377	38340	33304	14971
gluconic acid	693148	333	7501	6857417	C00800	148110	110747	71238	23962	174677	16774	170117	33962	75472	100179	36201	110355	210797	170057	116774
galactinol	1017580	204	1975	11727586	C01235	1029	1325	2383	2073	1286	993	2563	4575	2056	1452	4819	1448	1007	6023	1817
fumaric acid	390775	245	1718	444972	C00122	1100	1430	1845	1506	2529	2464	3868	2548	1157	3141	2220	5688	2795	2349	1501
fucose	578299	160	3009	439650	C02095	6873	9443	9211	9092	10034	7874	6312	8050	6755	8011	8489	7017	5967	9282	6902
fructose	639442	307	21	439709	C02336	201229	485620	376519	337038	307147	134424	104960	264108	275366	157456	194851	279110	360226	283588	294196
ethanolamine	342561	174	342038	700	C00189	43499	56288	26479	24431	50525	39735	45761	29145	22123	77391	31547	63267	18400	48618	56817
erythritol	471922	217	92	222285	C00503	21455	18317	15546	17916	6615	7924	8921	13523	12293	9321	11150	9755	9552	38040	11714
epsilon-caprolactam	353069	170	3101	7768	C06593	4926	3746	6379	9630	6016	7391	5251	10211	17688	3899	9243	4428	5370	13928	9722
docosahexaenoic acid	902819	91	87709	445580	C06429	1772	1269	4623	1971	3901	1443	2132	2268	1356	1332	4048	3396	2773	2539	2520
dihydrocholesterol	1082070	215	42937	66066	C12978	2668	5031	6733	6861	4796	3344	4699	4356	4021	1683	3387	4809	1807	3350	2329
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1000	1436	1112	1705	1067	1016	717	926	2321	816	1158	747	1167	1195	1257
cytosine	486724	254	2186	597	C00380	1924	1879	1612	687	1601	1873	1442	719	1644	1311	1668	1640	2650	941	1201
cystine	804619	218	94	595	C01420	5892	15368	19464	14736	5297	8261	13770	11580	17264	11246	7141	10128	18585	13737	1282
cysteine	500158	220	65	5862	C00097	2910	1316	5819	9625	4432	7175	7235	13768	12968	4790	3194	2556	5014	21373	5117
creatinine	502599	115	31	588	C00791	79197	353201	373030	40333	119877	118806	78529	62326	112711	59913	150495	182918	292595	78740	66662
conduritol-beta-epoxide	675635	318	2670	9989541		1888	2873	2374	2435	1407	1216	842	1313	2013	1421	1295	1006	2002	1567	1345
citrulline	621404	157	1712	9750	C00327	27384	45950	61067	34035	31348	49020	28457	30375	24057	28550	38451	37023	43297	34320	31475
citric acid	617342	273	288	311	C00158	211012	407073	370547	476010	237883	165792	409305	519835	378586	248769	409312	291551	327565	337506	401324
cis-gondoic acid	847372	367	87783	5282768	C16526	466	619	613	674	553	656	712	497	307	250	450	878	976	769	355
cholic acid	1109517	253	110403	221493	C05463	1256	527	956	689	632	674	515	12314	420	631	530	1139	743	931	694
cholesterol	1078536	129	19	5997	C00187	504680	594060	1120872	782199	863418	823884	496020	692437	757946	573609	1058624	1531245	886654	496405	582418
cellobiose	942758	361	120969	6255	C01971	956	429	1059	1526	985	1194	270	1184	576	1162	638	892	537	1480	301
capric acid	451790	229	726	2969	C01571	5417	3967	6590	14031	3759	4500	3999	4259	3590	12585	3873	4805	4925	4965	4583
butyrolactam	277199	142	2047	12025		28634	36594	33041	31278	35440	38710	31322	31598	2764	30524	44598	32188	38730	25484	28717
butane-2,3-diol	205778	117	485	262	C03046	332594	263027	164266	121841	34116	76852	224574	178130	302422	141205	106339	161418	193850	272405	222027
beta-sitosterol	1128225	129	3174	222284	C01753	3691	3690	1896	7804	2174	1920	1314	2975	2250	2822	1229	1658	1880	3207	2993
beta-glycerolphosphate	574470	243	22021	2526	C02979	1304	1839	1675	1704	1136	1447	976	1112	1210	1315	1400	1686	936	940	1412
beta-alanine	435564	248	148	239	C00099	1947	4021	1386	4379	1982	5180	2173	3825	1015	7940	980	3217	3152	3618	3540
benzoic acid	339067	179	36	243	C00180	130706	163347	147465	160740	140690	159998	138124	155792	223167	187869	196869	138444	192540	136511	123190
azelaic acid	610551	317	329430	19347555	C08261	1230	1069	1422	2383	1916	1607	1024	1117	1927	1343	1189	1623	1264	1721	1173
aspartic acid	480387	232	79	5960	C00049	18670	19900	25752	21710	20716	22178	28585	19905	19710	36914	35939	39347	25323	36846	19017
asparagine	553743	231	369588	6267	C00152	31146	31816	48680	45452	34061	41980	42845	26336	36351	28102	45139	27267	31385	61208	32717
arachidonic acid	837115	91	64589	444899	C00219	16236	26288	31993	19716	26236	21169	17123	15269	17918	9655	40689	27939	28646	10761	12971
arachidic acid	856421	117	291	10467	C06425	5234	6072	8006	7393	6848	7085	6398	5263	7355	4863	7068	7379	5177	6165	5269
arabitol	572730	103	372446	94154	C01904	6415	8547	11589	14986	3658	7313	6145	12512	11542	6072	9547	6701	7947	10350	10463
aminomalonate	455754	218	413	100714	C00872	30380	49393	47943	47914	31765	41312	18286	39265	19310	47694	25292	39992	47338	19764	52188
alpha-ketoglutarate	507392	198	294	51	C00026	1795	981	923	673	461	519	379	557	434	4425	589	360	391	1835	435
alpha-aminoadipic acid	573295	260	125502	92136	C00956	2470	1894	2126	3198	2309	2381	2983	1261	2838	1763	2820	1843	3804	1969	1448
allantoic acid	726050	259	117021	203	C00499	24609	35057	44410	25768	27629	26845	39492	25526	36159	28846	46202	58842	56600	33419	55545
alanine	243971	116	34178	5950	C00041	1803366	1147197	2153665	2633534	2437959	2220582	2471217	1703827	2040375	2167829	1921091	977558	826861	2696497	1614021
adipic acid	474435	111	125	196	C06104	3677	2550	4498	5402	4243	2445	2104	3136	9910	2803	2642	2175	3023	4679	2635
aconitic acid	586815	229	29	643757	C00417	869	832	1462	2010	2567	2097	4047	2888	1673	611	2288	1920	3392	939	720
5-methoxytryptamine	864466	174	284	1833	C05659	67915	130787	94166	83503	93671	113156	108141	50989	63810	75840	52781	165583	103428	254083	311245
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	891	1320	1095	6182	924	921	814	777	1184	1642	1772	2173	5191	776	1334
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	885	856	2173	753	1839	890	2072	601	4692	833	1212	1154	1460	11621	1114
5-aminovaleric acid	536657	174	1698	138	C00431	17218	8340	5302	28939	4977	7560	7565	29342	5777	56558	11608	21739	12298	3450	22964
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	2833	2661	2040	3941	1244	885	675	2153	3238	4079	691	2511	3183	1355	1327
4-hydroxymandelic acid	601658	267	131944	328	C11527	2109	1702	1387	1543	644	1315	1065	1648	844	1250	1009	978	1374	2077	1305
4-hydroxyhippuric acid	784581	294	12284	151012		377	398	368	954	174	396	951	524	87	363	233	405	289	365	423
3-ureidopropionate	554966	161	107897	111	C02642	1765	1946	1093	1918	1094	2289	2109	2150	887	2411	824	1170	1464	4377	1055
3-phosphoglycerate	610734	227	1667	724	C00597	940	801	656	530	960	668	335	501	519	1124	550	6370	704	1001	703
3-phenyllactic acid	516011	193	113643	3848		2429	1042	847	3019	716	1035	619	3366	2537	2656	898	4105	1004	21306	2297
3-hydroxybutyric acid	278632	191	145501	92135	C01089	122202	106692	68311	65753	774957	1431101	439301	79380	83456	62190	840462	401916	95735	43915	58522
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	300	1150	345	1034	628	698	314	560	153	860	413	386	348	571	1267
3-aminoisobutyric acid	452655	248	12265	64956	C05145	6563	10475	5759	10301	2684	3599	2874	16494	2411	2089	5615	3128	5133	20194	10470
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1193	1429	872	3696	1442	3488	803	1994	1802	1981	1718	2863	1072	1196	1589
2-picolinic acid	381532	180	389051	1018	C10164	2093	4299	2343	3938	1623	1704	1774	1599	2264	1735	1565	1358	1938	2542	3516
2-monopalmitin	890356	129	2080	123409		2374	3473	2615	4663	33943	2697	1814	4486	2012	2140	2270	2550	3325	35665	4535
2-ketoisocaproic acid	310761	89	208	70	C00233	11570	13143	13592	3941	1116	5731	619	2671	5430	13854	955	1989	1899	20120	2319
2-hydroxyvaleric acid	309587	131	25922	98009		11068	8597	5750	16560	6279	23112	6718	13414	6988	11543	9259	12760	13751	10456	14755
2-hydroxyglutaric acid	506306	247	2000	43	C02630	7565	12024	9406	19135	5387	7080	7974	11585	10450	13337	5462	8000	9603	12337	11377
2-hydroxybutanoic acid	258161	131	40	440864	C05984	70176	133423	41953	84645	181914	164644	145893	291534	75969	43162	208604	113403	160593	77576	59628
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		4847	14082	14036	18287	12830	25213	7557	5768	5822	5543	8921	15732	7988	9869	9216
2-deoxytetronic acid	433456	189	1208	150929		3522	7515	5044	6508	4853	4230	3937	3541	415	5478	9145	6778	10669	5150	5841
2-deoxypentitol	521785	231	21714	249377		1789	1139	1173	721	1425	2180	1059	1273	1281	1349	1400	1356	2032	1768	888
2-aminobutyric acid	285825	130	160842	6657	C02721	58713	34939	59616	90277	171082	338369	127403	65184	48999	57373	270916	57616	65672	42315	52899
2,5-dihydroxypyrazine	397526	241	2254	23368901		3010	2182	3489	3855	2211	3197	3234	5929	4227	5815	3496	4339	3018	3822	2487
2,3-dihydroxybutanoic acid	384796	292	31743	250402		1931	4103	2312	3147	1552	2151	1670	1387	1640	1668	2462	3952	6989	1948	1851
1-monostearin	959214	203	648	24699	D01947	2238	8780	6473	8253	1629	5733	3437	4807	2694	2951	4055	3369	4374	6443	1888
1-monopalmitin	901749	371	2070	14900	C01885	1940	8271	2934	7340	2780	3516	2621	3462	2691	3459	3938	4679	3311	3226	2712
1-kestose	1123027	361	14692	440080	C03661	800	803	626	501	353	409	170	365	860	1456	317	497	485	1063	1524

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						FMO14	FMO15	FMO16	FMO19	FMO33	FMO35	FMO37	FMO41	FMO55	FMO63	FMO66	FMO71	FMO75	FMO8	FMO9
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	1413	1741	1684	3163	2575	1416	2039	1622	1847	1417	2019	1492	2578	2475	1826
xylose	543267	103	169	135191	C00181	10050	11914	11376	16966	13776	9986	7613	22259	12387	9933	17815	8149	9643	20145	13879
xylitol	567437	217	5857	6912	C00379	2937	5464	3200	3784	4520	3238	3019	4425	2694	3392	6145	3730	4195	3213	4435
xanthine	701688	353	1669	1188	C00385	1600	3233	1171	1002	1048	1093	664	626	473	638	405	381	499	522	1438
valine	313502	144	3	6287	C00183	671323	714025	1217056	944086	1059390	971937	1514837	671078	1427146	915695	903377	882444	889947	503931	703421
uric acid	730691	441	23	1175	C00366	3704	18028	8259	7325	3842	4345	5742	5246	3503	6109	598	2672	5725	3116	3832
urea	329351	189	145496	1176	C00086	2222272	3267073	2914448	3807506	4220340	3321195	3173360	5745307	3740724	2638795	4253811	3001742	2803505	4355660	4094081
uracil	385735	241	1664	1174	C00106	12325	10273	7542	12430	15738	6402	4172	6066	4216	4774	10759	3356	9731	17209	8698
tyrosine	671252	218	16	6057	C00082	402912	365072	486453	383164	308838	326648	402090	568978	486196	243365	237942	560138	287534	466800	517222
tryptophan	780482	202	14	6305	C00078	379064	344237	348507	281957	352879	300499	478655	578405	350778	336055	255756	575303	365852	362003	589196
trans-4-hydroxyproline	484934	140	97	5810	C01157	562204	471162	539038	381438	454736	652548	380533	277098	686447	579455	281875	610344	533005	431613	407863
tocopherol gamma-	1026121	223	4545	92729	C02483	678	1044	1265	903	1890	2092	1866	1755	826	1320	969	535	922	1096	1560
tocopherol alpha-	1067809	237	100	14985	C02477	2939	22288	30416	4934	15729	19409	21938	34227	16330	23388	27727	23680	18215	12922	29698
thymine	420133	255	1692	1135	C00178	728	1498	1300	1290	863	723	525	1009	1130	828	699	538	550	920	1124
thymidine	349402	170	87703	5789	C00214	28624	36856	38088	36852	52931	52410	42927	88566	37607	31467	71905	58023	35359	49775	52555
threonine	409568	218	26	6288	C00188	172006	198686	300364	165212	163136	268402	270933	175218	646877	194661	170692	242540	242407	116365	169334
threonic acid	497572	292	172	5460407	C01620	4892	11485	17480	14220	13996	12675	30313	22744	7091	20791	12618	13785	38421	13454	8920
threitol	467595	217	770	169019	C16884	1842	1669	1735	1547	1414	1359	1043	3445	1392	1517	2081	1378	898	1805	1982
taurine	556690	326	411	1123	C00245	8817	6162	11407	6829	43555	60363	24030	10678	18458	46679	364	44776	68197	5119	15095
tartaric acid	534291	292	33985	444305	C00898	234	297	307	318	1145	282	241	596	467	245	325	282	223	252	321
tagatose	631835	307	33981	439312	C00795	4935	20597	1705	1303	1378	627	838	1341	409	648	689	717	1518	5732	1714
sucrose	915139	271	173	5988	C00089	2863	1911	6174	1252	5588	4160	5375	2060	715	1744	740	3453	1008	1510	1411
succinic acid	370608	247	161	1110	C00042	6411	9117	9808	11858	14690	19958	11902	8799	29618	8450	14867	6633	10629	19532	5949
sophorose	962064	307	132242	441432	C08250	340	388	372	603	370	328	536	326	397	181	823	219	474	511	266
shikimic acid	611100	204	286	8742	C00493	2478	1630	2568	15212	10456	2081	2651	17169	2980	8155	6571	5410	1555	4152	8876
serotonin	863824	174	364413	5202	C00780	99580	103969	144781	111323	47612	87210	71784	99632	24925	115367	65935	76103	44227	319173	153526
serine	395020	204	25	5951	C00065	882761	523726	802220	642706	724233	765316	781346	678055	1005381	794645	538836	1103866	823030	802725	944938
salicylic acid	480699	267	3063	338	C00805	1403	2040	1895	2857	3737	6901	3000	5753	3719	5281	6145	4360	2653	1451	3466
saccharic acid	699211	333	11214	33037	C00818	832	1569	301	1122	1495	807	1098	2270	984	1105	1516	1081	1232	1657	1375
ribose	553071	217	384948	10975657		14030	77138	45620	45078	39586	22715	34413	38536	30231	22170	83859	5297	36150	51021	52289
ribonic acid	599680	292	1683	5460677	C01685	4155	3511	4350	7286	15912	8172	1951	7943	5738	6744	4915	8131	6775	6969	8812
ribitol	575497	217	7362	827	C00474	1342	4026	1813	1619	3907	3234	1951	2011	1938	1419	2364	2549	1861	2481	3052
raffinose	1120886	361	3190	439242	C00492	1835	2631	4267	305	6692	5707	3659	349	1489	1711	274	1001	1075	655	456
pyrophosphate	547021	451	88522	1023	C00013	2178	2601	4047	2156	6763	3363	2242	4105	2557	3134	330	4679	5026	5735	4676
putrescine	588119	174	21703	1045	C00138	4606	3173	4354	5169	5956	7340	5432	6711	7482	7899	4409	9635	9204	6515	5867
pseudo uridine	813899	217	1688	15047	C02067	14168	14573	14618	29621	14948	14561	13496	37001	10667	17802	21881	11662	13020	23665	20831
proline	364716	142	8	145742	C00148	899226	583298	990856	455182	527775	852781	776360	173033	1128463	1169824	247361	1185543	787629	235977	302296
piperidone	275603	156	34023	12665		4156	24460	3614	1022	4055	6403	14326	3706	23067	3130	2120	11008	2953	7242	2444
pipecolinic acid	404121	156	2448	6931662		2901	3188	3692	3526	2600	3227	6266	1613	3029	4855	2037	2982	2370	1349	2776
pimelic acid	523205	155	33429	385	C02656	1650	1448	1540	1425	413	1724	1974	1861	1725	1684	1815	2067	1570	2176	636
phthalic acid	567345	147	46142	1017	C01606	9308	10787	8369	11466	10694	12044	17760	18395	7568	9558	28328	8574	13418	14849	9413
phosphoethanolamine	603912	299	1723	1015	C00346	2288	1662	1366	1689	23019	6519	7109	6672	7965	3597	7855	3948	10437	5825	8451
phosphate	345365	314	4	1004	C00009	645630	787189	827336	649299	1141070	698945	650941	1094768	656647	612750	1009783	790574	613584	1132214	745946
phenylethylamine	510327	174	2005	1001	C05332	13484	16675	11321	8801	15905	16248	8225	15629	14672	50593	4358	31822	12567	6066	21070
phenylalanine	537804	192	33	6140	C00079	176960	167489	202219	243932	283168	200548	197658	335818	375771	170157	229752	193011	174562	219738	239489
pentose	540818	103	360841	229		2660	1974	3234	5780	3054	2506	2340	2652	2544	1961	4768	1540	2301	2788	2656
pelargonic acid	399229	215	50	8158	C01601	16459	16470	18372	26671	34474	20862	26411	30929	26911	21861	42772	16302	22186	39610	26796
palmitoleic acid	706508	311	96	445638	C08362	1237	1070	878	5048	2625	2167	1610	4430	1965	2653	15125	1171	939	5524	8310
palmitic acid	713809	313	11	985	C00249	99504	79345	85616	213463	123322	127467	86621	236850	98161	133087	413654	94208	72863	211236	261071
oxoproline	485935	156	10	7405	C01879	874741	739490	933942	1144718	1096293	910979	790199	1318390	759542	729355	1007751	937350	924135	1127005	1166657
oxalic acid	260513	190	4923	971	C00209	4247	7786	4297	5831	664	8805	2324	5650	2743	3436	18354	2778	5360	4514	5960
ornithine 3TMS	527113	142	1821	6262	C00077	180971	151148	256460	206416	236372	226822	176045	138074	421204	207771	124481	234411	270538	139427	212119
oleic acid	779120	339	43	445639	C00712	23193	15136	16760	78831	1799	40519	1103	2740	922	49061	188231	2992	1407	85101	10226
oleamide	849710	144	20961	5283387	C19670	28191	13365	21115	28341	15892	34095	10802	21352	14044	36455	4087	34891	24363	16668	23884
nonadecanoic acid	822782	117	46258	12591	C16535	2465	2516	4439	3251	5352	1087	1384	6912	1451	4198	5754	4976	1133	5116	5761
nicotinic acid	353428	180	327312	938	C00253	504705	403267	623265	259490	3575	13900	2835	6459	6248	7472	8116	3872	4208	515868	167104
N-acetylglycine	356109	174	97747	10972		1438	1618	985	845	1785	1640	1869	603	1065	907	1075	1322	1445	1335	1007
myristic acid	634414	285	127	11005	C06424	3140	2905	2660	5096	5110	3962	9413	6666	3817	4806	30275	2567	2678	10338	7391
myo-inositol	730022	305	1741	892	C00137	213104	427144	365942	254012	618105	425678	339988	323556	382837	260535	546190	416397	629453	299567	567660
mevalonic acid	498785	247	127978	439230		659	986	1250	2443	606	725	682	621	1753	687	1062	655	855	785	870
methionine sulfoxide	637588	128	1678	158980	C02989	47660	29203	53485	43375	57440	114237	86738	60550	88912	117735	46482	161424	124234	30153	26507
methionine	483560	176	45	6137	C00073	148311	151275	230709	153531	164179	148796	183518	72758	291189	110152	69049	109036	109626	108239	146559
methanolphosphate	289520	241	5393	13130		24429	19336	24173	25370	31597	25546	36812	29605	29585	25828	23867	27380	31216	37921	25191
mannose	645856	205	70	18950	C00159	133231	191591	165375	216545	151580	163413	111215	366065	127924	142061	244893	163641	156739	223080	277627
maltose	946601	204	1979	439186	C00208	8867	34288	10500	26673	23961	17249	21457	28606	9638	3832	10166	9707	56304	14466	29649
malonic acid	305372	233	16918	867	C00383	439	181	161	323	190	305	475	280	218	392	395	291	209	413	358
malic acid	463180	233	1391	525	C00711	3726	9576	4617	4962	9212	4113	5162	5896	6906	3350	7904	3953	5146	6456	9993
maleimide	245118	154	1743	10935	C07272	12171	11900	11343	39200	13010	10301	13961	25484	10126	8729	11775	12961	7681	14508	23322
lyxitol	573587	217	233	439255	C00532	14616	13816	21395	10097	21665	24060	26337	17756	21121	16668	10548	11827	14354	15999	10608
lysine	663483	317	12	5962	C00047	49981	25784	45186	52928	29558	40378	30448	63112	61843	51137	19638	41150	44446	26731	37723
linoleic acid	777285	337	471765	5280450	C01595	12497	8789	13648	31643	20619	17854	15805	43052	15764	18545	67794	16643	11214	37000	43145
levoglucosan	569637	204	3169	2724705		706	745	1030	1023	1396	826	739	1827	840	934	1671	1087	848	1141	808
leucine	346101	158	9	6106	C00123	1022455	832597	1456272	1282684	1320155	1355308	1923136	944927	1363929	814981	1106993	1357282	917644	695531	825554
lauric acid	547906	117	49	3893	C02679	11711	10520	14079	20420	18811	15764	223471	25886	15212	19707	336109	10946	12069	256626	16051
lanosterol	1129573	393	133475	246983	C01724	233	223	282	373	160	226	205	209	283	237	294	274	186	328	342
lactose	936998	204	217651	6134	C01970	1188	1851	1496	5499	5105	1417	1689	4112	1202	1239	2275	1537	1301	1867	4357
lactic acid	217657	191	80	612	C01432	4075800	2498962	730953	1277279	3013528	3803807	3127148	350731	1514725	3668474	2386400	1783592	4589038	2521528	826188
lactamide	265698	232	415	94220		4674	5301	5286	2354	2179	1585	2910	1907	1846	3146	1395	1862	4278	2513	1686
kynurenine	769709	218	210712	25245862	C01718	8572	10579	19112	13281	13203	11846	8093	19750	7987	7007	10777	5705	6613	11912	10453
isothreonic acid	489385	292	1679	151152	C00639	8941	10041	8322	17883	15087	10331	9711	18989	15035	10342	13345	9174	10054	13978	14161
isomaltose	983199	160	127715	439193	C00252	371	541	724	197	646	126	802	518	291	314	513	455	464	438	733
isoleucine	359251	158	15	6306	C00407	414962	350674	589314	520835	450944	491445	745804	458729	747508	396795	599713	458091	405301	365488	453982
isocitric acid	616323	245	12267	5318532	C00451	7620	9911	7110	8256	11671	5833	8697	10442	6596	6621	12990	5986	6748	10655	11714
inositol-4-monophosphate	845976	315	4759	440043	C03546	779	1443	1657	1519	3139	1148	1866	3564	2981	1271	2230	1095	2502	2736	2950
inosine	897434	230	84524	6021	C00294	13083	20694	30129	19603	20192	26086	13990	39882	27137	30015	16747	30979	36424	44172	53518
indoxyl sulfate	577333	277	31543	10258		1331	1901	1736	2609	2444	1260	2755	5213	4538	2652	1994	2534	4026	2148	3211
indole-3-propionic acid	732249	202	112556	3744		9591	8706	5603	5819	11324	7810	15377	6199	1350	3952	2354	4515	7737	9729	12309
indole-3-lactate	764079	202	390397	92904		3389	8207	6799	4038	13774	11340	8135	6209	8645	3006	5049	6097	5971	6226	5942
indole-3-acetate	684929	202	69	802	C00954	4385	4579	4101	2314	10517	11971	8623	8530	2792	2834	10888	7622	6395	3215	6426
hypoxanthine	619128	265	1663	790	C00262	98991	139927	110183	105318	124024	94787	49615	81758	82465	74378	82660	40958	98545	100906	139864
hydroxycarbamate	325318	278	130396	16639161		3930	3110	12788	8785	12267	9737	9119	8530	16285	8998	7790	6361	7576	10963	5625
homoserine	443878	218	2849	12647	C00263	908	1000	1083	984	781	1069	762	1072	1066	1375	1261	1543	1013	1053	1299
homocystine	874865	128	2786	10010	C01817	762	1222	1508	1889	826	1108	834	1374	476	866	1276	913	877	879	951

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						Day 28- DOX														
						FMO14	FMO15	FMO16	FMO19	FMO33	FMO35	FMO37	FMO41	FMO55	FMO63	FMO66	FMO71	FMO75	FMO8	FMO9
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	94177	111268	113748	123957	50006	87004	51626	78479	69490	78209	4634	69530	44444	71662	131435
heptadecanoic acid	751309	117	727	10465		9921	10233	8745	20235	12809	12128	10251	25053	12541	15833	40139	10535	8801	23330	26243
guanosine	954962	324	1966	6802	C00387	1409	2520	2940	2210	1919	2452	1689	3854	3095	3557	1034	2794	4230	4466	4640
guanine	744307	352	2519	764	C00242	2825	4687	3336	4861	9690	2803	2590	3408	3505	1597	5952	1235	3770	4596	4195
glycyl proline	691357	174	18496	3013625		1458	685	1207	936	1318	1353	1782	1154	2201	1560	1125	2152	2780	853	1297
glycolic acid	227636	177	1971	757	C00160	15035	20218	17312	16890	53375	37116	22329	23249	18151	19522	22954	13909	89564	25948	17166
glycine	368707	248	6	750	C00037	927364	888925	958014	653420	677053	889321	529384	623427	1068458	985102	475335	1276012	1128621	741210	869525
glycerol-alpha-phosphate	590747	357	1687	754	C03189	30992	18045	38021	25615	56477	29048	34800	27905	37784	17833	30384	47844	32385	32868	50711
glycerol-3-galactoside	800205	204	100875	16048618	C05401	1398	2916	4116	13977	3426	3329	4168	10323	4281	10740	2171	5298	4590	3538	5609
glycerol	344466	205	30	753	C00116	459931	530115	371040	448920	513466	339778	338366	875354	333718	240820	628361	283016	336920	689667	698049
glyceric acid	377308	189	394878	752	C00258	21390	20109	21674	33539	37236	19128	17940	20234	23139	16023	22208	14161	26029	32075	27200
glutaric acid	421260	261	1727	743	C00489	1681	1001	933	773	755	579	668	948	1602	683	1138	762	719	1485	1331
glutamine	600315	156	18	5961	C00064	646292	718798	798822	1414170	472734	570798	498452	999050	451307	512412	507281	640274	366914	765050	927581
glutamic acid	529100	246	28	33032	C00025	59413	87253	77248	79713	90345	74559	61956	46512	58188	54893	56053	60133	75169	49557	73070
glucuronic acid	665901	333	344793	94715	C00191	6851	10977	5877	15820	6995	8536	6873	18742	8106	5223	9304	5249	7443	10646	8900
glucose-6-phosphate	808788	387	360626	5958	C00092	1772	1581	2902	1812	6822	1334	1530	1838	1417	1409	1875	1628	1255	1428	2516
glucose-1-phosphate	594647	217	3167	65533	C00103	6738	4648	2493	7018	7354	3443	3116	3789	5893	2166	5191	2317	5780	10744	8383
glucose	659798	319	22	64689	C00221	2231458	4104367	3040963	4260284	2810041	2848886	2445769	4810086	3107381	2820461	3905531	3252782	2879272	3408873	4142329
gluconic acid lactone	645815	220	3502	7027	C00198	14333	12411	6680	15008	6267	8621	9043	19156	8932	6111	18866	7694	18930	19033	20753
gluconic acid	693148	333	7501	6857417	C00800	93792	95354	22257	95456	46032	52047	53876	148471	78505	40328	144812	44831	117152	142261	181453
galactinol	1017580	204	1975	11727586	C01235	1721	2111	4040	1278	6171	4911	3786	2172	2043	2343	1295	2053	1569	1977	1659
fumaric acid	390775	245	1718	444972	C00122	1481	1577	1999	2596	5723	1555	3380	3916	3989	1715	3721	2287	2750	2224	2282
fucose	578299	160	3009	439650	C02095	5906	9501	6026	8775	6962	6081	6908	12775	7522	5017	6726	8460	7809	8123	11146
fructose	639442	307	21	439709	C02336	139316	210982	229085	296344	217149	209630	219207	442073	250832	219114	265700	257873	260946	238634	345069
ethanolamine	342561	174	342038	700	C00189	41388	61419	57042	45129	73369	48344	38849	62475	41652	46454	87516	34186	30281	78875	43483
erythritol	471922	217	92	222285	C00503	8813	12569	10651	12742	15519	11600	10672	18293	11773	10838	13183	9773	9160	12581	11087
epsilon-caprolactam	353069	170	3101	7768	C06593	7320	9255	9223	11404	6741	11951	4455	4625	5647	14784	3368	11690	8400	4400	6089
docosahexaenoic acid	902819	91	87709	445580	C06429	1360	1996	1629	2978	1377	2412	1234	2930	1738	1869	2074	2165	2388	2266	3372
dihydrocholesterol	1082070	215	42937	66066	C12978	4909	4511	4923	4034	6964	4629	9092	8514	5045	3735	5717	6516	2684	7549	5075
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1241	1101	1141	1265	1247	1133	1625	2549	1946	1040	1397	1079	951	1572	1981
cytosine	486724	254	2186	597	C00380	767	1905	2505	2456	1685	1605	1903	2135	2167	1165	1660	366	1605	1341	1599
cystine	804619	218	94	595	C01420	10662	22327	20341	21950	6817	12711	11165	32267	6523	15623	1075	27423	25112	31984	34570
cysteine	500158	220	65	5862	C00097	17668	18290	12428	18468	7556	9653	8182	3468	3071	8712	2806	9906	11644	2912	7961
creatinine	502599	115	31	588	C00791	44141	124859	91000	85652	195582	158947	110548	83229	142106	125666	85461	154435	180477	82110	99172
conduritol-beta-epoxide	675635	318	2670	9989541		1601	2748	1669	1232	1352	3008	2013	2231	1883	2316	1475	2031	1331	1800	1672
citrulline	621404	157	1712	9750	C00327	48675	30294	46951	57436	33410	35774	30724	58872	59978	34614	40250	34253	53143	34026	42506
citric acid	617342	273	288	311	C00158	320689	483251	355773	373105	501929	288443	435906	513943	354365	362703	706146	312638	337012	476530	462266
cis-gondoic acid	847372	367	87783	5282768	C16526	483	295	527	815	593	669	219	1349	623	813	1486	595	349	547	1047
cholic acid	1109517	253	110403	221493	C05463	408	618	474	1027	749	946	603	1036	451	618	662	1963	735	925	812
cholesterol	1078536	129	19	5997	C00187	538123	567438	637275	528984	705634	601427	993335	1186959	620373	662098	761994	862265	497881	1039126	814572
cellobiose	942758	361	120969	6255	C01971	420	610	488	2037	1102	791	960	1646	407	514	572	760	1473	546	1435
capric acid	451790	229	726	2969	C01571	3847	3566	3734	6231	4708	4469	10583	6108	4968	5662	20484	4020	4395	14255	5921
butyrolactam	277199	142	2047	12025		26398	19173	17900	36326	35099	24178	29988	52609	29580	19359	42444	20525	23575	27570	44988
butane-2,3-diol	205778	117	485	262	C03046	315481	519756	306877	111285	144785	96175	177604	160898	123395	138086	160992	109242	268072	144481	98441
beta-sitosterol	1128225	129	3174	222284	C01753	4885	5634	7586	4716	10501	6420	11117	6956	4943	2619	4296	7562	3200	9444	3698
beta-glycerolphosphate	574470	243	22021	2526	C02979	1370	1426	299	1538	1932	1237	2047	1654	1410	1028	2107	1373	1156	914	1825
beta-alanine	435564	248	148	239	C00099	2258	2941	2078	2471	2394	3588	5227	6165	6320	3063	242	3300	3301	3851	2930
benzoic acid	339067	179	36	243	C00180	102808	115543	130682	142013	249115	208542	204146	266061	163986	177058	239487	135888	162930	146689	168789
azelaic acid	610551	317	329430	19347555	C08261	1100	977	1160	1990	2461	1701	1361	815	1447	2303	2613	1003	1225	1981	1764
aspartic acid	480387	232	79	5960	C00049	27208	27050	33268	36206	46729	32083	25666	25784	27236	23003	38610	27497	29634	25904	28746
asparagine	553743	231	369588	6267	C00152	45422	33145	45011	63005	22018	29856	27746	39740	27566	28856	26905	49003	26172	35712	52939
arachidonic acid	837115	91	64589	444899	C00219	8179	8604	12842	17049	17056	11204	13395	23124	13321	15117	24213	15890	13772	17249	19850
arachidic acid	856421	117	291	10467	C06425	4989	3902	4560	5984	6705	5918	4860	8970	5211	7363	8794	5972	3897	6977	8443
arabitol	572730	103	372446	94154	C01904	11510	9129	14133	12039	17023	17279	17696	11163	16554	12210	10132	15858	10797	10511	8314
aminomalonate	455754	218	413	100714	C00872	51878	20234	56807	34315	30681	43359	29540	24599	45630	43602	17422	47881	61125	61569	42206
alpha-ketoglutarate	507392	198	294	51	C00026	3201	7421	2190	1669	2889	494	1165	1092	851	447	559	511	365	3695	2183
alpha-aminoadipic acid	573295	260	125502	92136	C00956	2904	2566	3532	3013	2253	2330	3620	2782	3139	3385	2653	2706	2428	2369	2412
allantoic acid	726050	259	117021	203	C00499	24906	71499	26662	51721	76214	77010	33785	67043	78392	42473	12082	27487	30347	24676	31090
alanine	243971	116	34178	5950	C00041	2571473	2203504	2432178	2160006	1546392	1456256	1541041	1337959	1630436	2763852	1221684	1713946	1308679	1401773	1796607
adipic acid	474435	111	125	196	C06104	4837	2632	2619	4002	2987	3944	2210	3838	2201	5494	5145	6003	2380	4137	3859
aconitic acid	586815	229	29	643757	C00417	530	1353	645	564	2977	1817	2725	3776	2334	2043	2836	1916	1870	768	1693
5-methoxytryptamine	864466	174	284	1833	C05659	81366	85770	117459	92283	59834	71327	56329	125509	29694	92759	52906	63500	35541	256612	192202
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	806	628	806	1037	911	1049	964	1582	471	944	1385	1120	999	1002	1005
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	571	2829	1693	1924	665	870	515	1102	492	1142	1336	1563	391	1096	2251
5-aminovaleric acid	536657	174	1698	138	C00431	14113	7186	8027	5327	13214	9911	13755	14830	26749	12072	2610	21769	7108	22257	2539
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	1027	850	1318	762	1744	2005	2709	1450	1571	828	1519	1252	2051	823	875
4-hydroxymandelic acid	601658	267	131944	328	C11527	1081	1251	1769	2020	1314	1134	1456	2417	1102	944	1348	1326	4631	1983	994
4-hydroxyhippuric acid	784581	294	12284	151012		344	396	421	415	424	523	324	354	243	207	338	364	436	585	497
3-ureidopropionate	554966	161	107897	111	C02642	961	1371	2653	1925	2250	995	2101	2679	1291	1844	1735	2030	2533	1666	1376
3-phosphoglycerate	610734	227	1667	724	C00597	1326	897	574	716	6895	1173	489	1755	1842	766	782	729	2768	2146	4832
3-phenyllactic acid	516011	193	113643	3848		3008	1519	2583	949	6827	5730	6068	1835	3814	1067	823	3441	1204	1053	1104
3-hydroxybutyric acid	278632	191	145501	92135	C01089	48750	59950	48846	87782	66279	50246	122049	95778	48875	79253	488851	64234	40326	119020	103722
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	459	438	1094	1378	727	482	375	942	1004	575	773	344	578	712	316
3-aminoisobutyric acid	452655	248	12265	64956	C05145	10078	7874	11802	9032	3749	4606	3201	13070	10173	2517	5286	9481	3955	15381	4292
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1255	1301	846	1230	2402	1619	1438	2648	1395	1001	1940	1241	1152	1883	2044
2-picolinic acid	381532	180	389051	1018	C10164	2992	2752	2995	2550	2273	1990	1608	2361	1437	1976	2383	1916	1362	3190	2075
2-monopalmitin	890356	129	2080	123409		2091	1664	29194	2368	37445	2156	2431	2811	2084	33052	40440	2361	1673	2939	3374
2-ketoisocaproic acid	310761	89	208	70	C00233	9384	22320	15248	17686	18670	2819	16371	3202	9710	1913	2437	836	4056	11630	18426
2-hydroxyvaleric acid	309587	131	25922	98009		6652	7983	8732	14883	11190	11760	13896	9575	7769	5816	12919	6174	6084	9982	16630
2-hydroxyglutaric acid	506306	247	2000	43	C02630	10118	7935	7788	13337	12031	13118	10538	21727	15635	11401	12334	13930	13464	10300	13842
2-hydroxybutanoic acid	258161	131	40	440864	C05984	57027	114916	51377	85284	183906	139785	127219	81909	39984	96490	259641	39048	60323	58450	85564
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		8084	6254	7124	21722	6305	9227	6031	8064	5376	8232	8918	7545	7929	6025	11093
2-deoxytetronic acid	433456	189	1208	150929		3166	2436	3099	6113	4185	3267	1078	2153	4273	4581	6297	4480	4138	4455	1644
2-deoxypentitol	521785	231	21714	249377		835	1269	1091	1747	1835	1188	491	1726	1042	854	2403	991	1303	1464	1027
2-aminobutyric acid	285825	130	160842	6657	C02721	42195	37228	44368	63494	40940	50512	33050	24230	30492	49235	73839	35860	26994	35324	43749
2,5-dihydroxypyrazine	397526	241	2254	23368901		5128	4138	4394	6322	6382	4351	4546	5515	3811	2686	3724	3887	5143	6768	5993
2,3-dihydroxybutanoic acid	384796	292	31743	250402		1580	1708	1778	2716	1638	2157	2501	2924	4919	1726	2862	1942	2548	2301	1599
1-monostearin	959214	203	648	24699	D01947	6248	2878	4219	9186	4052	4463	3799	5608	3535	2594	3878	2988	3675	7087	6444
1-monopalmitin	901749	371	2070	14900	C01885	2428	2156	2349	3451	3828	3414	2629	4951	3936	2635	2917	2373	2307	3482	3231
1-kestose	1123027	361	14692	440080	C03661	1432	1508	2698	671	3032	2591	880	515	758	1339	330	742	326	836	468

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						Day 300 - DOX														
						FMFO55	FMFO63	FMFO66	FMFO71	FMFO75	FMO14	FMO15	FMO16	FMO19	FMO33	FMO35	FMO37	FMO41	FMO8	FMO9
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
zymosterol	1088064	129	110304	92746	C05437	1607	1203	1630	2724	2563	1380	1528	2320	1270	2011	1230	1684	2446	3429	1396
xylose	543267	103	169	135191	C00181	8722	6716	11220	9575	12745	9177	8846	7779	8959	9099	10411	7206	8652	11436	8256
xylitol	567437	217	5857	6912	C00379	13602	2855	5449	3348	4724	2679	5927	3575	4941	11235	10473	3965	4376	4008	8730
xanthine	701688	353	1669	1188	C00385	589	573	768	663	753	600	549	444	806	813	440	594	491	388	394
valine	313502	144	3	6287	C00183	1016186	1000444	878664	863782	791980	987403	661839	900168	837415	880636	845847	1024470	656324	565065	618476
uric acid	730691	441	23	1175	C00366	5856	2802	6624	4953	7218	3354	3965	4597	8025	5410	6133	4009	3702	7005	5141
urea	329351	189	145496	1176	C00086	2776545	3756799	3527568	3244018	229276	3473375	2411906	3127400	3707141	927523	2881097	3644385	3199990	4805648	2572750
uracil	385735	241	1664	1174	C00106	1541	1921	4039	3155	6497	5047	2091	1338	3843	6249	4732	2384	2079	5766	6253
tyrosine	671252	218	16	6057	C00082	559405	501535	399376	478512	472540	339168	340295	339298	371538	414317	355960	326442	463619	545324	371347
tryptophan	780482	202	14	6305	C00078	519894	728098	752741	646892	595492	476270	508121	336112	455455	354806	428965	521131	594093	663631	440636
trans-4-hydroxyproline	484934	140	97	5810	C01157	143985	429937	311394	177152	285689	222411	362092	320610	162469	287880	499982	390276	410764	133039	224925
tocopherol gamma-	1026121	223	4545	92729	C02483	1394	1346	1645	887	1321	1582	1408	813	797	552	702	980	626	776	1168
tocopherol alpha-	1067809	237	100	14985	C02477	19194	28652	67422	16544	30460	15244	23662	27641	27506	16971	17512	29747	24101	38087	20525
thymine	420133	255	1692	1135	C00178	568	1841	843	1276	1377	1572	624	745	759	1289	1359	538	423	420	656
thymidine	349402	170	87703	5789	C00214	37445	39579	42207	42701	36582	31540	32398	22826	25719	55276	43863	27940	40920	33150	34546
threonine	409568	218	26	6288	C00188	311910	200022	214271	215974	293739	211585	249010	277429	154140	200390	350055	240241	177552	229218	169105
threonic acid	497572	292	172	5460407	C01620	12295	6057	18649	23053	18642	5557	27974	28873	22161	11849	11785	31159	7207	10985	5085
threitol	467595	217	770	169019	C16884	1688	1635	1915	1255	1475	1442	1338	1746	2264	1421	1552	1209	1911	2505	1183
taurine	556690	326	411	1123	C00245	33492	4449	3548	61337	41536	9528	4159	3819	7987	18603	76039	8530	25900	6813	74194
tartaric acid	534291	292	33985	444305	C00898	1647	248	270	305	1077	240	1795	1283	315	1184	2309	1223	291	235	827
tagatose	631835	307	33981	439312	C00795	2344	752	969	973	6414	915	2201	14091	1445	1018	1209	1272	845	5998	2500
sucrose	915139	271	173	5988	C00089	368	3442	1827	1161	719	1950	2143	347	605	649	2270	486	3195	4826	4871
succinic acid	370608	247	161	1110	C00042	9753	9570	16013	9539	11175	6802	13402	12951	14294	7538	13923	8390	16251	15526	8621
sophorose	962064	307	132242	441432	C08250	349	410	474	275	475	433	376	414	351	353	363	258	276	449	747
shikimic acid	611100	204	286	8742	C00493	8512	3425	3166	13601	1799	3499	5582	4952	5264	10207	2193	3119	8148	4062	3203
serotonin	863824	174	364413	5202	C00780	61415	72421	53442	87193	38877	116041	21315	90036	204914	67160	56660	101709	92007	67777	87696
serine	395020	204	25	5951	C00065	591288	675718	702683	658012	613349	597807	747240	546779	405187	810199	1017344	745588	782688	770166	670028
salicylic acid	480699	267	3063	338	C00805	2978	6857	5539	6610	5676	1578	2550	1531	3207	8221	7207	2527	10296	3479	2545
saccharic acid	699211	333	11214	33037	C00818	985	1195	1144	1481	1101	1142	1132	1084	1331	795	1333	1350	1159	5588	755
ribose	553071	217	384948	10975657		28207	27607	42779	21121	38124	15810	24092	17555	47278	19338	22114	20776	16798	31839	16246
ribonic acid	599680	292	1683	5460677	C01685	10557	2102	10489	3478	8230	1190	8080	3453	2469	5503	7498	7891	3554	2178	5638
ribitol	575497	217	7362	827	C00474	2239	1884	2230	2744	1513	1186	1804	528	2771	2035	3097	1652	2144	2956	2619
raffinose	1120886	361	3190	439242	C00492	359	1804	1538	801	319	754	1252	4006	348	691	1975	1978	2162	2705	548
pyrophosphate	547021	451	88522	1023	C00013	3350	3712	1973	1662	3145	3193	1184	4711	3054	2295	1973	3021	3314	2238	3041
putrescine	588119	174	21703	1045	C00138	6043	7037	7862	4511	6126	3467	4235	5249	5808	6526	8218	8057	6725	5818	4239
pseudo uridine	813899	217	1688	15047	C02067	13606	9015	11631	14236	17983	12399	12049	12771	17871	13401	13927	8408	13573	15066	12903
proline	364716	142	8	145742	C00148	489002	653091	565872	357839	635716	494533	903818	643849	284490	432801	854022	625158	575096	244134	507209
piperidone	275603	156	34023	12665		4236	4845	14385	4539	3404	6081	6549	5998	3384	1049	18087	8801	3531	25975	5732
pipecolinic acid	404121	156	2448	6931662		6155	2283	2154	2104	3557	11150	3542	3639	2413	1651	3605	4845	3486	1943	9979
pimelic acid	523205	155	33429	385	C02656	2192	2011	2255	1002	1715	2082	3563	958	2662	1481	1824	968	1538	1068	1165
phthalic acid	567345	147	46142	1017	C01606	21184	7925	10993	10226	10466	7438	12458	9251	12521	41889	18583	7768	33800	10239	15635
phosphoethanolamine	603912	299	1723	1015	C00346	1210	1731	2643	4372	1818	2244	522	1614	2039	4731	9688	3311	1276	828	3745
phosphate	345365	314	4	1004	C00009	410683	634603	578120	557363	543634	458953	487413	456528	416018	416598	591653	781548	412607	415005	433257
phenylethylamine	510327	174	2005	1001	C05332	10123	20312	4825	26787	8260	7195	13996	43089	8692	13394	21974	10975	14762	23239	17005
phenylalanine	537804	192	33	6140	C00079	239607	286976	259583	246178	211987	223786	187408	159524	227708	228800	231987	190365	263521	250957	208121
pentose	540818	103	360841	229		2196	2000	13950	2724	2729	2528	2181	2206	2263	2616	14374	1231	8572	10595	1833
pelargonic acid	399229	215	50	8158	C01601	35290	29801	32576	20898	31064	20628	21524	16876	23242	27562	30791	19654	25778	26291	22368
palmitoleic acid	706508	311	96	445638	C08362	2756	3158	2673	6814	980	4054	2500	2507	2286	2427	644	1928	3389	1586	3054
palmitic acid	713809	313	11	985	C00249	141661	183775	113474	245454	102829	171487	159795	148079	167031	136373	90028	113669	152988	128623	160216
oxoproline	485935	156	10	7405	C01879	928966	998031	1151699	1162480	976156	939884	893627	633928	1067492	905932	1128179	1001989	936667	1061935	1367367
oxalic acid	260513	190	4923	971	C00209	5575	3935	7143	3692	1737	5520	4109	2725	6915	7059	4055	6643	6920	3271	7237
ornithine 3TMS	527113	142	1821	6262	C00077	152458	162648	165090	157365	130153	151058	118592	199375	118660	142755	241403	156384	130409	130386	186831
oleic acid	779120	339	43	445639	C00712	2039	58927	38758	86396	43782	5555	3228	43853	54741	1164	13930	40697	1948	858	55993
oleamide	849710	144	20961	5283387	C19670	15757	25327	25597	37297	15362	25651	43233	23947	28280	14914	23862	24603	16800	16825	35518
nonadecanoic acid	822782	117	46258	12591	C16535	4220	3887	4771	5500	6288	3799	6412	6655	6718	3876	4030	3707	5872	1505	5632
nicotinic acid	353428	180	327312	938	C00253	1957	4040	3361	2224	3540	187845	188781	596714	186748	2129	4487	3557	2592	1356858	343581
N-acetylglycine	356109	174	97747	10972		566	796	1175	1144	1191	877	1023	814	1487	938	958	515	565	2232	443
myristic acid	634414	285	127	11005	C06424	10274	7214	4547	8774	3565	5269	4953	3345	4343	13717	3159	3255	15060	4924	4863
myo-inositol	730022	305	1741	892	C00137	185858	145960	210441	442523	213124	178430	181599	144294	232099	309128	519200	198798	247696	241809	529957
mevalonic acid	498785	247	127978	439230		988	893	1308	2227	3429	639	683	1066	760	1250	887	1878	739	1648	1256
methionine sulfoxide	637588	128	1678	158980	C02989	93960	103568	121913	69017	99141	28650	60515	46310	66216	62429	105905	125543	102780	55274	44198
methionine	483560	176	45	6137	C00073	82219	117932	87660	87383	94595	133118	111392	103532	78240	74765	103132	91185	111899	84502	79273
methanolphosphate	289520	241	5393	13130		23045	50032	34487	31494	28209	19323	29666	42218	26558	25652	23044	37994	32456	42172	23424
mannose	645856	205	70	18950	C00159	208170	183844	201610	212365	207320	208678	186978	238285	206851	180452	149759	246493	237861	242659	228372
maltose	946601	204	1979	439186	C00208	3307	2710	2559	2434	17306	12358	9465	4787	2641	33405	19765	9916	3344	8398	30842
malonic acid	305372	233	16918	867	C00383	533	347	452	396	342	363	741	531	514	438	300	525	256	240	454
malic acid	463180	233	1391	525	C00711	4788	4704	10094	6939	5684	5247	5019	4330	11404	8689	8101	4726	6758	2874	15896
maleimide	245118	154	1743	10935	C07272	11162	9188	12237	10052	8604	12165	28883	14238	13098	7589	6978	11257	10679	17454	12577
lyxitol	573587	217	233	439255	C00532	9359	13211	15519	8611	10189	12124	12603	15145	9705	11882	30522	13006	15429	16533	10538
lysine	663483	317	12	5962	C00047	64751	47276	52345	60431	38462	55953	22150	55735	55443	57440	70278	51213	38036	38863	43158
linoleic acid	777285	337	471765	5280450	C01595	20587	26696	21388	40458	14850	28149	25505	21431	21209	15494	8122	15993	22829	16428	25225
levoglucosan	569637	204	3169	2724705		1038	741	1311	1189	1266	829	2961	1386	1119	2470	1401	1089	994	3386	1031
leucine	346101	158	9	6106	C00123	1135587	1414393	1226959	1117199	1128275	1360817	912304	873066	1080329	1135483	796378	1108348	970433	661052	781355
lauric acid	547906	117	49	3893	C02679	263355	25736	18218	17128	16074	17383	17219	9386	13606	268623	13887	13289	243592	11158	14281
lanosterol	1129573	393	133475	246983	C01724	302	318	298	319	340	425	313	479	330	296	312	325	395	467	246
lactose	936998	204	217651	6134	C01970	2380	2043	1538	4425	2208	1729	1507	1440	2298	5854	1225	7178	1552	1995	1739
lactic acid	217657	191	80	612	C01432	1431240	2378928	2366995	3172624	1455157	3170806	1544689	1822899	3237525	2640501	2839172	2198420	3280325	559227	2297147
lactamide	265698	232	415	94220		991	2479	2199	2287	590	3589	1677	1920	3962	1692	2475	2507	2754	798	2001
kynurenine	769709	218	210712	25245862	C01718	5343	9113	9709	5706	12966	9453	7088	8770	11148	14263	12055	9423	12249	11996	9168
isothreonic acid	489385	292	1679	151152	C00639	8738	5779	8863	7457	9548	6520	7674	7562	7707	7647	8990	6160	7460	8305	6711
isomaltose	983199	160	127715	439193	C00252	392	219	763	426	717	548	156	639	562	222	367	532	364	889	186
isoleucine	359251	158	15	6306	C00407	433010	578883	566013	480797	425267	536533	325178	375470	482329	454350	363348	507035	377590	283474	329584
isocitric acid	616323	245	12267	5318532	C00451	8338	4186	7444	6993	10316	6773	5875	5464	6177	4960	6336	5017	7268	7337	6389
inositol-4-monophosphate	845976	315	4759	440043	C03546	1694	3158	2389	2353	1884	1375	1285	1740	1571	2833	2278	2619	2748	2703	559
inosine	897434	230	84524	6021	C00294	23133	19989	25802	32879	22977	35511	26757	27345	42666	56502	31174	41360	43162	9135	69085
indoxyl sulfate	577333	277	31543	10258		2040	2928	5081	3064	3125	2211	1027	1165	2306	2103	4580	3136	2385	3320	1349
indole-3-propionic acid	732249	202	112556	3744		5566	6648	14669	8761	14207	7465	13674	3648	9860	4017	3901	7474	11536	26367	4423
indole-3-lactate	764079	202	390397	92904		6454	9792	13284	5773	12218	6950	7706	5558	6804	5914	6608	10235	10407	25565	5124
indole-3-acetate	684929	202	69	802	C00954	3804	7304	10528	6718	7595	7913	8204	4466	9244	2871	6545	5883	3548	7664	4975
hypoxanthine	619128	265	1663	790	C00262	65560	53310	77661	68173	76407	69260	37529	35380	78291	105581	35749	38614	58868	26256	91640
hydroxycarbamate	325318	278	130396	16639161		4241	9241	8965	5024	3883	7450	2816	9499	9331	5731	11925	8681	3443	10518	4723
homoserine	443878	218	2849	12647	C00263	751	663	1278	863	1071	1030	968	873	960	1052	1254	771	1331	822	923
homocystine	874865	128	2786	10010	C01817	877	888	1305	997	1193	1024	822	1011	1141	772	977	960	1105	994	1042

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													Day 300 - DOX							
						FMFO55	FMFO63	FMFO66	FMFO71	FMFO75	FMO14	FMO15	FMO16	FMO19	FMO33	FMO35	FMO37	FMO41	FMO8	FMO9
BinBase name	**ret.index**	**quant mz**	**BB id**	**PubChem**	**KEGG**															
histidine	663790	154	150	6274	C00135	71044	113678	100449	82682	56173	144934	122325	92570	119650	87449	71601	79800	76596	78122	102074
heptadecanoic acid	751309	117	727	10465		18548	18246	13953	26108	15686	20420	20664	17083	18084	13863	8899	16145	15315	12613	22387
guanosine	954962	324	1966	6802	C00387	2356	1733	2599	3000	2218	4098	2263	3069	4289	5527	3134	3125	4501	656	3537
guanine	744307	352	2519	764	C00242	2011	2269	2785	2843	3742	1988	1662	2104	3612	2914	2952	1440	1271	1927	2522
glycyl proline	691357	174	18496	3013625		1365	1302	1093	1077	989	574	1318	1298	592	1330	1296	1760	1164	1158	955
glycolic acid	227636	177	1971	757	C00160	12991	16613	16486	13450	11758	8316	16374	13204	9691	27997	22519	14094	28182	22588	12390
glycine	368707	248	6	750	C00037	593724	534354	396073	494454	822247	526752	1028284	573144	404702	708237	874392	571990	780644	522389	851303
glycerol-alpha-phosphate	590747	357	1687	754	C03189	18300	36094	44747	29165	27486	33804	43713	33525	25508	16720	22940	29284	30595	36786	47906
glycerol-3-galactoside	800205	204	100875	16048618	C05401	8150	2585	2789	14578	3114	2654	4431	3824	4566	9123	3852	2287	3079	3062	3397
glycerol	344466	205	30	753	C00116	395330	601003	555904	674556	217439	653048	482515	411995	516290	642775	343188	279098	486243	366727	478473
glyceric acid	377308	189	394878	752	C00258	12534	19484	29579	18274	18298	11852	15098	18719	21380	20358	19616	13706	16102	16597	18898
glutaric acid	421260	261	1727	743	C00489	782	739	1188	1107	671	1140	1182	899	1233	713	847	1031	771	1876	921
glutamine	600315	156	18	5961	C00064	1209056	1386995	1453627	879666	1150473	1063475	1293386	776428	1253865	1096595	567463	1021429	970463	865722	883099
glutamic acid	529100	246	28	33032	C00025	68638	56007	66715	67339	73245	63115	64303	50289	76851	108144	81605	47401	57118	68316	106533
glucuronic acid	665901	333	344793	94715	C00191	9599	6890	8174	8803	10682	6618	9848	11210	11232	9595	10906	6560	8616	13727	8893
glucose-6-phosphate	808788	387	360626	5958	C00092	2966	2173	1213	2270	2662	2347	2588	2133	2103	2033	1291	2565	962	2171	721
glucose-1-phosphate	594647	217	3167	65533	C00103	3320	2704	3716	2858	4623	2963	3975	7502	3240	4701	816	2349	1226	6505	2727
glucose	659798	319	22	64689	C00221	4926607	3513142	3826779	3342804	5034130	2832811	4712337	5523861	4048213	4226377	2921137	4170532	3386035	6860630	4123031
gluconic acid lactone	645815	220	3502	7027	C00198	7627	3525	3706	9717	5242	10361	4267	4123	10130	15514	8609	8842	4906	4402	20885
gluconic acid	693148	333	7501	6857417	C00800	34166	7438	12101	60158	37925	48536	13160	4664	51262	155133	31242	42825	16972	10509	125292
galactinol	1017580	204	1975	11727586	C01235	1145	2547	2154	1062	1445	1334	2504	3448	989	1022	2080	1910	2518	2835	1555
fumaric acid	390775	245	1718	444972	C00122	2884	2875	6481	3974	3139	1437	552	1597	1269	4184	3579	2526	3833	2482	1594
fucose	578299	160	3009	439650	C02095	11437	9323	7875	7138	10483	5326	8793	14346	8042	7916	9125	10109	4956	16345	8886
fructose	639442	307	21	439709	C02336	566330	304902	356338	269033	832847	245585	482338	658739	349401	311360	315645	389384	317715	914999	388866
ethanolamine	342561	174	342038	700	C00189	28257	38374	35783	25181	17831	33966	18406	29702	33606	40240	71993	37589	24609	79343	34096
erythritol	471922	217	92	222285	C00503	11007	10025	13623	10198	9261	9317	10570	10747	9909	9613	14127	7658	10684	10950	7955
epsilon-caprolactam	353069	170	3101	7768	C06593	7194	5913	5956	9902	10212	13271	16001	13677	9306	5194	9407	5410	5034	3517	15181
docosahexaenoic acid	902819	91	87709	445580	C06429	2823	2593	2237	3191	2556	1714	3358	3101	2073	2644	1369	1568	3346	2482	2362
dihydrocholesterol	1082070	215	42937	66066	C12978	4487	5524	6211	2784	2491	3608	6439	6476	6337	3486	4145	6393	6939	7431	6056
dihydro-3-coumaric acid	582960	192	384891	91	C11457	1422	1895	2218	1327	1544	1160	2018	1528	1885	1701	1280	1526	1802	1964	2033
cytosine	486724	254	2186	597	C00380	1220	1896	1736	738	1072	1756	2269	477	1427	1393	1938	1607	952	1191	1808
cystine	804619	218	94	595	C01420	21179	1725	2221	22076	16277	26245	21485	23306	13730	6855	26528	14657	5283	15209	12240
cysteine	500158	220	65	5862	C00097	9445	3624	1546	15252	10385	25232	13277	14910	6294	5388	14563	9452	3670	4182	13520
creatinine	502599	115	31	588	C00791	194951	164793	203169	253732	193376	190981	206672	218380	150225	236427	358751	187472	219598	137354	203092
conduritol-beta-epoxide	675635	318	2670	9989541		2350	1768	1595	1282	2443	1510	2109	2390	1764	1568	2369	1818	1372	10129	1594
citrulline	621404	157	1712	9750	C00327	29739	39521	45669	32535	28601	38138	28407	41954	30865	31431	45014	47389	28948	33586	33316
citric acid	617342	273	288	311	C00158	354934	259428	425093	361435	403359	350154	315666	281753	352495	254697	305880	261065	318805	391162	312399
cis-gondoic acid	847372	367	87783	5282768	C16526	574	706	578	797	579	366	1166	433	528	417	369	446	546	391	627
cholic acid	1109517	253	110403	221493	C05463	608	2622	1004	718	731	505	755	852	743	558	520	861	1446	871	893
cholesterol	1078536	129	19	5997	C00187	562944	771334	779588	519890	607131	461043	834942	680325	626642	434536	548326	889239	771521	813205	716633
cellobiose	942758	361	120969	6255	C01971	594	511	344	448	629	706	784	504	381	1343	941	563	517	777	1770
capric acid	451790	229	726	2969	C01571	15934	5492	6624	4357	6102	4688	4934	4351	3738	8146	4109	4636	9781	4256	5039
butyrolactam	277199	142	2047	12025		33817	44202	44950	18040	27763	30462	16235	27495	37116	36502	32585	30149	40591	31723	15805
butane-2,3-diol	205778	117	485	262	C03046	93997	25175	141168	177490	93116	171610	102700	111631	128575	151659	151307	91907	187893	51520	125967
beta-sitosterol	1128225	129	3174	222284	C01753	5083	7904	6684	6086	2815	4959	8531	2065	8051	5861	5113	4658	1120	7901	4059
beta-glycerolphosphate	574470	243	22021	2526	C02979	1634	1417	1472	1402	996	1167	2100	1336	1624	933	796	1621	1664	1922	1840
beta-alanine	435564	248	148	239	C00099	3316	6099	3782	1879	4556	3134	2202	2160	2311	334	6825	3558	3698	5846	2984
benzoic acid	339067	179	36	243	C00180	182912	226083	229604	206348	227169	133752	148294	143299	170379	190667	219122	152288	233222	195494	142905
azelaic acid	610551	317	329430	19347555	C08261	1593	1400	1521	1970	1182	1044	2722	966	1116	2190	1447	1063	1791	1319	1731
aspartic acid	480387	232	79	5960	C00049	24710	24745	25099	22598	27930	20068	21239	15245	21157	21391	31642	18826	20112	26954	20889
asparagine	553743	231	369588	6267	C00152	39769	29401	28713	31622	33747	31985	35199	20398	30757	27996	33485	31013	29008	29163	34486
arachidonic acid	837115	91	64589	444899	C00219	18302	20863	20639	19159	17916	17897	29664	23277	25680	14468	13585	23796	26037	20137	24119
arachidic acid	856421	117	291	10467	C06425	5328	6584	5532	7518	5514	5256	11403	5940	6463	4654	4894	5245	6454	7130	6816
arabitol	572730	103	372446	94154	C01904	8703	12934	11417	9754	7946	8604	8825	9559	8097	6353	22285	7967	12083	8819	6235
aminomalonate	455754	218	413	100714	C00872	9704	31154	21638	17724	14086	24193	14142	44168	20530	18231	51751	32956	18293	48608	24953
alpha-ketoglutarate	507392	198	294	51	C00026	535	664	483	488	458	4751	545	396	458	623	693	467	757	649	445
alpha-aminoadipic acid	573295	260	125502	92136	C00956	3297	1621	2672	2815	2430	3524	2440	2713	2543	3020	3362	4185	2202	3279	3007
allantoic acid	726050	259	117021	203	C00499	35808	25209	32319	29833	36309	20821	26896	25261	25804	26385	46049	14713	36597	20879	70445
alanine	243971	116	34178	5950	C00041	2462484	1684296	1436324	2137149	2088361	2970283	2220276	2267882	2118453	1981900	2447989	2235645	1992905	1054212	2103762
adipic acid	474435	111	125	196	C06104	3704	3487	4671	8737	3405	2904	14608	2672	4479	2908	3153	2337	4491	8190	7822
aconitic acid	586815	229	29	643757	C00417	2127	2304	3028	2744	2401	1123	1421	789	411	1704	2382	2069	2971	763	1385
5-methoxytryptamine	864466	174	284	1833	C05659	50148	59463	43570	71262	31137	144301	27295	73672	165471	53167	45128	82351	74714	54677	109863
5-hydroxymethyl-2-furoic acid	497561	123	31858	80642	C20448	1029	1786	2164	2339	1846	1587	1540	1189	2294	1117	1797	1370	1467	1699	1198
5-hydroxy-3-indoleacetic acid	777606	290	31552	1826	C05635	1631	801	640	1718	1136	2318	2358	2032	2285	1038	603	1002	2017	1295	2639
5-aminovaleric acid	536657	174	1698	138	C00431	3278	3807	5290	2690	3473	3368	3480	2768	3161	4165	9553	7491	5718	31529	5516
4-hydroxyphenylacetic acid	542795	179	31555	127	C00642	2891	1405	1555	929	1644	2121	1468	685	1101	469	1514	1733	1384	897	1283
4-hydroxymandelic acid	601658	267	131944	328	C11527	1254	1165	1751	1489	1258	1142	1051	1466	869	975	1242	1472	1622	1221	990
4-hydroxyhippuric acid	784581	294	12284	151012		229	2630	539	2242	200	395	379	2522	273	491	597	345	477	864	1468
3-ureidopropionate	554966	161	107897	111	C02642	1200	2237	882	1291	831	1222	802	524	768	1824	1984	650	1270	2333	1286
3-phosphoglycerate	610734	227	1667	724	C00597	477	430	383	1315	625	918	447	373	404	1613	2073	843	481	301	2954
3-phenyllactic acid	516011	193	113643	3848		1394	1886	2840	1020	1334	1113	1080	915	1168	1065	1623	753	5064	6246	1430
3-hydroxybutyric acid	278632	191	145501	92135	C01089	69567	84430	90338	61354	48432	54534	78110	54361	166478	54187	62311	56689	65323	55910	96783
3-hydroxy-3-methylglutaric acid	521554	247	32000	1662	C03761	894	865	1037	1373	370	864	501	545	668	643	847	725	329	1474	1072
3-aminoisobutyric acid	452655	248	12265	64956	C05145	4477	3113	3873	3110	5048	2897	4253	11943	3320	4968	5558	7828	7658	9293	8037
3-(4-hydroxyphenyl)propionic acid	598147	179	110341	10394	C01744	1544	1308	2247	1153	1133	957	1432	1044	1453	1695	1599	1340	1360	1720	1039
2-picolinic acid	381532	180	389051	1018	C10164	1685	1745	2410	2570	1636	2537	4036	4167	2556	1286	2226	1682	1414	5827	2993
2-monopalmitin	890356	129	2080	123409		2472	2127	2137	1253	2492	3086	2292	34910	3469	34798	3032	1861	39033	2711	2945
2-ketoisocaproic acid	310761	89	208	70	C00233	831	4433	1433	2224	832	25044	4253	5943	3368	2342	655	1079	5565	2233	2599
2-hydroxyvaleric acid	309587	131	25922	98009		5011	7218	11385	6986	5974	8413	6808	5570	11308	6868	6843	6171	8068	9404	8010
2-hydroxyglutaric acid	506306	247	2000	43	C02630	3360	3388	3924	3389	5151	4324	3561	6591	4539	4524	4135	4664	6529	5031	3265
2-hydroxybutanoic acid	258161	131	40	440864	C05984	77451	57022	102349	60714	52666	84220	60182	79997	96519	105474	108407	86208	101634	40694	102053
2-hydroxy-2-methylbutanoic acid	264833	145	32675	95433		5640	6074	6685	5853	5285	6741	6195	8327	7574	5229	9464	5504	6642	29756	6935
2-deoxytetronic acid	433456	189	1208	150929		2324	2219	2599	3009	3189	2178	3133	353	2312	2908	3394	2476	2765	3288	1931
2-deoxypentitol	521785	231	21714	249377		1169	997	1653	1283	1227	942	994	964	1285	1026	1756	780	1130	1360	1485
2-aminobutyric acid	285825	130	160842	6657	C02721	88381	28382	28378	44315	44039	72127	55194	52045	53620	62771	88973	49201	49128	23663	77346
2,5-dihydroxypyrazine	397526	241	2254	23368901		1976	1774	1528	4246	2415	4802	4291	4791	2170	1659	5344	3782	1917	2612	4182
2,3-dihydroxybutanoic acid	384796	292	31743	250402		1929	1818	2638	1601	1988	2130	1491	2189	1743	898	2824	1058	1319	1593	1432
1-monostearin	959214	203	648	24699	D01947	2363	6017	2984	1305	2411	3730	3830	3284	5400	3514	4561	3324	4432	6194	3184
1-monopalmitin	901749	371	2070	14900	C01885	2554	3066	3167	2573	2293	3232	3912	2818	5113	3444	2593	2436	3110	5129	3385
1-kestose	1123027	361	14692	440080	C03661	257	1053	677	1788	483	871	789	3551	310	565	1479	1662	1696	1738	755

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Supplementary table S2: List of metabolites identified in serum samples by untargeted metabolomics. Mean and standard deviation by group and time point.

	Day 0						Day 28						Day 300					
	AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
zymosterol	2193,00	672,04	2076,33	1342,69	1962,80	997,06	1974,93	574,66	2280,13	835,31	1953,80	525,07	1909,93	636,74	2151,27	826,51	1894,73	662,39
xylose	14843,27	5531,27	12665,67	3808,20	13374,07	4695,82	10360,80	2667,92	11332,00	2373,76	13059,40	4409,59	9774,47	2902,61	17971,93	33817,97	9253,27	1625,50
xylitol	4779,40	3365,39	4240,00	2366,54	4036,07	1114,30	3321,47	628,32	3693,73	979,87	3892,73	977,50	5311,33	2872,09	4851,80	2010,51	5992,47	3383,73
xanthine	633,6667	335,5864	554,4667	424,2479	745,3333	319,0577	879,8667	574,141	641,9333	223,5044	986,2	729,6619	681,8667	293,5212	542,2667	153,5938	591	145,1295
valine	965732,3	380569,8	976547,7	224277,5	986482,1	330456,3	1006056	264913,9	885909,8	191252,6	932646,2	281378,6	862679,9	172381,6	846068,6	181814,5	835246,6	149289
uric acid	6902,6	5455,65	4913,267	2828,887	5566	2632,503	4781,267	1946,593	5071,867	2028,857	5469,733	3966,051	5069,533	1839,997	4621,133	1985,987	5252,933	1544,936
urea	2670368	1156979	2927211	867573,2	2859787	817376	2500491	1032479	2729634	1428811	3570655	883768,6	3185413	434369,1	3061793	1305636	2952361	1130647
uracil	5508,933	2809,345	4474,067	1466,931	6916,733	3400,806	6180,533	2823,441	4458,867	1647,67	8912,733	4261,359	4285,667	2151,853	4117,533	1688,066	3795,667	1863,845
tyrosine	348497,1	112479	352378,6	52448,81	342803,9	88686,69	389054,9	76789,12	378889,9	110001,3	402890,1	108835,6	426431,3	75040,67	409423,2	77645,41	418578,4	78953,55
tryptophan	250388,2	119739,6	255630,3	96825,52	267090	124026,4	389432,2	66866,96	344259,7	139221,4	393276,4	108905,4	486581,9	95354,48	441120,2	137367,7	534822,5	126493,5
trans-4-hydroxyproline	255037,8	192296,1	362099,6	180627,3	256459,3	126726,4	460027,4	112402	463524,6	154783	483290,6	125486,6	291014,1	128520,9	229341	113943,6	290840,3	112972
tocopherol gamma-	1113,933	462,0449	1014,8	412,8272	1015,8	303,9892	1093,4	503,0323	1320,467	498,9507	1248,067	481,4787	1012,4	307,0653	1098,2	386,5753	1066,467	361,5512
tocopherol alpha-	32348,87	23394,28	38259,67	22116,45	41000,87	22358,58	22279,67	8333,725	22664,6	10313,59	20256	8868,455	21629,67	10279,02	21665,13	9209,884	26884,53	12928,69
thymine	692,3333	293,5976	714,1333	258,2557	700,8	255,3102	782,9333	288,6816	712,4667	235,2576	915	302,8109	826,8667	368,4987	804,2667	404,0468	952,6667	455,7905
thymidine	29481,33	13895,33	29113,47	8965,079	30479,2	11403,82	36056,73	9856,072	38496,87	10815,26	47596,33	16194,7	35570,73	7553,519	39462,6	12095,58	36446,13	8196,678
threonine	200577,9	108054,2	186455,7	60399,04	155280	71885,31	317721,1	255426,8	220900,4	85493,13	233122,2	125192,8	277046,8	109534	234702,4	78769,61	232976,1	55123,92
threonic acid	23324,47	13271,69	31888,73	21050,81	29323,27	19581,61	17031,67	6611,915	16298,4	9022,621	16192,33	8831,639	20062,8	13165,56	13589,4	7100,223	16088,73	8939,143
threitol	6119,933	8254,787	1801,6	585,8082	2897,133	2568,826	1677,8	497,0791	1728,067	434,6775	1673,8	586,8295	1619,667	523,2339	1741,733	630,8271	1635,933	383,2341
taurine	26540,13	32695,92	19326,33	22457,52	21726,93	23325,63	29549,07	21933,72	18007	17035,29	24701,93	22041,22	26203,33	30432,98	19823,53	19493,46	25328,93	26223,54
tartaric acid	455,1333	348,3696	366,5333	152,9014	518,9333	447,1014	380,8	139,1326	397,6	165,5958	369	235,9337	1108,667	706,4969	1094,733	1317,876	883,2667	680,0949
tagatose	2116,667	2291,142	1149,067	661,0626	2056	2854,528	1241,2	597,4966	1408,533	1478,943	2943,4	5124,924	1992,067	1359,877	3759,333	6685,461	2863,067	3580,798
sucrose	3886,267	3536,012	10390,93	32957,62	2317,8	1928,891	2258,133	1319,543	2239,667	1067,536	2664,267	1852,333	2850,533	5595,481	1233	705,7441	1923,933	1548,719
succinic acid	9456,267	6525,959	13106,4	10027,37	9854,933	6090,376	8235,267	2945,055	10102,8	3839,204	12548,07	6413,913	12161,8	4173,579	12940,27	5227,334	11583,2	3217,162
sophorose	595,9333	565,1016	399,7333	137,478	440,8	228,9586	329,8	170,0009	354,6667	151,9397	408,9333	162,5706	375,4667	121,9238	354,4667	149,2452	400,2	118,2058
shikimic acid	5820,933	4388,854	5121,467	3219,912	5864,133	4483,487	3667,8	2227,912	5604,267	3946,937	6129,6	4963,79	7066,6	2701,727	6673,333	4817,004	5382,133	3331,929
serotonin	126501,4	75948,36	83366,47	36347,45	138556,3	95321,71	93110,8	31402,04	85772,33	40067,07	104343,1	69275,46	74286,67	27759,37	54524,8	32985,28	81244,2	42095,64
serine	835185,6	331042	934373,2	222882,1	840489,6	219048,2	774372,7	163221,8	886272,1	235951,3	787585,6	158580,6	631428,2	117380,3	681525,5	180244,3	688938,4	139003
salicylic acid	4058,6	2289,722	5806,267	6858,738	4435,733	3377,332	4081,467	3768,927	5652,333	4014,982	3644,067	1732,641	3830,867	2021,519	5767,667	4102,748	4720,067	2678,112
saccharic acid	1613,8	970,8036	1261,133	554,0265	1460,467	955,4405	1084,067	542,3307	1240,533	663,3808	1229,6	453,5339	1093,267	416,1939	999,9333	253,0182	1438,333	1164,449
ribose	17584,47	10043,5	21027,8	12089,31	31123	16217,63	34281,67	15372,68	24271,6	15111,72	39875,53	21165,45	26158,07	10523,5	21787,27	9626,039	25978,93	9971,424
ribonic acid	6795,267	2790,017	5952,333	4258,951	5965,267	3176,091	5797,6	3241,231	4471,733	2031,741	6757,6	3210,347	7105,667	4661,183	6632,067	3670,86	5487,333	3124,888
ribitol	2170,533	655,5222	2230	628,7444	2158,867	487,3991	2027,733	782,5382	1936,333	395,6195	2371,133	842,8814	2245,2	731,6051	1919,4	614,1996	2093,467	701,4755
raffinose	1438,867	1160,658	859,5333	598,9832	908,3333	777,5287	1930,267	1258,389	2265,333	1677,596	2140,4	2048,468	1582,133	1927,406	784,5333	544,6038	1416	1045,521
pyrophosphate	3104,4	1982,675	3244,4	1780,218	3068,333	1303,26	2965,267	1100,507	3669,867	1894,587	3572,8	1655,413	1921,2	1081,597	2511,067	1477,966	2791,067	899,9723
putrescine	8462,733	3795,526	8201,2	2687,849	8902,133	4849,25	7001	2926	7366,467	3102,74	6250,133	1834,545	6402,2	2619,924	5258,8	1630,891	5994,733	1463,761
pseudo uridine	16271,33	4110,525	15377,93	6106,896	18234,6	4993,624	14276,4	4154,985	17688,73	2480,517	18167,6	7313,929	12659,47	2338,497	12642,2	3254,301	13255,93	2608,427
proline	569693,3	271790,2	842596,3	403881,9	596257,9	219616,4	776006,5	276746,1	757982,9	315010,9	687706,9	354382,7	607518,4	179500,9	528693,5	245932,4	551108,7	184051,7
piperidone	14527	23337,3	12712,07	27489,45	12318,73	34767,03	7799,8	7086,731	8653,2	9695,378	7580,4	7458,63	4956,667	3592,361	4670,333	4871,988	7773,067	6693,518
pipecolinic acid	4381,467	4063,832	3332,667	2104,688	2861,333	1161,669	3970	4519,069	3981,333	2902,137	3094,067	1225,108	3832,8	3029,456	4053,667	3612,83	4167,067	2865,872
pimelic acid	1726,467	749,6834	1603,4	615,6201	1761,533	570,5701	1471	592,689	1491,333	516,2113	1580,533	480,7326	1928,667	690,6597	1662	624,3471	1765,6	730,6281
phthalic acid	11360,87	4248,228	19548,6	25325,08	10623,8	4752,945	11113,47	5092,284	15601,2	15281,19	12702,07	5420,48	13325,67	6390,377	12246,4	3070,826	15358,4	10047,34
phosphoethanolamine	5252,333	3882,3	4733,933	2622,341	5073,533	5258,455	4987,933	3600,883	5175,133	4180,236	6560,133	5362,297	3942,667	3311,199	4275,533	2784,707	2784,8	2285,834
phosphate	585752,1	180423,3	658084,3	154258,3	646227,6	185512,5	724383,7	135884,5	740668,7	228235,7	803778,4	194685,7	461411,7	112401,6	474287,5	128407,8	506265,5	107415
phenylethylamine	86072,6	127334,4	49633,73	59675,08	28350,8	23642,39	19914,53	8793,035	31497	19925,08	16495,73	11520,05	24564,47	32353,75	11004,53	8318,653	16308,53	9799,028
phenylalanine	204594,4	65119,99	211804,7	54762,85	196901,6	39441,72	200347,5	37292,83	212861,4	53743,65	227351,5	61520,37	202495,1	38510,69	223981,7	59562,87	227767,2	32915,26
pentose	3683,667	2494,255	4541,333	4272,682	3292,867	1075,308	5087,133	4592,493	2804,4	632,961	2850,533	1089,454	4944,733	3673,475	4604,933	6583,508	4799,867	4612,953
pelargonic acid	24781,47	10935,58	24880,07	6101,206	23111,67	6256,479	20997,93	4176,217	24165,2	7030,382	25805,73	8264,894	27022,8	19050,28	26460,87	6977,469	25622,87	5426,615
palmitoleic acid	2931,867	1584,784	2481,933	1067,633	3224,2	1601,499	2402,2	998,5203	2847,867	1831,096	3650,133	3820,701	2271,267	1754,016	2517,4	1626,188	2717,067	1437,093
palmitic acid	153159,3	40920,23	124425,9	37750,5	150973,7	49217,77	118610,9	32892,14	134649,7	45865,41	155764,5	94729,65	137194,7	42998,39	148562,9	54136,23	147698,8	38102,78
oxoproline	721708,1	174709,3	810308,3	186281,5	831416,6	159222,9	815968,9	134778,9	887491,3	144406,9	964036,5	176627,4	981791,6	184254,1	977598,2	204673,6	1010289	163668,6
oxalic acid	11651,53	11402,56	4967,133	2701,378	7197,2	3645,576	3960,867	1538,318	6045,467	1781,282	5516,6	4127,149	4962,067	1775,717	4894,867	2681,112	5102,4	1845,402
ornithine 3TMS	258699,9	170933,7	210686,4	91827,7	212528,1	96399,54	269824,5	122418,9	217029,7	66118,15	212150,6	73136,07	163427,5	66909,43	144327,5	34873,81	156237,8	32992,07
oleic acid	42896,67	50115,25	23347,8	33416,67	34733,8	44660,41	26404,53	24760,56	26343,53	31918	34534,73	50865,86	15105,93	27644,22	26239,07	28974,72	30124,6	27645,49
oleamide	18083,13	8130,379	23278,93	8277,719	19514,87	8007,081	21418,93	9409,091	23573,53	7596,614	21836,33	9485,911	30178,8	10253,79	27719,2	9942,212	24864,87	8545,433
nonadecanoic acid	4061,133	1818,604	3737,2	1481,53	3771,467	1090,968	5517,467	4496,124	5050,867	1633,828	3719,667	1943,892	4665,333	1294,01	5005	878,111	4858,133	1461,025
nicotinic acid	100072,4	132055,7	136994,4	244571,2	162849	215620,3	192881,3	290466,6	64469,07	99755,06	168692,3	230028,3	205904	306124,6	131235,8	228952,1	192560,9	364973,1
N-acetylglycine	1613,667	943,3746	1149,333	639,18	1543,867	773,2189	1100,267	430,4168	1233,733	461,9189	1262,6	371,7443	858,0667	368,7302	1045,6	512,5177	981,6	451,8446
myristic acid	5541,2	2509,825	6684,333	4900,827	6124,667	2617,423	4167,333	2131,671	5691,667	3809,261	6721,6	6959,062	5073,2	2147,489	5487,267	2435,561	6484,133	3808,622
myo-inositol	368462,9	161285,6	231902,7	60889,88	328115,7	196034,9	361323,7	132796,6	325713,6	117770,6	404677,9	133018,8	311080,7	150539,5	240775,5	80902,08	265394,4	128091,3
mevalonic acid	2738,4	2015,133	2365,333	2869,302	1754,733	1434,075	1106,867	434,4736	1909,133	1610,408	975,9333	507,1039	1449,933	647,2986	1451,867	917,8752	1310,067	744,6182
methionine sulfoxide	111978,3	64721,77	107175,1	52419,99	112105	109978,4	96373,53	47668,75	93536,93	35520,21	72542,33	40971,05	82147,87	40212,45	59856,47	33237,29	79027,93	30222,3
methionine	238448,1	195002,7	174398,3	126587,9	212317,9	259756	148626,7	58229,81	137644,5	52987,39	146461,8	57801,74	103550,3	33931,29	95538,73	35383,02	96055,13	16888,76
methanolphosphate	27860,67	9609,816	28699,93	8461,306	30985	12764,23	25096,4	8649,483	29373,27	7113,679	27857,07	4997,26	27568,47	12095,79	32730,87	12548,75	31318,27	8672,714
mannose	208673	66982,59	214075,9	62188,88	209332,9	38983,32	171264,7	44527,21	191779,3	54210,62	188998,7	67426,6	196698,5	51051,53	225714,3	81775,51	209313,1	26885,3
maltose	41611	71559,73	15491,4	7688,443	24549,4	19609,39	17306,4	10965,18	10346,93	4911,986	20357,53	13558,16	10231,8	9841,106	6515,733	2847,936	10882,47	10225,46
malonic acid	511,6667	263,4683	315,0667	107,283	401,4667	127,724	324,2667	201,5378	432,6667	198,4586	308,6667	101,4408	335,8667	188,2741	425,4667	184,678	428,8	130,4575
malic acid	5453,733	3538,82	4789,6	1959,821	5383,867	2209,375	5402,333	1893,754	4697,133	1626,093	6064,8	2204,165	7667,133	3324,888	6639,933	3042,886	7016,867	3385,341
maleimide	13923,47	7911,275	14484,07	7208,98	14390,07	5707,943	11127,13	2230,389	12274,67	3308,478	15098,13	8255,829	11051,07	3099,413	10638,33	3278,559	12410,73	5276,589
lyxitol	11550,13	4831,587	12286,6	3873,83	11056,2	3042,097	14805	2616,863	16352,73	5302,316	16724,47	5177,899	14383,87	6856,221	11433,2	3557,312	13625,07	5278,313
lysine	58003,87	29737,87	55021,73	37982,35	59681,93	40793,41	42254,07	11742,76	46927	15808,8	41336,2	13151,98	45941,6	15461,59	52029,93	13093,93	50102,27	12328,45
linoleic acid	23510,6	9718,845	17667,2	7060,726	20055,93	6975,682	17965,93	5307,951	21480,13	8329,758	24934,13	16397,23	20543,27	8250,412	20242,6	8813,351	21624,27	7456,142
levoglucosan	1365	1194,836	1254,467	499,5834	1151	534,3621	1093,467	379,8046	1330,467	804,3257	1041,4	341,6282	1905,6	1492,999	1730,067	796,2714	1480,733	795,8234
leucine	1240261	317665,8	1094755	254657,4	1149739	313216,4	1267271	354695	1131698	279541,2	1147963	328184,6	1015463	165607,6	1013278	257091,2	1046799	212891,9
lauric acid	44025,6	77310,69	97879,27	135329,4	48865,6	66974,17	28455,8	65583,7	67074,6	110731,1	67158,8	108360,9	42189,73	71567,61	48308,33	85726,79	64195,67	100765,2
lanosterol	473,2667	247,7047	402,6667	290,456	372,5333	180,3326	277,8	69,93895	338,0667	129,3696	257	60,49321	274,8	86,10641	331,3333	110,8968	344,3333	66,63404
lactose	2740,733	2070,449	7877,4	22063,46	2784,467	1196,054	2112,2	1337,945	1998,467	892,3214	2409	1530,06	5700,8	12892,68	3285,333	4573,287	2607,4	1772,87
lactic acid	2697984	1050573	2779013	1305981	2531916	1268749	3093343	1115794	2784086	1205260	2411210	1309149	2475192	1077058	2464733	908727,2	2293044	805501

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	Day 0						Day 28						Day 300					
	AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
lactamide	2692,667	902,1314	2933,467	1205,723	2893,867	1036,71	3338,933	1242,989	3044,933	700,0304	2861,467	1366,755	2434,733	983,7592	2372,4	823,2405	2128,067	933,0261
kynurenine	10250,33	5780,444	8815,867	2405,483	10503,6	5329,586	9116,133	3961,308	9775,4	2150,767	10992,67	4150,274	7720	1784,477	8724	3732,548	9896,667	2587,161
isothreonic acid	13534,67	5666,044	11551,93	3362,319	12508,33	3518,413	9540,8	1845,574	10556,8	1533,222	12359,6	3379,755	8052,733	1190,707	8767	4040,795	7674,733	1083,554
isomaltose	753,2	738,2847	519,6	325,1131	646,1333	490,5181	498,3333	161,2042	478,6667	206,3861	475,5333	197,1127	508,4667	235,5079	510,5333	257,6661	465,4667	224,0354
isoleucine	514101,6	188354,3	491051,3	126964,1	501807,9	165120,8	503052,9	83031,91	454583,9	68953,7	496639	123971,1	404230,9	72426,12	438187,9	105433,6	434590,7	91135,69
isocitric acid	5523,4	2056,49	6597,6	2349,378	7311,933	2223,421	6639,2	1629,621	6947,2	1530,646	8723,333	2340,125	6290,067	1733,493	5876,8	1864,797	6591,533	1508,227
inositol-4-monophosphate	2096,867	874,424	1922,6	645,3251	2102,2	874,4604	1289,867	466,5865	2072,133	653,2389	2058,667	872,0943	1592,2	607,7818	1737,067	713,9325	2079,267	710,5208
inosine	33664,67	10497,02	27975,67	8229,817	35954,87	21606,43	28073,8	10599,49	29647,27	11246,47	28176,73	11577,48	30733,13	9269,003	27151,93	8384,943	33831,8	15070,65
indoxyl sulfate	2620,667	1638,838	2742,733	1826,82	2487,733	1425,697	2064,667	1564,257	4154,333	3092,28	2690,133	1138,189	2477,8	1534,229	3044,733	2258,399	2654,667	1145,746
indole-3-propionic acid	13576,13	14657,01	7699,933	7617,686	7124,2	5863,861	2624	3382,159	8815,067	3066,811	7491,667	3823,445	8706,533	6595,026	7034,533	3233,964	9481,067	6029,085
indole-3-lactate	7358,867	7747,492	6976,733	5359,402	6051,667	7175,183	6230,467	1992,653	6539,733	2057,034	6855,133	2874,63	8372,467	3762,468	10427,73	5192,508	9226,133	5183,651
indole-3-acetate	15311,4	18000,97	9736,6	8383,126	10135,27	7717,598	5407,933	2056,274	9955,8	9652,758	6346,133	3210,388	6766,2	3546,698	7335,267	5538,009	6484,133	2202,214
hypoxanthine	64699,67	31102,47	54919,47	18003,39	74971	24171,85	84182,93	35210,82	58815,73	23693,67	94958,6	28239,21	76146,27	27867,7	58515,07	23217,41	61218,6	23140,6
hydroxycarbamate	5802,733	2743,048	8513,4	3195,316	7954	3503,514	7077,2	2588,799	7698,267	3502,097	8790,933	3426,363	7971,8	3491,23	8631,133	3624,364	7031,4	2908,029
homoserine	1242,2	555,0101	1354,933	399,4669	1181,933	491,9161	1173,4	315,3759	1221,133	330,9108	1084,6	210,9725	1053	266,9738	1113,6	291,025	974	198,7482
homocystine	998,5333	324,3501	1520,667	1024,357	1436,867	753,3547	1073,733	282,0769	1278,933	300,6104	1050,733	351,8852	963,7333	247,6352	1006,333	313,083	1007,2	140,5038
histidine	62456,47	28665,98	89653,87	45444,27	80170,4	40570,37	81451,13	30696,85	85960	28594,42	78644,6	33658,99	84483,33	25015,93	86698,13	31378,42	93276,47	23799,66
heptadecanoic acid	16670,53	4902,249	13796,73	3652,845	16354,2	6818,334	13201,67	3880,405	16082,67	5263,999	16453,13	8915,913	16909,73	4570,422	17757,2	5056,124	17200,93	4233,503
guanosine	2820,733	1111,366	2231,667	677,4945	2944,933	1569,452	2603,533	1139,236	2735,667	1283,652	2853,933	1120,101	2945,667	1025,029	2580,2	841,3346	3073,667	1212,466
guanine	2168,467	1102,456	1778,933	803,2468	2480,4	1313,967	3031,8	1878,708	2071,133	946,5145	3936,667	2018,543	2949,4	1260,029	2463,467	1067,822	2402,8	736,231
glycyl proline	1596,2	750,9192	1373,067	588,558	1411,333	410,8882	1291,733	439,6278	1297,933	380,6627	1457,4	564,145	1207,2	593,5437	1014,733	361,2748	1151,4	300,139
glycolic acid	16578,47	6620,168	17580,2	6804,908	16366,8	5030,322	16124,13	2687,256	17618,27	4914,183	27515,87	19908,96	15070,4	3082,287	16664,13	7736,325	16443,53	6169,686
glycine	777976,4	345920,9	883554,5	378246,9	798730,1	243021,4	880398,7	296307,1	887547,3	233365,1	846078,1	226912,5	617497,1	170787,1	546185,6	165401,4	645512,6	187588,5
glycerol-alpha-phosphate	29469,53	9005,6	24677,6	6534,857	25838,87	9117,017	29523,53	8036,46	29324	9742,492	34047,47	10958,2	31302,6	8771,638	29195,33	10955,38	31771,53	9181,92
glycerol-3-galactoside	7090,733	7578,941	5949,467	3568,91	7369	6590,047	3857,267	1155,907	4880,733	2999,167	5325,333	3541,863	6979,333	3510,366	4800,133	2703,694	4766,067	3361,647
glycerol	439937,5	107753,7	441378,5	110553,3	585720,3	514929,2	368215,5	138348,4	418779,8	124623,4	472501,4	181944,4	446133,7	224196,5	591414,6	167958,2	473638,9	138382,5
glyceric acid	27312,73	11511,93	18797,2	5325,146	31637,67	16222,37	19689,07	4479,99	16918,53	4292,786	23472,33	6589,853	17796,2	4727,295	17970	9254,946	18033	4288,259
glutaric acid	1216,267	779,9142	882,3333	256,8317	855,8667	279,0381	728,4667	143,6448	876,4667	483,9099	1003,867	361,7495	949,8	314,7233	925,7333	258,7112	1006,667	307,0625
glutamine	552948,1	263874,5	872940,5	336986,6	735477	296473	619356,8	214353,1	811040,7	305329,3	685995,7	270345,3	969464,5	344844,1	1073720	270517,7	1058116	241969,6
glutamic acid	57885,4	18528,55	60413	13580,35	64914,93	18768,07	61714	12837,86	54507,8	14480,08	66937,47	13577,07	71530,6	19779,98	67211,33	14787,42	70374,6	17613,05
glucuronic acid	9124,733	2202,494	9337,333	3708,239	9607,2	4247,422	7615,733	1437,779	8146,133	1455,272	9036,133	3806,101	9606,133	2710,191	9058,8	1990,313	9423,533	1970,737
glucose-6-phosphate	1462,933	574,202	2230,533	1019,743	1798,133	710,8191	2191,667	761,5159	1632,667	391,8707	2074,6	1386,853	2387,4	1133,53	1791,8	709,7698	2013,2	662,8379
glucose-1-phosphate	3737,667	1871,375	3210,533	1140,912	4023,067	1574,049	3507,267	1384,437	3440,733	1207,826	5271,533	2485,502	3924,533	1090,912	4739,933	2027,581	3548,333	1767,125
glucose	3145430	643471,8	3290883	471590,4	3423921	579059,9	3215997	497544,2	3191863	458827,5	3337899	743758	4251770	1155169	4077366	1123162	4229895	1063955
gluconic acid lactone	15805,87	8931,2	13047,87	6077,201	15977,2	9925,684	12758,6	6723,204	10444,47	6490,212	12789,2	5488,536	10491,2	4407,091	8848,8	5846,902	8123,733	4885,017
gluconic acid	107534,1	65285,09	78888,07	42225,44	104628,1	61378,78	76451	44109,56	62554,2	52543,55	90441,8	47982,55	62391,2	31365,73	49544,87	42237,34	43425,53	43335,11
galactinol	1805,4	1053,624	2190	1535,739	2323,267	1563,27	2096,267	721,0268	2496	1101,641	2608,6	1444,932	2127,133	1530,072	1558,333	630,46	1903,2	758,3921
fumaric acid	2629	1423,727	2378,2	853,1751	2409,4	1190,402	2212,667	929,5952	2200,267	905,3708	2746,333	1190,926	3049,733	1798,348	2600	1163,778	2827,067	1487,258
fucose	7136,6	1408,805	8388,133	1904,038	7954,133	1273,983	7344,867	1362,049	8413,6	2630,526	7849,133	2078,069	9371,2	2347,566	8942,8	2758,461	9340	3012,075
fructose	245355,1	97707,69	239211,1	65696,08	270389,2	100509,2	245007,1	66226,88	253124,6	60945,27	253463,6	69322,23	460974,5	219229,6	437246	297641	446898,8	206582,1
ethanolamine	33652,4	11511,54	39959,47	8922,187	42268,4	16990,66	44036,07	14646,55	43542,47	17412,89	52697,47	16908,21	38178,07	9346,952	37588,4	12276,99	36598,4	17309,17
erythritol	11999,8	3872,773	12511,4	4017,196	14136,13	7851,397	10979,4	2370,096	12764,2	1622,587	11950,27	2445,408	11721,73	2015,846	10485,6	1623,15	10376,27	1735,746
epsilon-caprolactam	7160	4378,601	8741,533	3444,633	7855,2	3957,559	10128,33	4214,631	8096,8	3596,17	7956,8	3376,899	11495,13	3360,8	11439,4	4444,834	9011,667	4009,788
docosahexaenoic acid	2308,867	656,9552	2506,933	839,8647	2489,533	1070,664	1989,6	517,7019	2438,8	494,3394	2119,2	628,0543	2122,533	521,3788	2618,733	654,1094	2494,467	624,6942
dihydrocholesterol	2775,067	1484,946	5023,067	3152,068	3991,6	1571,923	4476,133	1884,747	4871,333	2515,778	5593,133	1798,381	4220,667	1533,755	5489,667	2041,174	5253,8	1602,823
dihydro-3-coumaric acid	1206,867	380,0297	1210	353,0528	1176	407,5333	1194,4	355,9504	1526,267	502,3242	1417,867	444,0267	1646,267	733,2896	1567,2	462,486	1686,867	316,082
cytosine	1746,667	753,025	1491	632,4802	1519,467	505,863	1812,6	630,3419	1781,067	578,7134	1657,6	584,2192	1394,533	482,8414	1405,067	737,9462	1432	492,771
cystine	10950,4	6761,655	14542,33	9063,571	11583,4	5265,194	18670,33	10262,1	16488,27	8662,16	18703,33	10429,52	15685,53	8728,739	15638,27	9350,503	15267,73	8318,982
cysteine	7163,533	4792,409	7832,4	4190,372	7152,8	5333,629	10303,13	5529,27	7314,467	3135,171	9515	5426,09	9790,267	3943,839	10457,53	4811,828	10049,33	6264,538
creatinine	169183,1	97973,98	107839,3	52332,62	144622,2	108647,8	110233,1	39656,46	119931,7	39720,38	117559	42094,26	181369,3	57411,77	188484,1	41887,75	207931,5	51552,74
conduritol-beta-epoxide	2009,867	1259,542	1712,133	495,8346	1666,467	576,401	2507,467	2400,691	2062,067	823,6174	1890,8	515,0586	2177,933	877,0035	1888,467	608,8691	2404,067	2172,205
citrulline	33450,67	9390,997	40282,67	12408,53	36320,6	9875,463	38281,33	7993,692	45474,87	11757,01	42727,07	10655,82	31867,2	6246,817	35552,6	7250,261	35674,2	6702,284
citric acid	257011,9	124738,6	332840,9	112121,4	346138	99573,53	320806,8	77425,34	333533	83141,41	418979,9	108935,1	311789,4	82476,75	315176,5	98557,99	329888,3	53211,18
cis-gondoic acid	756,6	291,3189	554,7333	237,1285	585	204,7961	493,6	168,5208	561,9333	208,7362	694	361,864	626,5333	200,4209	583,4	220,1593	568,2	207,4599
cholic acid	732,8667	532,2989	1045,4	888,2293	1510,067	2998,168	702,2	319,9224	810,8	244,4519	801,8	378,8609	758,2	245,9007	814,9333	281,9244	912,4667	526,8919

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	Day 0						Day 28						Day 300					
	AMC		CON		DOX		AMC		CON		DOX		AMC		CON		DOX	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
cholesterol	709847,8	397488,3	654575,1	157976,8	784298,1	285283,9	590877	189202,4	675103,7	183641,2	734498,9	206840,8	601702,2	184952,9	727598,9	240252,1	667819,9	142505,9
cellobiose	3291,467	6699,524	649,8667	315,9973	879,2667	403,2193	675,2667	256,0021	687,6	279,9175	917,4	510,2081	671,4	276,5708	507,8667	203,4407	720,8	383,3717
capric acid	5118,6	2475,006	6607,067	3254,858	5723,2	3182,914	4602,867	2353,281	5632,333	2014,428	6863,4	4744,982	5348,2	1791,155	6025,333	3081,692	6145,8	3170,388
butyrolactam	38616,13	13594,98	26796,13	6912,497	31308,13	9252,548	26262,4	7131,216	33360,73	7117,621	29980,8	10411,34	26885,87	7367,485	27617,93	8572,931	31162,33	9179,818
butane-2,3-diol	205432,5	85022,49	200629	108408,8	186337,7	84463,91	193805,5	74536,45	194928,9	55713,59	191704,7	115631,9	132736,1	44412,23	141802,1	48729,71	120381	45790,17
beta-sitosterol	2458,267	1340,64	4459,2	2159,011	2766,867	1602,595	5775,733	3217,586	5953,133	3332,171	6238,467	2606,496	6342,333	3243,212	7510,933	2757,768	5392,667	2244,612
beta-glycerolphosphate	1621,667	462,0808	1248,733	452,8857	1339,467	292,9895	1277,533	326,6227	1390,4	310,3739	1421,067	473,1582	1652,8	467,8426	1604,667	486,7002	1461,6	371,5429
beta-alanine	3028,8	1820,984	3244,333	1801,143	3223,667	1817,154	3366,133	1108,888	3817,067	1562,732	3341,933	1584,806	4421,467	1582,84	4327,733	2429,759	3512,267	1742,914
benzoic acid	159552,2	41961,39	180393,2	70669,29	159696,8	28599,54	155622,7	42539,01	183531,9	42833,04	174249,1	49533,48	170421,6	30171,81	196641,6	66852,78	186769,2	36123,9
azelaic acid	1562	869,9223	1606,267	516,3522	1467,2	388,8041	1332,467	458,6117	1605	544,733	1593,4	574,5136	1987,133	782,2844	1851	859,9464	1537	485,143
aspartic acid	22166,73	6100,172	22953,67	4229,601	26034,13	7550,821	27773,67	6181,815	23535,27	5158,251	30308,27	6213,474	24414,67	9567,562	24418,07	8656,301	22840,33	4077,988
asparagine	28024,47	8064,522	39820,6	14906,18	37632,33	9713,014	35357,87	8345,583	38056,07	8542,514	36873,07	11858,96	29799,87	5652,458	31909,6	5144,244	31116,13	4294,271
arachidonic acid	20304,87	7954,043	15331,67	7136,385	21507,27	8645,357	12796,87	4318,196	15529,47	4525,467	15391	4627,571	19069,73	5576,966	21009,53	6215,79	21035,93	4419,123
arachidic acid	8337,733	5322,757	6427,4	1468,757	6371,667	1017,429	5894,8	1233,371	6363,533	1968,186	6169,667	1675,942	7114	2943,351	7090,4	3870,209	6315,4	1642,685
arabitol	9362	4741,085	9453,467	3557,989	8919,133	3010,503	12314,73	3305,101	13775,6	3221,101	12956,53	3184,342	10662,73	5162,346	8836,2	2273,959	9972,067	3891,156
aminomalonate	30384,27	17025,76	42813,33	22563,62	37189,07	12086,11	36200,2	10423,14	35252,33	13754,2	40723,2	14183,39	25267,4	11846,67	24782,87	12314,96	26142,07	13007,23
alpha-ketoglutarate	850,3333	937,805	1138,067	1885,527	983,8	1064,422	1011,2	1073,258	1008,6	1562,504	1915,467	1871,85	477,3333	129,6896	1370,133	1744,372	827,4667	1090,614
alpha-aminoadipic acid	2739,533	529,0202	2570,4	838,0137	2340,467	692,4618	2805,467	547,353	3036,2	651,9881	2806,133	447,3185	2751,867	557,2649	2962,2	824,1837	2874	618,0717
allantoic acid	41306,8	13786,23	31623,27	9395,563	37663,27	12042,86	37455,73	15104,58	45895,8	13730,25	45025,8	23038,8	38307,13	21722,99	34621,13	20671,28	31555,2	13272,99
alanine	1571042	777177	2077073	473101,5	1921039	581830,5	1912679	460982,8	2181099	611749,4	1805719	496370,9	2243351	548445,7	2463761	873550,1	2080128	447153,3
adipic acid	5131,067	5757,448	4154,333	2099,246	3728,133	1981,065	3920,933	2432,355	4537,867	3202,208	3752,533	1232,73	7455,667	4666,829	6156,4	4466,072	5171,2	3336,195
aconitic acid	2615,333	1457,688	2398,733	1457,915	1887,667	1030,973	1594,467	837,7686	2273,933	829,8991	1856,467	974,1205	1614,4	882,5178	1851,867	866,2408	1841,467	831,8663
5-methoxytryptamine	105089,4	60702,93	78750,6	34590,47	117939,9	74132,77	77431,8	26048,48	77920,47	50103,01	94206,07	60434,62	61336,27	21410,9	49624,13	41836,06	72414,6	39642,41
5-hydroxymethyl-2-furoic acid	5903,467	9134,785	1222,533	487,041	1799,733	1639,323	993,6667	256,4354	1163,733	267,1218	980,6	267,9757	1571,4	388,3393	1563,467	433,1855	1628,133	417,6393
5-hydroxy-3-indoleacetic acid	2030,267	1809,446	1334,467	716,3506	2143,667	2811,118	1427,267	756,0496	1775,4	1642,748	1229,333	712,2572	1600,8	1545,672	1157,8	652,5817	1567,533	683,1753
5-aminovaleric acid	27554	25615,28	20423,2	16898,19	16242,47	14153,32	12374,53	10395,64	18715,87	15041,16	12097,8	7193,887	4658,133	2946,946	4234,667	2062,482	6352,467	7222,199
4-hydroxyphenylacetic acid	3647,667	3120,275	3015,067	1602,169	2187,733	1135,875	1510,133	726,5525	2829,467	2052,867	1385,6	565,5259	1357,067	683,763	1252,333	525,8076	1405,267	592,2586
4-hydroxymandelic acid	1253	271,7759	1295,867	348,8821	1350	419,1934	1251,067	369,2298	1491,533	305,478	1651,333	928,1925	1243,867	380,3646	1317,533	366,9556	1264,467	251,7322
4-hydroxyhippuric acid	471,9333	411,4194	430,7333	276,9101	420,4667	241,0669	327	64,62419	468,8	190,373	391,4	99,38152	345,8667	111,717	468,9333	350,5107	910,0667	865,3385
3-ureidopropionate	1251,4	510,4933	1662,733	523,1306	1770,133	900,1463	2126,467	1023,872	1499,933	721,7157	1827,333	559,778	1514,533	599,8457	1412,4	555,7393	1273,6	575,9889
3-phosphoglycerate	843,6667	429,936	816,8	294,993	1090,8	1476,574	1280,733	894,2851	960,5333	560,4493	1846	1798,083	1235,4	1295,439	1049,467	786,9712	909,1333	769,2213
3-phenyllactic acid	4808,667	9500,773	2524,533	2191,656	3191,733	5131,73	2910,533	1491,295	3665,133	2560,256	2735	2041,242	2261,067	1989,738	1724,4	622,7454	1928,733	1608,662
3-hydroxybutyric acid	1192910	2274124	112391,5	80512,71	311592,9	407090,2	57513,07	23638,19	86163,8	32683,07	101597,4	110369,5	60262,67	32852,16	68674,07	43689,41	73253,8	29622,4
3-hydroxy-3-methylglutaric acid	1259,067	1940,939	545,2	199,3246	601,8	337,7472	546,9333	234,2595	668,6	310,0394	679,8	310,5935	867,1333	311,8101	735,8667	261,2842	813,8	331,4613
3-aminoisobutyric acid	9769,6	12655	9558,2	10131,19	7185,933	5432,935	9586,667	10505,28	11754,2	11207	7633,133	4009,771	5655,4	3010,729	6686,067	5097,782	5691,733	2679,79
3-(4-hydroxyphenyl)propionic acid	3952,8	8838,947	1461,067	561,1234	1809,2	889,5726	1181,2	289,6595	1557,4	438,713	1559,667	519,6695	1417,933	281,4088	1284,067	360,4886	1401,6	334,9023
2-picolinic acid	2618,733	1278,167	2313,733	538,14	2286,067	914,9093	2277,333	689,7902	2129,667	562,3317	2257,333	567,4164	2938,267	1203,737	2922,733	1045,496	2584,667	1246,088
2-monopalmitin	6471,8	9431,771	3804	6324,679	7237,467	11235,4	4712,4	7532,541	9250,2	14319,68	11072,2	15135,79	2567,733	1138,664	3070,2	2758,655	9241,2	14016,98
2-ketoisocaproic acid	7171,267	7501,986	7045,667	7302,876	6596,6	6186,635	5995,6	6357,123	6570,2	6304,176	10313,87	7399,254	3619,133	2334,25	8524,533	8403,269	4188,933	6015,264
2-hydroxyvaleric acid	21326,33	16138,24	10612,2	3961,408	11400,67	4625,103	9355,467	3539,66	11974,73	6597,591	10003	3438,607	8858,8	3034,347	8327,867	2164,845	7602,467	1892,593
2-hydroxyglutaric acid	9528,333	4490,5	12753,53	5398,852	10048,13	3521,992	12206,4	3939,574	10301,87	3394,811	12499,87	3377,28	4244,067	1019,977	4327,333	906,8773	4425	1062,776
2-hydroxybutanoic acid	193658,1	170262,6	93973,8	61660,47	123541,1	69982,64	74315,13	22329,85	85974,07	23796,89	98728,2	60143,03	79136,67	19102,29	78563,6	33259,68	81039,33	22061,67
2-hydroxy-2-methylbutanoic acid	12287,93	7297,707	11851,73	5531,192	11047,4	5676,185	6737,467	1685,297	9429,2	3784,935	8528,6	3942,858	6593	1501,075	6686,733	1321,855	8126,933	6095,857
2-deoxytetronic acid	21788,53	43917,63	5091	1750,639	5508,4	2467,534	3684,467	1165,066	4289,867	628,0284	3691	1492,9	2623,6	680,7041	3354,467	1802,827	2538,533	754,122
2-deoxypentitol	3796,4	5408,742	1187,8	292,9896	1388,867	404,1992	1185,267	366,7877	1136,533	239,1162	1284,4	483,3481	1252,6	433,654	1186,467	397,5467	1203,4	274,4191
2-aminobutyric acid	87422,4	68388,09	58866,93	27809,05	102758,2	90053,82	37605,13	11767,96	47510,8	20207,07	42100,67	13279,2	54484,53	27146	51210,2	18499,71	54504,2	20406,91
2,5-dihydroxypyrazine	3553,267	1211,81	4110,533	1930,083	3620,733	1120,036	3916,667	1132,084	3591,467	1311,041	4852,533	1168,583	3468,6	1225,778	3732,267	1718,173	3165,933	1353,18
2,3-dihydroxybutanoic acid	3400,533	2509,571	2210,067	717,3481	2584,2	1478,603	2630,2	1902,573	2155,067	800,8603	2326,6	860,9717	2099,667	992,983	1946,067	543,8745	1776,733	532,3374
1-monostearin	4527,533	1645,637	4488,067	1249,013	4474,933	2238,341	3861,6	1012,729	3844,933	802,3543	4710,267	1839,474	3299,867	665,8949	5377,733	6322,573	3768,867	1363,173
1-monopalmitin	3290,4	1344,46	3842,867	1308,62	3792	1757,546	2799,067	789,5843	3511,533	1110,859	3072,467	782,1329	2978,2	373,0556	4894,133	6493,126	3255	874,0412
1-kestose	931,5333	723,8854	822,4	556,1707	681,9333	405,4106	1166,8	373,2812	1221,8	556,4458	1208,4	892,3384	994,2667	746,539	620,5333	348,0396	1178,267	847,753

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Supplementary Table S3: List of raw metabolites identified in fecal samples by targeted metabolomics.

		BA (ng/mg)				
NO	ID	cholic acid (ng/mg)	chenodeoxycholic acid (ng/mg)	lithocholic acid (ng/mg)	deoxycholic acid (ng/mg)	ursodeoxycholic acid (ng/mg)
1	FMF4-0	17,9	53,8	276,0	1260,6	1,5
2	FMF4-28	51,9	56,7	193,4	1904,0	1,5
3	FMF4-60	597,7	145,2	1,3	516,6	1,4
4	FMF4-120	251,2	120,0	386,4	2453,9	16,9
5	FMF4-300	790,9	146,2	221,1	2036,0	1,5
6	FMF6-0	46,4	48,7	78,1	897,2	1,5
7	FMF6-28	1975,3	403,2	463,9	3144,0	1,3
8	FMF6-60	867,0	233,7	557,8	3024,0	26,3
9	FMF6-120	2670,4	470,9	400,8	3002,3	173,2
10	FMF6-300	245,7	182,7	779,8	4517,7	1,4
11	FMF7-0	39,0	68,6	1158,2	4662,6	90,0
12	FMF7-20	289,8	134,5	183,1	1437,0	1,3
13	FMF7-60	41,8	56,7	393,8	2535,8	1,3
14	FMF7-120	88,2	97,8	763,1	4331,0	30,2
15	FMF7-300	621,1	202,7	67,2	1145,6	68,1
16	FMF8-0	2522,5	374,5	1,3	280,0	1,5
17	FMF8-28	656,3	221,0	122,9	1288,2	1,3
18	FMF8-60	740,8	390,2	393,5	1711,7	330,7
19	FMF8-120	37,7	53,7	408,1	1657,2	106,5
20	FMF8-300	14,7	60,2	684,0	2453,5	212,1
21	FMF9-0	91,9	104,2	378,8	1519,4	373,8
22	FMF9-28	53,7	65,8	422,5	1091,1	89,8
23	FMF9-60	57,5	83,7	1326,2	4580,2	183,7
24	FMF9-120	60,7	72,9	639,5	2792,5	127,1
25	FMF9-300	283,0	187,3	109,2	1489,2	169,7
26	FMF13-0	19,6	49,5	230,9	1296,9	1,6
27	FMF13-20	2344,1	428,3	1,4	18,4	79,2
28	FMF13-60	3405,5	699,6	79,6	1613,2	133,4
29	FMF13-120	889,8	207,5	275,4	2316,8	172,5
30	FMF13-300	277,3	107,6	173,3	2056,5	166,1
31	FMF14-0	65,5	67,9	595,3	3475,3	84,5
32	FMF14-28	95,4	86,9	461,7	2177,0	205,6
33	FMF14-60	178,9	191,8	288,0	1697,0	154,1
34	FMF14-120	2640,9	497,7	26,2	1533,4	292,6
35	FMF14-300	45,4	50,9	235,7	1061,1	58,0
36	FMF15-0	54,7	118,8	425,6	1721,8	1,4
37	FMF15-28	482,8	195,3	96,0	997,4	47,8
38	FMF15-60	297,3	139,1	472,7	3044,1	55,7
39	FMF15-120	182,4	134,6	574,6	3379,7	492,6
40	FMF15-300	77,8	77,7	509,5	2577,8	165,5
41	FMF16-0	211,2	127,2	315,5	2092,8	14,9
42	FMF16-28	969,0	262,9	103,1	1447,7	1,5
43	FMF16-60	15,0	54,3	297,6	1051,2	69,8
44	FMF16-120	112,3	94,7	682,7	2290,3	104,3
45	FMF16-300	73,2	78,6	699,5	3214,3	146,4
46	FMF18-0	41,6	55,4	719,1	5066,6	116,4
47	FMF18-20	1156,7	306,5	66,7	1152,9	126,4
48	FMF18-60	72,7	51,8	353,0	2497,5	52,2
49	FMF18-120	602,1	128,5	681,2	3515,5	103,0
50	FMF18-300	47,3	88,8	524,4	2136,7	118,9
51	FMF20-0	482,8	317,4	202,4	1445,0	295,4
52	FMF20-20	18,1	47,0	363,6	1860,4	104,2
53	FMF20-60	69,4	71,3	642,3	2678,5	184,8
54	FMF20-120	256,5	169,6	411,5	4504,0	613,6
55	FMF20-300	135,3	80,7	352,2	2818,6	300,7
56	FMF22-0	429,6	228,2	1061,6	4240,5	80,4
57	FMF22-20	197,4	262,1	1197,2	5064,7	75,1
58	FMF22-60	41,9	67,7	469,6	2929,2	26,6
59	FMF22-120	5703,8	1057,1	219,5	1964,7	194,1
60	FMF22-300	593,6	210,2	696,6	5004,8	202,0
61	FMF23-0	537,1	236,0	968,3	5855,1	409,5
62	FMF23-28	34,8	55,3	872,9	4062,8	172,6
63	FMF23-60	131,3	152,8	535,4	2569,8	448,9
64	FMF23-120	15,6	58,9	384,4	1533,9	93,4
65	FMF23-300	1074,0	230,7	231,1	2414,5	185,1
66	FMF24-0	413,2	216,4	192,3	1829,5	41,4
67	FMF24-20	496,6	523,6	1,4	18,8	107,9
68	FMF24-60	66,0	104,8	604,0	2434,0	249,2
69	FMF24-120	611,9	235,9	254,5	2201,3	374,9
70	FMF24-300	137,4	164,2	449,5	3228,5	253,9
71	FMF26-0	15,0	52,9	1,1	15,0	1,3
72	FMF26-28	467,8	257,9	116,0	1243,7	31,3
73	FMF26-60	57,1	126,0	296,2	1915,8	206,7
74	FMF26-120	159,5	153,1	866,9	4026,3	435,5
75	FMF26-300	17,6	77,2	731,9	3343,5	81,5
76	FMF29-0	17,8	85,8	566,5	522,1	40,9
77	FMF29-20	2452,2	846,0	1,4	19,0	425,6
78	FMF29-60	879,8	350,9	184,7	2317,7	155,8
79	FMF29-120	417,1	192,0	338,4	3432,0	301,4
80	FMF29-300	129,7	160,2	452,8	1693,7	286,2

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		BA (ng/mg)				
NO	**ID**	**cholic acid (ng/mg)**	**chenodeoxycholic acid (ng/mg)**	**lithocholic acid (ng/mg)**	**deoxycholic acid (ng/mg)**	**ursodeoxycholic acid (ng/mg)**
81	FMF31-0	318,3	427,9	489,1	2286,0	550,7
82	FMF31-28	178,5	271,3	381,8	2776,0	329,5
83	FMF31-60	1048,5	467,4	144,6	1435,8	307,4
84	FMF31-120	400,0	224,8	356,6	3195,6	188,2
85	FMF31-300	104,6	235,7	299,7	2182,1	77,9
86	FMF32-0	3388,8	1027,0	235,2	2434,7	845,9
87	FMF32-20	422,9	164,0	1,3	17,1	1,4
88	FMF32-60	2085,2	548,2	127,4	2295,6	747,7
89	FMF32-120	1096,8	494,3	203,5	1956,6	406,7
90	FMF32-300	86,9	138,9	1560,6	7265,5	418,9
91	FMF33-0	33,2	73,2	980,7	4119,3	59,5
92	FMF33-28	7628,4	1359,3	35,1	736,3	258,9
93	FMF33-60	2062,9	565,6	238,4	2467,1	370,5
94	FMF33-120	503,7	315,8	248,5	2050,8	135,3
95	FMF33-300	62,6	84,8	327,1	2052,6	80,0
96	FMF34-0	15,1	16,5	206,7	1540,8	1,3
97	FMF34-20	8641,5	1206,1	53,7	17,6	97,8
98	FMF34-60	136,4	140,5	514,2	1904,7	1,5
99	FMF34-120	1901,0	461,4	392,0	3599,4	57,4
100	FMF34-300	128,4	199,0	560,3	2734,4	17,6
101	FMF35-0	17,9	39,2	1387,4	4790,9	80,0
102	FMF35-28	4615,3	726,2	20,2	17,3	73,5
103	FMF35-60	120,2	168,2	424,1	1968,2	36,3
104	FMF35-120	268,5	102,9	1,1	305,2	1,3
105	FMF35-300	384,9	67,7	385,0	2323,7	1,5
106	FMF36-0	15,6	29,7	725,7	1965,6	107,9
107	FMF36-28	1333,9	262,9	464,9	3432,5	407,5
108	FMF36-60	104,5	58,0	666,0	3206,2	220,2
109	FMF36-120	226,1	103,8	522,2	2395,0	246,3
110	FMF36-300	46,3	39,4	259,0	1567,7	84,4
111	FMF37-0	15,3	57,9	626,5	3184,4	32,3
112	FMF37-28	1954,0	391,8	514,7	3411,1	995,8
113	FMF37-60	52,9	68,1	233,7	1192,6	95,9
114	FMF37-120	182,9	91,4	602,7	3063,7	370,4
115	FMF37-300	4071,0	476,7	621,3	3844,2	346,2
116	FMF38-0	15,3	49,8	159,2	2052,4	26,6
117	FMF38-28	18,1	37,0	676,4	2487,0	97,3
118	FMF38-60	444,7	108,5	239,3	2214,7	223,1
119	FMF38-120	58,5	29,3	425,5	1629,3	122,5
120	FMF38-300	96,6	91,5	1140,4	5422,6	144,2
121	FMF41-0	1673,9	193,9	1,4	445,5	39,8
122	FMF41-28	622,4	197,2	1,1	15,0	183,1
123	FMF41-60	16,0	55,0	360,2	1512,9	1,3
124	FMF41-120	87,6	75,4	325,8	806,9	1,3
125	FMF41-300	234,6	192,4	1083,1	3450,9	32,0
126	FMF43-0	2047,6	218,0	1,4	18,6	1,6
127	FMF43-28	3156,2	479,8	1,4	19,0	1,6
128	FMF43-60	3617,4	434,6	1,3	17,8	276,6
129	FMF43-120	3543,1	432,8	1,4	2161,0	24,5
130	FMF43-300	170,2	66,9	265,0	2649,6	49,9
131	FMF45-0	1686,9	304,7	1,3	17,8	1,5
132	FMF45-28	6534,3	784,0	1,3	17,9	257,7
133	FMF45-60	1365,2	224,2	1,2	16,0	1,3
134	FMF45-120	1461,3	322,5	1,3	18,3	129,4
135	FMF45-300	71,6	37,6	1,2	16,0	13,9
136	FMF47-0	2327,8	837,7	1,3	18,1	104,4
137	FMF47-28	60,0	123,5	317,9	1825,4	1,5
138	FMF47-60	70,1	86,4	523,8	1928,6	98,3
139	FMF47-120	53,8	63,3	118,9	1347,6	46,4
140	FMF47-300	65,0	64,2	451,4	2288,6	53,9
141	FMF48-0	1185,4	256,8	1,4	19,0	1,6
142	FMF48-28	134,4	216,5	599,0	2790,9	1,3
143	FMF48-60	67,5	78,1	637,0	3174,8	1,5
144	FMF48-120	37,3	62,5	207,7	1168,4	56,8
145	FMF48-300	298,1	126,6	348,7	2070,0	107,4
146	FMF49-0	52,3	90,1	873,0	2680,9	125,9
147	FMF49-28	52,6	71,0	395,8	2049,0	146,7
148	FMF49-60	79,2	79,7	593,3	1818,7	108,7
149	FMF49-120	72,2	67,4	286,4	1873,8	29,6
150	FMF49-300	206,2	91,7	1456,9	7875,5	192,9
151	FMF55-0	995,6	541,2	495,6	2061,4	244,8
152	FMF55-28	16,8	52,2	269,4	1353,6	1,4
153	FMF55-60	49,4	57,6	416,9	1940,3	55,6
154	FMF55-120	61,5	74,3	454,0	2556,4	90,8
155	FMF55-300	446,3	136,4	442,5	3153,0	176,3
156	FMF56-0	310,0	214,0	288,7	1366,7	142,3
157	FMF56-20	44,1	109,9	461,5	1133,5	76,7
158	FMF56-60	107,1	98,0	554,8	2671,2	166,5
159	FMF56-120	56,9	56,9	609,2	2376,3	1,4
160	FMF56-300	137,3	65,0	461,7	2364,3	1,3

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		BA (ng/mg)				
NO	**ID**	**cholic acid (ng/mg)**	**chenodeoxycholic acid (ng/mg)**	**lithocholic acid (ng/mg)**	**deoxycholic acid (ng/mg)**	**ursodeoxycholic acid (ng/mg)**
161	FMF58-0	1238,9	330,5	442,6	3067,2	65,0
162	FMF58-20	262,4	210,2	334,9	2704,2	150,0
163	FMF58-60	163,1	111,5	307,0	2144,3	259,7
164	FMF58-120	332,0	112,8	305,0	2560,8	139,2
165	FMF58-300	55,0	49,4	172,5	2403,8	18,7
166	FMF59-0	1104,2	335,9	1,2	16,8	26,7
167	FMF59-28	18,3	59,6	90,6	800,4	1,5
168	FMF59-60	47,2	70,4	168,8	1554,2	44,9
169	FMF59-120	127,7	91,7	646,8	2986,1	62,4
170	FMF59-300	71,1	68,2	507,7	2491,4	114,7
171	FMF61-0	866,5	177,6	1,2	1035,0	26,7
172	FMF61-28	266,0	108,6	1,4	500,2	59,2
173	FMF61-60	883,8	202,0	202,7	2925,8	260,5
174	FMF61-120	562,0	145,5	113,3	2383,7	184,2
175	FMF61-300	238,9	108,5	237,4	2742,6	35,0
176	FMF62-0	17,4	45,0	89,0	1094,5	1,5
177	FMF62-28	15,4	55,6	131,7	1167,8	29,6
178	FMF62-60	423,3	150,4	158,4	1430,2	120,5
179	FMF62-120	682,8	188,7	101,7	1710,3	164,7
180	FMF62-300	1094,2	220,6	133,4	1453,4	121,8
181	FMF63-0	14,8	44,1	24,1	859,5	1,3
182	FMF63-28	15,3	44,2	1,1	348,9	1,3
183	FMF63-60	16,2	46,0	212,6	1507,9	1,4
184	FMF63-120	55,6	63,0	604,0	2260,2	70,3
185	FMF63-300	104,6	73,6	470,6	3021,3	51,7
186	FMF64-0	3062,3	741,6	1,3	17,0	45,2
187	FMF64-28	1051,7	317,8	1,4	18,8	24,8
188	FMF64-60	151,1	85,2	623,3	2657,8	22,4
189	FMF64-120	19,0	71,8	499,6	2360,6	35,8
190	FMF64-300	119,2	136,2	550,1	2329,1	186,9
191	FMF66-0	220,9	104,5	91,9	2371,9	1,5
192	FMF66-28	91,2	176,7	447,4	1854,9	57,4
193	FMF66-60	83,9	233,0	325,3	1546,2	25,9
194	FMF66-120	48,8	86,4	334,9	1527,1	1,3
195	FMF66-300	204,4	90,2	635,2	4872,2	1,5
196	FMF67-0	693,7	182,8	1,3	17,6	1,5
197	FMF67-20	1683,8	292,0	1,3	18,1	1,5
198	FMF67-60	1202,8	624,4	303,7	2252,6	27,2
199	FMF67-120	48,2	89,3	263,2	1623,8	1,3
200	FMF67-300	127,0	125,0	660,7	3085,9	20,4
201	FMF68-0	253,5	80,7	1,3	17,6	1,5
202	FMF68-20	1148,5	383,0	1,1	15,6	54,6
203	FMF68-60	229,5	224,1	168,6	1069,5	187,3
204	FMF68-120	80,0	80,0	276,5	2595,4	84,0
205	FMF68-300	442,2	195,0	261,1	1946,1	109,8
206	FMF70-0	2102,2	733,6	1,4	19,0	81,6
207	FMF70-20	317,6	98,0	49,9	1141,1	52,3
208	FMF70-60	1063,4	317,2	1,1	14,6	300,2
209	FMF70-120	1414,6	473,9	1,3	17,0	34,6
210	FMF70-300	731,8	315,7	57,7	1228,5	76,4
211	FMF71-0	3424,4	534,7	1,2	16,8	918,4
212	FMF71-28	1894,5	503,8	1,2	16,4	150,9
213	FMF71-60	3334,9	501,4	1,1	15,1	322,2
214	FMF71-120	73,8	137,8	245,0	3177,8	15,6
215	FMF71-300	83,1	92,4	202,0	3073,8	46,0
216	FMF74-0	42,7	101,3	302,2	2005,4	1,4
217	FMF74-20	17,8	65,4	44,7	1009,0	1,5
218	FMF74-60	112,7	124,7	185,0	1744,1	1,5
219	FMF74-120	77,4	100,2	246,2	1772,5	120,2
220	FMF74-300	191,3	125,1	421,3	2640,4	123,5
221	FMF75-0	2391,0	482,1	1,3	17,8	1,5
222	FMF75-28	1727,3	378,3	1,2	15,8	1,3
223	FMF75-60	45,1	120,3	300,2	1853,8	86,8
224	FMF75-120	693,2	270,6	456,8	3569,6	356,4
225	FMF75-300	226,5	174,9	704,1	3941,1	336,6

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		FA (ug/mg)											
NO	**ID**	**myristate**	**alpha-linolenate**	**cis-vaccenate**	**palmitate**	**oleate**	**linoleate**	**stearate**	**arachidonate**	**gondate**	**erucate**	**docosanoate**	**nervonate**
1	FMF4-0	0,2	0,1	1,2	18,9	18,9	6,3	10,4	0,4	0,3	0,1	0,1	0,1
2	FMF4-28	0,1	0,1	0,6	6,1	8,7	5,5	2,5	0,5	0,1	0,0	0,1	0,1
3	FMF4-60	0,1	0,2	0,3	6,7	10,4	7,1	2,4	0,4	0,1	0,0	0,1	0,1
4	FMF4-120	0,3	0,3	4,6	18,4	18,4	8,8	18,4	1,2	0,3	0,1	0,2	0,3
5	FMF4-300	0,1	0,2	0,5	7,4	11,9	8,1	2,8	0,8	0,1	0,0	0,1	0,1
6	FMF6-0	0,3	0,2	1,9	18,9	18,9	5,9	11,8	0,6	0,4	0,1	0,1	0,2
7	FMF6-28	0,3	0,6	1,5	15,0	16,1	15,2	5,8	0,8	0,3	0,1	0,1	0,1
8	FMF6-60	0,4	0,6	4,5	18,0	18,0	18,0	13,9	0,8	0,4	0,1	0,2	0,3
9	FMF6-120	0,3	0,6	2,1	16,5	16,5	16,5	9,1	0,9	0,3	0,1	0,1	0,2
10	FMF6-300	0,2	0,3	0,9	11,7	17,7	11,0	4,2	0,7	0,2	0,0	0,1	0,1
11	FMF7-0	0,4	0,7	5,0	20,0	20,0	20,0	16,3	0,8	0,5	0,1	0,2	0,3
12	FMF7-20	0,2	0,4	1,1	12,5	15,8	10,4	5,3	0,6	0,2	0,0	0,1	0,1
13	FMF7-60	0,3	0,4	3,3	16,3	16,3	10,1	8,2	0,6	0,3	0,1	0,1	0,2
14	FMF7-120	0,5	0,8	2,6	19,6	19,6	19,6	19,6	1,4	1,0	0,2	0,2	0,4
15	FMF7-300	0,2	0,2	0,4	7,7	8,3	4,1	2,8	0,6	0,1	0,0	0,1	0,1
16	FMF8-0	0,4	0,3	0,7	18,2	18,2	10,5	16,4	0,8	0,5	0,1	0,2	0,2
17	FMF8-28	0,3	0,6	1,9	16,8	16,8	16,8	6,2	0,7	0,3	0,1	0,1	0,1
18	FMF8-60	0,3	0,6	4,2	11,6	16,7	11,0	6,7	1,0	0,4	0,1	0,2	0,2
19	FMF8-120	0,2	0,4	1,0	7,0	8,3	6,8	3,3	0,6	0,2	0,0	0,1	0,1
20	FMF8-300	0,2	0,4	2,8	7,8	7,0	5,8	4,9	0,5	0,2	0,0	0,1	0,1
21	FMF9-0	0,5	0,7	2,2	19,3	19,3	19,3	10,2	1,3	0,4	0,1	0,2	0,2
22	FMF9-28	0,3	0,5	2,9	15,4	15,4	10,8	6,1	0,8	0,3	0,1	0,2	0,2
23	FMF9-60	0,5	0,4	4,8	19,3	19,3	11,3	11,2	1,1	0,6	0,2	0,2	0,3
24	FMF9-120	0,2	0,4	0,7	10,7	17,9	9,3	4,0	0,8	0,2	0,1	0,1	0,2
25	FMF9-300	1,1	0,3	2,1	17,7	17,7	12,7	17,7	1,1	0,8	0,1	0,2	0,3
26	FMF13-0	2,0	0,2	5,2	20,6	20,6	7,5	20,6	1,3	2,1	0,7	1,7	2,1
27	FMF13-20	0,2	0,3	0,4	8,5	11,0	8,1	3,5	0,9	0,2	0,0	0,1	0,1
28	FMF13-60	0,2	0,3	0,4	7,0	9,4	7,4	3,3	0,8	0,2	0,1	0,1	0,1
29	FMF13-120	0,6	0,3	4,0	11,4	10,9	8,7	7,6	2,0	0,4	0,1	0,2	0,3
30	FMF13-300	0,3	0,3	2,3	10,3	13,2	7,2	5,4	1,0	0,2	0,1	0,1	0,2
31	FMF14-0	0,6	0,3	4,7	18,9	18,9	5,6	18,9	1,0	0,9	0,2	0,3	0,6
32	FMF14-28	0,4	0,5	1,4	12,1	18,5	12,4	4,5	0,8	0,3	0,1	0,1	0,2
33	FMF14-60	0,1	0,2	0,4	5,6	7,4	5,9	2,2	0,7	0,2	0,0	0,1	0,1
34	FMF14-120	0,3	0,3	0,6	10,5	11,4	8,9	5,7	1,7	0,3	0,1	0,1	0,2
35	FMF14-300	0,4	0,5	2,1	15,5	15,5	15,4	6,8	1,3	0,3	0,1	0,2	0,2
36	FMF15-0	0,3	0,5	1,0	14,9	17,6	13,4	4,7	0,6	0,2	0,0	0,1	0,2
37	FMF15-28	0,3	0,5	0,9	10,9	17,4	11,0	4,1	0,8	0,2	0,1	0,1	0,1
38	FMF15-60	0,2	0,3	0,5	6,1	8,2	6,7	2,4	0,6	0,2	0,0	0,1	0,1
39	FMF15-120	0,3	0,3	1,3	6,9	8,3	6,6	3,7	1,0	0,3	0,1	0,1	0,2
40	FMF15-300	0,4	0,3	1,0	7,4	8,3	6,9	3,8	0,7	0,2	0,0	0,2	0,2
41	FMF16-0	1,0	0,2	4,0	16,0	16,0	11,8	16,0	2,8	1,6	0,4	0,5	1,3
42	FMF16-28	0,2	0,2	0,6	5,8	6,8	5,4	2,7	0,7	0,2	0,0	0,1	0,1
43	FMF16-60	0,2	0,4	0,6	7,3	10,3	7,6	3,0	0,6	0,2	0,0	0,1	0,1
44	FMF16-120	0,3	0,4	1,0	6,8	7,6	7,4	3,6	0,9	0,2	0,1	0,2	0,2
45	FMF16-300	0,2	0,4	0,9	13,3	17,9	11,9	7,3	0,4	0,1	0,0	0,1	0,1
46	FMF18-0	0,9	0,3	4,0	15,8	15,8	7,9	15,8	0,4	0,8	0,1	0,3	0,4
47	FMF18-20	0,2	0,4	0,3	4,4	5,6	5,4	2,4	0,7	0,2	0,0	0,1	0,1
48	FMF18-60	0,1	0,3	0,6	3,4	4,0	3,8	1,8	0,5	0,1	0,0	0,1	0,1
49	FMF18-120	0,2	0,4	1,4	7,2	9,8	7,8	4,2	0,6	0,2	0,0	0,1	0,1
50	FMF18-300	0,4	0,3	4,1	16,3	16,3	14,3	16,3	16,3	0,7	0,1	0,2	0,3
51	FMF20-0	0,4	5,0	0,4	19,8	19,8	14,0	12,8	0,7	0,5	0,1	0,2	0,1
52	FMF20-20	3,8	4,8	4,8	19,1	19,1	19,1	3,1	19,1	1,9	1,0	1,9	1,9
53	FMF20-60	0,3	0,3	3,0	3,8	6,1	6,0	3,3	0,9	0,4	0,1	0,1	0,2
54	FMF20-120	0,3	0,3	3,2	8,1	10,5	7,7	6,7	0,7	0,2	0,0	0,2	0,2
55	FMF20-300	1,0	0,2	4,3	13,9	17,0	10,5	17,0	2,3	1,7	0,2	0,4	0,6
56	FMF22-0	3,6	4,5	4,5	17,9	17,9	17,9	17,9	7,2	1,8	0,9	1,8	1,8
57	FMF22-20	0,2	0,8	1,3	9,4	10,4	9,5	5,1	0,8	0,2	0,1	0,1	0,2
58	FMF22-60	0,3	0,5	1,7	6,6	9,8	8,0	5,2	0,7	0,4	0,3	0,1	0,2
59	FMF22-120	0,1	0,4	0,4	4,7	5,5	4,8	2,8	1,1	0,2	0,1	0,1	0,1
60	FMF22-300	0,4	0,4	1,0	8,7	7,9	6,9	5,3	1,6	0,4	0,1	0,2	0,2
61	FMF23-0	0,6	0,3	1,8	14,5	18,0	10,7	7,1	1,4	0,7	0,1	0,2	0,3
62	FMF23-28	0,4	0,3	2,1	6,5	8,2	6,0	4,0	0,7	0,4	0,1	0,1	0,2
63	FMF23-60	0,4	0,3	1,0	6,7	8,4	6,8	4,0	1,5	0,6	0,1	0,2	0,3
64	FMF23-120	0,1	0,1	0,4	3,7	4,5	3,7	2,1	0,3	0,1	0,0	0,0	0,1
65	FMF23-300	0,2	0,5	1,5	11,1	18,2	10,6	6,8	1,1	0,4	0,1	0,1	0,1
66	FMF24-0	0,3	0,3	3,8	8,6	15,1	8,2	6,6	1,4	0,5	0,1	0,1	0,2
67	FMF24-20	0,1	0,2	0,2	6,0	9,0	6,6	2,5	0,4	0,1	0,1	0,0	0,1
68	FMF24-60	0,1	0,3	0,7	7,3	11,8	8,3	3,7	0,4	0,2	0,0	0,1	0,1
69	FMF24-120	0,1	0,2	0,5	6,7	11,1	7,2	3,8	0,5	0,2	0,0	0,1	0,1
70	FMF24-300	0,1	0,3	0,2	6,8	10,6	8,3	3,0	0,4	0,1	0,0	0,0	0,1
71	FMF26-0	0,7	0,4	0,9	15,8	15,8	14,9	15,8	0,7	0,4	0,0	0,1	0,1
72	FMF26-28	0,4	0,6	0,7	17,4	17,4	17,4	17,4	2,5	1,5	0,2	0,2	0,3
73	FMF26-60	0,2	0,4	0,9	7,9	10,4	8,3	4,3	0,5	0,2	0,0	0,1	0,1
74	FMF26-120	0,2	0,4	4,1	16,5	16,5	16,5	10,0	1,3	0,4	0,1	0,1	0,2
75	FMF26-300	0,4	0,5	1,3	18,5	18,5	15,3	10,1	1,9	0,8	0,1	0,1	0,2
76	FMF29-0	0,3	0,2	3,3	13,8	11,2	5,1	7,7	0,7	0,2	0,0	0,1	0,2
77	FMF29-20	0,2	0,5	0,4	12,2	20,0	13,2	5,2	0,7	0,2	0,0	0,1	0,1
78	FMF29-60	0,1	0,3	0,6	7,7	9,7	7,2	4,4	0,6	0,2	0,0	0,1	0,1
79	FMF29-120	0,3	0,7	1,5	11,4	15,7	11,9	6,7	1,0	0,5	0,1	0,1	0,2
80	FMF29-300	0,3	0,4	1,3	11,2	17,1	10,0	7,1	1,0	0,5	0,1	0,1	0,2

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		FA (ug/mg)											
NO	ID	myristate	alpha-linolenate	cis-vaccenate	palmitate	oleate	linoleate	stearate	arachidonate	gondate	erucate	docosanoate	nervonate
81	FMF31-0	0,4	0,3	4,0	8,2	8,0	5,3	5,8	0,7	0,4	0,1	0,1	0,2
82	FMF31-28	0,3	0,4	3,2	12,7	18,2	9,8	7,7	0,7	0,4	0,1	0,1	0,2
83	FMF31-60	0,2	0,4	1,0	8,2	10,4	8,8	5,1	0,8	0,3	0,1	0,1	0,1
84	FMF31-120	0,1	0,3	0,9	6,5	8,2	6,9	3,8	0,7	0,3	0,0	0,1	0,1
85	FMF31-300	0,2	0,4	0,8	5,3	6,3	5,7	3,3	0,8	0,2	0,0	0,1	0,1
86	FMF32-0	0,3	0,3	1,9	10,7	10,3	6,5	6,5	1,0	0,5	0,1	0,1	0,2
87	FMF32-20	0,3	0,5	0,7	11,2	18,0	11,1	6,3	1,2	0,5	0,1	0,1	0,2
88	FMF32-60	0,4	0,5	1,2	9,8	16,8	10,1	5,7	1,5	0,7	0,1	0,2	0,3
89	FMF32-120	0,2	0,5	1,5	17,7	17,7	17,7	8,9	0,7	0,3	0,1	0,1	0,1
90	FMF32-300	0,2	0,5	1,8	19,1	19,1	10,6	9,5	0,6	0,2	0,0	0,1	0,2
91	FMF33-0	0,6	0,1	1,7	17,0	17,0	3,4	10,3	0,5	0,2	0,0	0,2	0,2
92	FMF33-28	0,2	0,4	0,6	13,2	18,7	13,1	6,7	1,0	0,3	0,1	0,1	0,2
93	FMF33-60	0,2	0,5	0,9	15,9	15,9	15,9	9,9	1,6	0,5	0,1	0,1	0,2
94	FMF33-120	0,3	0,4	1,3	8,6	13,0	8,5	5,3	1,3	0,4	0,1	0,1	0,2
95	FMF33-300	0,3	0,3	1,3	7,1	9,7	6,4	4,9	1,1	0,2	0,0	0,1	0,1
96	FMF34-0	0,3	0,2	1,6	11,4	15,9	3,4	8,5	2,0	0,6	0,1	0,2	0,5
97	FMF34-20	0,2	0,2	0,3	6,2	7,2	6,0	4,1	1,7	0,2	0,1	0,1	0,2
98	FMF34-60	0,2	0,2	0,6	6,5	8,7	6,6	3,1	0,9	0,2	0,0	0,1	0,1
99	FMF34-120	0,3	0,4	0,5	6,1	7,9	7,1	3,2	1,0	0,3	0,1	0,1	0,2
100	FMF34-300	0,4	0,3	1,3	5,3	6,9	4,9	3,6	0,5	0,2	0,1	0,1	0,2
101	FMF35-0	0,3	0,3	1,3	7,5	7,2	2,1	4,8	1,1	0,3	0,1	0,1	0,4
102	FMF35-28	0,2	0,3	0,5	6,3	8,4	6,5	3,3	0,9	0,3	0,1	0,1	0,2
103	FMF35-60	0,2	0,2	1,1	4,9	6,1	3,9	2,9	0,6	0,2	0,0	0,1	0,2
104	FMF35-120	0,1	0,1	0,2	2,1	2,8	2,2	1,1	0,3	0,1	0,0	0,0	0,1
105	FMF35-300	0,1	0,1	0,5	2,4	2,8	1,7	1,7	0,3	0,1	0,0	0,0	0,1
106	FMF36-0	0,6	0,3	1,3	16,4	16,4	4,0	13,1	0,8	0,4	0,1	0,2	0,2
107	FMF36-28	0,4	0,3	0,8	6,0	7,9	6,2	3,9	1,0	0,3	0,1	0,1	0,2
108	FMF36-60	0,7	0,3	4,2	11,1	16,7	8,4	10,0	1,4	0,5	0,1	0,3	0,5
109	FMF36-120	0,3	0,5	0,7	7,2	10,7	8,4	3,7	1,0	0,3	0,1	0,1	0,2
110	FMF36-300	0,2	0,2	0,4	4,8	6,7	5,0	2,3	0,5	0,2	0,0	0,1	0,1
111	FMF37-0	0,7	0,2	4,0	16,1	16,1	5,0	16,1	1,9	1,2	0,2	0,3	0,8
112	FMF37-28	0,3	0,3	2,2	7,8	10,5	6,8	4,8	1,1	0,4	0,1	0,2	0,3
113	FMF37-60	0,3	0,3	1,7	10,0	10,9	6,9	5,1	0,9	0,3	0,1	0,1	0,1
114	FMF37-120	0,4	0,4	2,3	8,2	10,4	7,2	5,4	1,1	0,4	0,1	0,2	0,2
115	FMF37-300	0,7	0,5	1,7	16,6	19,3	14,3	7,9	2,3	0,9	0,2	0,2	0,4
116	FMF38-0	0,4	0,1	1,9	10,9	9,4	2,8	7,3	1,3	0,6	0,1	0,2	0,6
117	FMF38-28	0,3	0,6	0,7	6,2	7,7	7,0	3,1	0,9	0,3	0,1	0,1	0,2
118	FMF38-60	1,7	0,9	4,6	18,2	18,2	18,2	18,2	5,0	1,8	0,4	0,5	0,9
119	FMF38-120	0,8	0,5	1,2	9,8	11,4	9,4	7,2	2,7	0,7	0,2	0,4	0,7
120	FMF38-300	0,2	0,4	0,8	6,2	7,5	5,5	3,1	0,8	0,2	0,0	0,2	0,1
121	FMF41-0	0,8	0,3	5,0	19,8	19,8	6,5	19,8	0,9	0,6	0,1	0,3	0,4
122	FMF41-28	0,2	0,2	0,7	6,3	6,9	5,0	2,8	0,5	0,2	0,0	0,1	0,1
123	FMF41-60	0,2	0,1	0,6	5,4	5,8	4,5	2,7	0,4	0,2	0,0	0,1	0,1
124	FMF41-120	0,3	0,3	1,5	12,7	16,5	8,6	5,6	0,8	0,3	0,1	0,2	0,2
125	FMF41-300	0,4	0,4	2,0	13,1	15,1	8,5	7,1	1,1	0,3	0,1	0,3	0,3
126	FMF43-0	0,5	0,1	0,6	15,2	5,9	3,5	10,9	0,7	0,4	0,0	0,2	0,2
127	FMF43-28	0,3	0,3	0,7	9,2	9,9	7,9	3,9	0,6	0,3	0,1	0,1	0,1
128	FMF43-60	0,5	0,6	1,5	18,7	18,7	18,7	9,1	1,2	0,7	0,1	0,2	0,3
129	FMF43-120	1,1	0,5	4,9	19,4	19,4	19,4	19,4	2,2	1,3	0,2	0,3	0,4
130	FMF43-300	0,4	0,2	2,6	16,5	16,5	5,7	16,5	2,2	0,4	0,1	0,3	0,3
131	FMF45-0	0,3	0,2	0,4	9,4	7,7	4,8	5,2	1,0	0,3	0,0	0,2	0,1
132	FMF45-28	0,3	0,3	2,1	11,8	14,5	10,0	5,8	0,9	0,4	0,1	0,2	0,2
133	FMF45-60	0,1	0,2	0,5	6,5	5,6	4,9	3,8	2,0	0,2	0,0	0,1	0,1
134	FMF45-120	0,3	0,3	1,4	9,5	11,5	8,5	4,8	0,8	0,3	0,1	0,1	0,2
135	FMF45-300	0,1	0,7	0,3	2,4	2,6	1,7	1,2	0,1	0,1	0,0	0,0	0,1
136	FMF47-0	0,6	0,2	1,9	15,8	11,2	8,1	7,0	0,9	0,7	0,1	0,3	0,3
137	FMF47-28	0,3	0,4	1,3	9,6	12,1	8,4	4,8	0,7	0,3	0,1	0,2	0,2
138	FMF47-60	0,3	0,3	1,1	7,0	8,9	6,7	3,6	0,9	0,2	0,1	0,1	0,2
139	FMF47-120	0,2	0,2	0,5	5,6	7,0	5,4	2,7	0,6	0,2	0,0	0,1	0,1
140	FMF47-300	0,5	0,4	0,9	8,3	9,6	7,9	4,2	0,9	0,3	0,1	0,2	0,2
141	FMF48-0	0,2	0,1	1,1	7,0	5,6	2,3	3,7	0,4	0,3	0,2	0,1	0,2
142	FMF48-28	0,3	0,3	1,1	7,8	8,7	6,7	4,2	0,9	0,3	0,1	0,2	0,2
143	FMF48-60	0,4	0,3	2,8	13,2	18,7	9,6	7,2	1,0	0,4	0,1	0,2	0,3
144	FMF48-120	0,2	0,2	1,1	5,6	6,3	4,9	3,4	0,7	0,2	0,0	0,1	0,2
145	FMF48-300	0,3	0,3	0,8	7,7	13,1	7,3	3,8	0,8	0,2	0,1	0,1	0,2
146	FMF49-0	1,3	0,3	4,6	18,4	18,4	13,9	18,4	1,8	1,1	0,1	0,4	0,5
147	FMF49-28	0,3	0,3	1,4	8,4	8,2	6,0	5,3	1,3	0,3	0,1	0,2	0,3
148	FMF49-60	0,3	0,2	1,5	7,8	8,7	6,6	4,6	0,9	0,3	0,1	0,2	0,3
149	FMF49-120	0,3	0,4	0,9	8,4	9,8	8,1	3,9	0,8	0,2	0,1	0,2	0,2
150	FMF49-300	0,3	0,2	2,3	7,8	10,7	5,5	4,8	1,2	0,2	0,1	0,2	0,2
151	FMF55-0	0,4	0,3	1,0	9,0	11,4	8,5	4,5	0,8	0,3	0,1	0,2	0,2
152	FMF55-28	0,2	0,2	0,5	4,6	6,2	4,6	2,2	0,5	0,2	0,0	0,1	0,1
153	FMF55-60	0,3	0,2	0,9	5,5	6,8	5,1	3,0	0,5	0,2	0,1	0,1	0,1
154	FMF55-120	0,3	0,3	0,9	7,6	8,6	6,0	4,7	1,1	0,3	0,1	0,2	0,2
155	FMF55-300	0,4	0,4	1,2	10,1	17,9	10,1	5,3	1,3	0,4	0,1	0,2	0,3
156	FMF56-0	0,2	0,1	0,7	4,4	4,0	2,8	2,5	0,6	0,2	0,0	0,1	0,1
157	FMF56-20	0,4	0,4	1,1	11,4	16,3	8,8	5,4	1,1	0,4	0,1	0,1	0,2
158	FMF56-60	0,4	0,4	1,8	9,8	15,4	8,6	5,0	1,1	0,4	0,1	0,2	0,2
159	FMF56-120	0,4	0,3	1,2	9,6	17,0	8,1	6,7	0,8	0,4	0,1	0,2	0,3
160	FMF56-300	0,3	0,3	0,7	6,4	8,0	6,5	3,3	0,8	0,3	0,1	0,1	0,2

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		FA (ug/mg)											
NO	**ID**	**myristate**	**alpha-linolenate**	**cis-vaccenate**	**palmitate**	**oleate**	**linoleate**	**stearate**	**arachidonate**	**gondate**	**erucate**	**docosanoate**	**nervonate**
161	FMF58-0	0,4	0,3	1,7	11,9	18,4	9,0	6,5	1,1	0,6	0,1	0,1	0,2
162	FMF58-20	0,2	0,2	0,6	6,1	7,5	4,9	3,2	0,8	0,2	0,1	0,1	0,1
163	FMF58-60	0,4	0,3	2,0	9,0	9,7	6,0	5,3	0,9	0,4	0,1	0,2	0,3
164	FMF58-120	0,3	0,3	1,0	7,4	9,1	7,1	3,9	1,0	0,3	0,1	0,1	0,2
165	FMF58-300	0,2	0,4	0,7	5,8	7,9	6,4	3,1	0,7	0,3	0,1	0,1	0,2
166	FMF59-0	0,2	0,2	1,0	4,9	5,3	3,1	2,7	0,5	0,2	0,0	0,1	0,1
167	FMF59-28	0,2	0,2	1,0	5,7	6,2	4,1	3,2	0,6	0,2	0,1	0,1	0,1
168	FMF59-60	0,3	0,2	1,2	7,4	7,9	5,3	4,5	0,7	0,3	0,1	0,1	0,1
169	FMF59-120	1,0	0,3	3,4	17,4	17,4	7,9	9,4	1,0	0,4	0,1	0,3	0,3
170	FMF59-300	0,3	0,3	1,0	7,1	9,8	6,8	4,2	1,0	0,2	0,1	0,2	0,2
171	FMF61-0	0,7	0,2	2,7	16,9	17,1	7,3	5,6	0,6	0,3	0,0	0,1	0,1
172	FMF61-28	0,3	0,2	1,8	11,4	20,0	7,9	5,9	1,1	0,4	0,1	0,1	0,1
173	FMF61-60	0,4	0,4	2,0	18,0	18,0	14,8	7,7	1,6	0,6	0,1	0,2	0,3
174	FMF61-120	0,3	0,6	0,8	9,9	14,0	7,5	5,3	1,0	0,3	0,1	0,2	0,2
175	FMF61-300	0,3	0,8	0,7	6,8	8,5	6,7	3,4	0,8	0,2	0,1	0,2	0,1
176	FMF62-0	0,2	0,1	2,4	9,8	6,4	4,6	4,8	0,5	0,3	0,0	0,1	0,1
177	FMF62-28	0,2	0,1	1,0	5,2	5,3	3,2	3,4	0,5	0,2	0,0	0,1	0,1
178	FMF62-60	0,4	0,3	0,9	11,1	17,6	8,6	5,4	1,1	0,5	0,1	0,2	0,3
179	FMF62-120	0,4	0,2	0,9	12,1	17,4	7,7	6,7	1,4	0,4	0,1	0,2	0,3
180	FMF62-300	0,5	0,6	1,8	13,5	20,0	11,4	7,0	1,9	0,5	0,1	0,3	0,3
181	FMF63-0	0,2	0,1	2,3	9,0	11,9	5,1	5,0	0,5	0,3	0,0	0,1	0,1
182	FMF63-28	0,1	0,1	0,7	3,6	3,6	2,2	2,2	0,3	0,1	0,0	0,1	0,1
183	FMF63-60	0,3	0,1	2,0	6,4	6,3	4,0	4,3	0,9	0,2	0,1	0,1	0,2
184	FMF63-120	0,5	0,5	4,2	13,1	16,8	7,3	7,6	1,1	0,4	0,1	0,3	0,4
185	FMF63-300	0,4	0,3	3,1	10,6	13,6	9,2	6,9	1,5	0,4	0,1	0,2	0,3
186	FMF64-0	0,3	0,3	0,6	5,8	6,7	5,4	2,9	0,7	0,2	0,0	0,1	0,2
187	FMF64-28	0,2	0,3	0,9	7,8	9,5	7,5	4,0	0,6	0,3	0,1	0,1	0,2
188	FMF64-60	0,3	0,3	1,1	18,5	18,5	10,4	7,9	1,0	0,5	0,1	0,2	0,2
189	FMF64-120	0,6	0,2	2,0	8,0	7,3	5,1	4,9	0,5	0,3	0,1	0,2	0,2
190	FMF64-300	0,2	0,3	1,0	6,9	8,4	7,0	3,7	0,8	0,2	0,1	0,1	0,2
191	FMF66-0	0,3	0,1	0,7	8,3	4,8	1,4	7,5	0,9	0,2	0,0	0,1	0,2
192	FMF66-28	0,3	0,3	2,6	15,5	15,5	8,6	6,9	0,8	0,3	0,1	0,1	0,1
193	FMF66-60	0,3	0,2	1,0	9,1	11,1	6,1	4,8	0,8	0,3	0,1	0,1	0,1
194	FMF66-120	0,3	0,3	1,0	9,7	16,5	7,9	4,8	0,7	0,3	0,1	0,1	0,1
195	FMF66-300	0,5	0,3	4,6	18,5	18,5	12,6	8,4	1,2	0,6	0,1	0,2	0,3
196	FMF67-0	0,1	0,1	0,2	4,4	3,3	1,5	3,2	0,6	0,1	0,0	0,1	0,2
197	FMF67-20	0,2	0,1	0,2	6,6	7,0	4,2	2,9	0,6	0,2	0,0	0,1	0,1
198	FMF67-60	0,5	0,3	0,7	7,4	10,6	6,2	3,6	1,1	0,2	0,1	0,2	0,1
199	FMF67-120	0,3	0,3	0,8	10,9	16,0	8,5	4,8	0,8	0,3	0,1	0,1	0,1
200	FMF67-300	0,3	0,4	1,5	12,4	17,9	9,1	5,8	0,9	0,3	0,1	0,1	0,2
201	FMF68-0	0,1	0,1	0,2	3,7	2,7	1,1	2,4	0,6	0,1	0,0	0,1	0,1
202	FMF68-20	0,3	0,3	1,1	9,2	16,4	7,9	4,5	0,9	0,3	0,1	0,1	0,2
203	FMF68-60	0,3	0,3	1,2	7,8	9,3	6,0	4,6	0,8	0,3	0,1	0,2	0,2
204	FMF68-120	0,5	0,2	2,1	17,6	17,6	9,6	9,5	1,3	0,5	0,1	0,2	0,3
205	FMF68-300	0,3	0,3	0,9	10,1	16,0	10,6	4,8	1,1	0,4	0,1	0,1	0,1
206	FMF70-0	0,3	0,5	0,6	8,2	9,6	7,3	3,7	0,9	0,3	0,1	0,1	0,1
207	FMF70-20	0,1	0,1	0,7	6,4	2,7	0,9	4,6	0,6	0,1	0,0	0,2	0,3
208	FMF70-60	0,2	0,2	0,5	4,7	5,4	4,0	2,4	0,4	0,1	0,0	0,1	0,1
209	FMF70-120	0,1	0,1	0,2	3,2	4,1	3,0	1,5	0,5	0,1	0,0	0,1	0,1
210	FMF70-300	0,2	0,2	0,9	4,7	5,7	4,4	2,7	0,8	0,2	0,0	0,1	0,1
211	FMF71-0	0,6	0,1	4,4	17,7	9,7	2,6	17,7	2,2	0,7	0,1	0,8	1,2
212	FMF71-28	0,2	0,3	0,8	5,7	6,8	4,9	2,7	0,7	0,2	0,0	0,1	0,1
213	FMF71-60	0,3	0,4	1,3	7,6	8,2	5,7	4,0	0,7	0,3	0,1	0,2	0,2
214	FMF71-120	0,3	0,3	0,8	8,8	10,1	7,2	4,3	0,7	0,3	0,1	0,1	0,2
215	FMF71-300	0,3	0,3	1,1	8,6	8,9	6,5	4,7	1,0	0,4	0,1	0,1	0,2
216	FMF74-0	0,8	0,1	4,5	18,0	18,0	5,1	18,0	1,3	0,8	0,1	0,6	0,8
217	FMF74-20	0,3	0,2	1,6	8,3	7,6	4,6	4,9	0,8	0,4	0,1	0,1	0,2
218	FMF74-60	0,2	0,1	0,5	5,5	4,6	3,4	2,9	0,7	0,2	0,0	0,1	0,1
219	FMF74-120	0,4	0,2	1,2	8,2	9,2	6,3	4,7	0,6	0,3	0,1	0,2	0,2
220	FMF74-300	0,3	0,3	1,3	8,4	8,9	7,2	4,7	1,3	0,3	0,1	0,2	0,2
221	FMF75-0	1,2	0,1	1,6	18,7	18,7	9,2	18,7	1,5	1,1	0,1	0,6	0,6
222	FMF75-28	0,3	0,3	0,9	8,5	10,1	7,3	3,9	0,7	0,3	0,1	0,1	0,1
223	FMF75-60	0,3	0,1	1,5	6,3	4,7	3,4	4,6	0,8	0,2	0,1	0,2	0,2
224	FMF75-120	0,7	0,3	2,1	10,9	18,9	13,2	10,0	2,3	0,8	0,2	0,3	0,5
225	FMF75-300	0,3	0,4	1,3	9,2	11,8	9,4	5,1	1,6	0,4	0,1	0,2	0,3

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		Sterols (ug/mg)									
NO	**ID**	**coprostanol**	**cholesterol**	**cholestanol**	**brassicasterol**	**lathosterol**	**campesterol**	**stigmasterol**	**fusosterol**	**beta-sitosterol**	**sitostanol**
1	FMF4-0	0,1	1,2	0,4	0,0	0,0	0,2	0,1	0,0	0,7	0,4
2	FMF4-28	0,0	0,6	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
3	FMF4-60	0,1	0,4	0,1	0,0	0,0	0,2	0,1	0,0	0,7	0,4
4	FMF4-120	3,7	0,6	0,2	0,1	0,0	0,2	0,1	0,0	0,5	0,8
5	FMF4-300	0,1	0,7	0,1	0,0	0,0	0,4	0,2	0,0	1,0	0,8
6	FMF6-0	0,0	1,3	0,3	0,0	0,0	0,2	0,1	0,0	0,6	0,3
7	FMF6-28	0,1	0,9	0,1	0,0	0,0	0,4	0,3	0,1	1,3	0,9
8	FMF6-60	0,0	3,2	0,2	0,1	0,0	0,6	0,3	0,1	1,4	0,9
9	FMF6-120	0,0	1,6	0,2	0,1	0,0	0,6	0,3	0,1	1,6	1,1
10	FMF6-300	0,1	1,0	0,1	0,1	0,0	0,6	0,3	0,1	1,7	1,1
11	FMF7-0	4,0	1,0	0,2	0,1	0,0	0,3	0,2	0,0	0,7	1,0
12	FMF7-20	0,0	0,7	0,1	0,0	0,0	0,3	0,2	0,1	0,9	0,6
13	FMF7-60	1,3	0,6	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,6
14	FMF7-120	3,9	1,2	0,2	0,1	0,0	0,3	0,1	0,0	0,6	0,9
15	FMF7-300	0,1	0,3	0,0	0,0	0,0	0,1	0,1	0,0	0,4	0,3
16	FMF8-0	0,0	1,0	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,4
17	FMF8-28	0,0	0,9	0,1	0,0	0,0	0,3	0,2	0,1	1,0	0,7
18	FMF8-60	0,4	1,4	0,1	0,1	0,0	0,5	0,3	0,1	1,5	1,0
19	FMF8-120	0,3	0,8	0,1	0,0	0,0	0,3	0,2	0,1	0,9	0,7
20	FMF8-300	0,0	1,3	0,2	0,0	0,0	0,3	0,1	0,0	0,6	0,3
21	FMF9-0	0,0	1,7	0,2	0,1	0,0	0,5	0,3	0,1	1,2	0,9
22	FMF9-28	1,7	0,5	0,2	0,0	0,0	0,2	0,2	0,0	0,6	1,1
23	FMF9-60	0,0	2,5	0,2	0,0	0,0	0,4	0,3	0,1	1,2	0,8
24	FMF9-120	1,5	0,8	0,2	0,1	0,0	0,4	0,2	0,0	0,9	1,0
25	FMF9-300	0,5	1,8	0,2	0,0	0,0	0,4	0,1	0,0	0,8	0,6
26	FMF13-0	0,0	2,3	0,4	0,1	0,1	0,1	0,1	0,0	0,2	0,0
27	FMF13-20	0,0	0,8	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,5
28	FMF13-60	0,0	0,8	0,1	0,1	0,0	0,4	0,2	0,1	1,1	0,8
29	FMF13-120	1,7	3,6	0,2	0,0	0,0	0,5	0,2	0,1	1,0	0,6
30	FMF13-300	0,5	1,5	0,2	0,1	0,0	0,4	0,2	0,1	1,0	0,8
31	FMF14-0	1,2	3,9	0,1	0,0	0,0	0,3	0,1	0,0	0,6	0,3
32	FMF14-28	1,1	1,1	0,2	0,1	0,0	0,5	0,3	0,1	1,4	1,1
33	FMF14-60	0,0	0,6	0,1	0,0	0,0	0,3	0,1	0,0	0,7	0,5
34	FMF14-120	0,1	2,0	0,1	0,1	0,0	0,5	0,2	0,1	1,1	0,7
35	FMF14-300	1,6	1,0	0,2	0,0	0,0	0,4	0,2	0,1	0,9	1,2
36	FMF15-0	0,0	1,4	0,2	0,1	0,0	0,4	0,3	0,1	1,2	0,8
37	FMF15-28	0,2	0,9	0,2	0,0	0,0	0,4	0,3	0,1	1,1	0,8
38	FMF15-60	0,4	0,8	0,1	0,1	0,0	0,4	0,2	0,1	1,1	0,9
39	FMF15-120	0,6	1,9	0,2	0,1	0,0	0,7	0,3	0,1	1,7	1,2
40	FMF15-300	1,6	1,2	0,2	0,0	0,0	0,5	0,3	0,1	1,3	1,1
41	FMF16-0	3,2	5,4	0,5	0,0	0,0	0,3	0,1	0,0	0,4	0,2
42	FMF16-28	0,1	0,7	0,1	0,1	0,0	0,3	0,2	0,1	0,9	0,6
43	FMF16-60	0,1	1,0	0,1	0,0	0,0	0,4	0,2	0,1	0,9	0,6
44	FMF16-120	0,5	1,2	0,2	0,1	0,0	0,5	0,3	0,1	1,5	1,3
45	FMF16-300	0,1	2,0	0,2	0,1	0,0	0,3	0,2	0,1	0,8	0,6
46	FMF18-0	3,2	0,5	0,1	0,0	0,0	0,1	0,1	0,0	0,2	0,1
47	FMF18-20	0,0	0,9	0,1	0,1	0,0	0,3	0,2	0,1	1,2	0,8
48	FMF18-60	0,0	0,8	0,1	0,0	0,0	0,2	0,2	0,1	0,9	0,6
49	FMF18-120	0,5	1,1	0,1	0,1	0,0	0,4	0,3	0,1	1,1	1,1
50	FMF18-300	3,3	3,4	0,2	0,0	0,0	0,5	0,2	0,1	1,0	0,9
51	FMF20-0	0,1	1,4	0,1	0,1	0,0	0,3	0,3	0,1	1,1	0,7
52	FMF20-20	3,8	2,5	0,3	0,1	0,0	0,2	0,1	0,0	0,5	0,5
53	FMF20-60	1,1	1,1	0,1	0,0	0,0	0,3	0,3	0,1	1,3	1,0
54	FMF20-120	0,2	5,4	0,3	0,1	0,0	0,7	0,3	0,2	1,8	1,2
55	FMF20-300	2,1	5,6	0,2	0,0	0,0	0,6	0,2	0,1	1,2	0,8
56	FMF22-0	0,2	4,1	0,2	0,0	0,0	0,2	0,1	0,0	0,3	0,1
57	FMF22-20	0,1	2,4	0,2	0,1	0,0	0,5	0,4	0,2	1,8	1,3
58	FMF22-60	1,5	0,7	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,8
59	FMF22-120	0,1	1,5	0,2	0,0	0,0	0,5	0,4	0,2	2,0	1,0
60	FMF22-300	0,3	2,2	0,1	0,1	0,0	0,3	0,2	0,1	0,9	0,5
61	FMF23-0	1,5	2,1	0,1	0,0	0,0	0,2	0,2	0,1	0,8	0,6
62	FMF23-28	2,8	0,9	0,1	0,0	0,0	0,1	0,1	0,0	0,4	0,5
63	FMF23-60	1,5	1,7	0,1	0,1	0,0	0,3	0,2	0,1	1,2	1,0
64	FMF23-120	0,2	0,5	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
65	FMF23-300	0,4	1,0	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,5
66	FMF24-0	0,9	2,0	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,2
67	FMF24-20	0,0	0,5	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
68	FMF24-60	1,1	0,9	0,1	0,1	0,0	0,2	0,2	0,1	0,8	0,8
69	FMF24-120	0,0	1,0	0,1	0,0	0,0	0,2	0,1	0,0	0,7	0,5
70	FMF24-300	0,1	0,6	0,1	0,0	0,0	0,2	0,2	0,0	0,8	0,6
71	FMF26-0	0,0	1,6	0,1	0,0	0,0	0,1	0,0	0,0	0,2	0,0
72	FMF26-28	0,2	3,3	0,1	0,0	0,0	0,3	0,1	0,1	0,8	0,5
73	FMF26-60	0,5	0,8	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,5
74	FMF26-120	0,0	2,5	0,1	0,0	0,0	0,4	0,2	0,1	1,4	0,9
75	FMF26-300	1,9	1,0	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,4
76	FMF29-0	1,1	2,0	0,1	0,1	0,0	0,1	0,1	0,0	0,4	0,1
77	FMF29-20	0,1	1,1	0,1	0,1	0,0	0,3	0,2	0,1	1,2	0,9
78	FMF29-60	0,2	0,9	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,5
79	FMF29-120	0,0	1,3	0,1	0,0	0,0	0,2	0,2	0,1	0,8	0,7
80	FMF29-300	0,2	1,6	0,1	0,0	0,0	0,4	0,2	0,1	1,3	1,0

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		Sterols (ug/mg)									
NO	**ID**	**coprostanol**	**cholesterol**	**cholestanol**	**brassicasterol**	**lathosterol**	**campesterol**	**stigmasterol**	**fusosterol**	**beta-sitosterol**	**sitostanol**
81	FMF31-0	0,0	3,2	0,1	0,0	0,0	0,3	0,2	0,1	0,8	0,6
82	FMF31-28	0,1	3,3	0,1	0,0	0,0	0,4	0,2	0,1	1,0	0,7
83	FMF31-60	0,0	1,6	0,1	0,0	0,0	0,3	0,2	0,1	0,9	0,6
84	FMF31-120	0,0	0,9	0,1	0,0	0,0	0,2	0,1	0,1	0,7	0,5
85	FMF31-300	0,0	1,6	0,2	0,0	0,0	0,4	0,3	0,1	1,4	1,0
86	FMF32-0	0,0	1,7	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
87	FMF32-20	0,1	1,5	0,1	0,0	0,0	0,2	0,2	0,0	0,7	0,6
88	FMF32-60	0,0	2,5	0,1	0,0	0,0	0,4	0,2	0,1	1,2	0,8
89	FMF32-120	0,4	1,7	0,1	0,0	0,0	0,3	0,2	0,1	1,1	0,9
90	FMF32-300	2,8	1,3	0,3	0,1	0,0	0,3	0,2	0,1	1,0	1,4
91	FMF33-0	0,5	4,0	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,0
92	FMF33-28	0,1	1,4	0,1	0,1	0,0	0,3	0,2	0,1	1,1	0,7
93	FMF33-60	0,0	2,4	0,1	0,0	0,0	0,4	0,2	0,1	1,1	0,8
94	FMF33-120	0,0	1,7	0,1	0,0	0,0	0,4	0,2	0,1	1,0	0,5
95	FMF33-300	0,0	1,6	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,2
96	FMF34-0	0,1	4,2	0,1	0,0	0,0	0,1	0,0	0,0	0,2	0,0
97	FMF34-20	0,1	2,7	0,2	0,1	0,0	0,7	0,3	0,2	2,0	0,9
98	FMF34-60	0,0	1,1	0,1	0,1	0,0	0,3	0,2	0,1	1,1	0,8
99	FMF34-120	0,0	1,5	0,1	0,1	0,0	0,5	0,4	0,1	1,6	1,1
100	FMF34-300	0,0	2,3	0,1	0,1	0,0	0,3	0,1	0,0	0,5	0,3
101	FMF35-0	0,5	2,2	0,1	0,0	0,0	0,1	0,1	0,0	0,4	0,1
102	FMF35-28	0,1	1,2	0,1	0,1	0,0	0,5	0,3	0,1	1,4	1,0
103	FMF35-60	0,0	1,3	0,1	0,1	0,0	0,4	0,2	0,1	1,1	0,8
104	FMF35-120	0,0	0,4	0,0	0,0	0,0	0,1	0,1	0,0	0,4	0,2
105	FMF35-300	0,0	0,9	0,0	0,0	0,0	0,1	0,1	0,0	0,3	0,1
106	FMF36-0	0,8	1,4	0,4	0,0	0,0	0,2	0,2	0,1	0,9	0,4
107	FMF36-28	0,5	2,2	0,2	0,1	0,0	0,5	0,2	0,1	1,2	0,8
108	FMF36-60	3,4	3,1	0,3	0,1	0,0	0,6	0,2	0,1	1,0	1,1
109	FMF36-120	0,2	1,4	0,2	0,1	0,0	0,7	0,4	0,1	1,9	1,3
110	FMF36-300	0,1	0,5	0,1	0,1	0,0	0,3	0,2	0,0	0,8	0,5
111	FMF37-0	0,0	7,5	0,2	0,0	0,0	0,3	0,1	0,0	0,4	0,1
112	FMF37-28	1,0	1,8	0,2	0,1	0,0	0,6	0,5	0,2	2,2	1,7
113	FMF37-60	0,7	1,2	0,1	0,0	0,0	0,3	0,1	0,0	0,8	0,6
114	FMF37-120	2,6	0,9	0,2	0,1	0,0	0,3	0,2	0,0	0,7	0,9
115	FMF37-300	0,3	2,2	0,1	0,1	0,0	0,5	0,3	0,1	1,3	1,0
116	FMF38-0	0,0	3,6	0,1	0,0	0,0	0,2	0,0	0,0	0,3	0,0
117	FMF38-28	0,2	1,2	0,1	0,1	0,0	0,5	0,3	0,1	1,4	1,1
118	FMF38-60	3,7	3,1	0,2	0,0	0,0	0,5	0,2	0,1	0,8	0,7
119	FMF38-120	3,7	2,0	0,3	0,1	0,0	0,4	0,3	0,1	1,0	1,4
120	FMF38-300	0,4	1,4	0,2	0,1	0,0	0,6	0,2	0,1	1,6	1,1
121	FMF41-0	2,6	2,1	0,2	0,1	0,0	0,4	0,2	0,1	0,9	1,0
122	FMF41-28	0,1	1,0	0,1	0,0	0,0	0,4	0,1	0,1	0,9	0,6
123	FMF41-60	0,7	0,7	0,1	0,0	0,0	0,2	0,1	0,0	0,7	0,6
124	FMF41-120	1,0	1,4	0,2	0,0	0,0	0,5	0,2	0,1	1,4	1,0
125	FMF41-300	3,7	2,1	0,3	0,1	0,0	0,8	0,3	0,1	1,9	1,7
126	FMF43-0	0,0	1,6	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,5
127	FMF43-28	0,4	1,3	0,2	0,1	0,0	0,5	0,2	0,1	1,5	1,0
128	FMF43-60	0,1	2,0	0,2	0,0	0,0	0,5	0,2	0,1	1,3	0,9
129	FMF43-120	0,1	3,7	0,2	0,0	0,0	0,6	0,2	0,1	1,0	0,7
130	FMF43-300	1,9	2,4	0,2	0,0	0,0	0,3	0,2	0,1	1,0	0,8
131	FMF45-0	0,0	1,3	0,1	0,0	0,0	0,3	0,1	0,0	0,8	0,3
132	FMF45-28	0,3	2,1	0,2	0,1	0,0	0,8	0,3	0,1	2,1	1,2
133	FMF45-60	0,0	0,5	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,3
134	FMF45-120	0,0	1,3	0,1	0,0	0,0	0,4	0,2	0,1	1,1	0,7
135	FMF45-300	0,0	0,2	0,0	0,0	0,0	0,1	0,0	0,0	0,2	0,1
136	FMF47-0	0,0	2,7	0,1	0,1	0,0	0,7	0,3	0,1	1,7	0,8
137	FMF47-28	0,0	1,8	0,2	0,1	0,0	0,6	0,2	0,1	1,5	1,0
138	FMF47-60	0,0	1,4	0,1	0,0	0,0	0,5	0,2	0,1	1,5	1,0
139	FMF47-120	0,1	0,9	0,1	0,0	0,0	0,4	0,2	0,1	0,9	0,7
140	FMF47-300	0,1	2,2	0,1	0,0	0,0	0,7	0,3	0,1	1,8	1,3
141	FMF48-0	0,0	1,2	0,0	0,0	0,0	0,2	0,1	0,0	0,4	0,1
142	FMF48-28	0,0	1,4	0,1	0,0	0,0	0,5	0,2	0,1	1,4	0,9
143	FMF48-60	0,2	3,1	0,2	0,1	0,0	0,8	0,3	0,1	1,8	1,1
144	FMF48-120	0,9	0,8	0,1	0,0	0,0	0,3	0,1	0,0	0,7	0,7
145	FMF48-300	1,0	0,9	0,1	0,0	0,0	0,3	0,2	0,1	1,0	1,0
146	FMF49-0	3,7	1,4	0,2	0,0	0,0	0,3	0,1	0,0	0,7	0,8
147	FMF49-28	0,3	2,5	0,2	0,1	0,0	0,5	0,2	0,1	1,3	0,8
148	FMF49-60	0,3	2,1	0,2	0,0	0,0	0,6	0,3	0,1	1,7	1,1
149	FMF49-120	0,6	1,0	0,2	0,1	0,0	0,4	0,3	0,1	1,1	1,1
150	FMF49-300	3,2	1,3	0,1	0,1	0,0	0,3	0,2	0,1	0,9	0,6
151	FMF55-0	1,5	1,4	0,2	0,1	0,0	0,5	0,2	0,1	1,2	0,9
152	FMF55-28	0,0	0,5	0,1	0,0	0,0	0,1	0,1	0,0	0,4	0,2
153	FMF55-60	1,3	0,8	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,7
154	FMF55-120	1,4	1,3	0,1	0,1	0,0	0,4	0,2	0,1	0,9	0,9
155	FMF55-300	0,2	1,8	0,2	0,0	0,0	0,6	0,3	0,1	1,5	1,3
156	FMF56-0	0,5	0,7	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,4
157	FMF56-20	0,0	1,1	0,1	0,0	0,0	0,2	0,2	0,0	0,6	0,5
158	FMF56-60	0,3	1,3	0,1	0,0	0,0	0,4	0,2	0,1	1,4	1,0
159	FMF56-120	2,7	1,1	0,1	0,1	0,0	0,3	0,2	0,0	0,8	0,9
160	FMF56-300	0,6	1,1	0,2	0,1	0,0	0,5	0,3	0,1	1,5	1,2

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		Sterols (ug/mg)									
NO	**ID**	**coprostanol**	**cholesterol**	**cholestanol**	**brassicasterol**	**lathosterol**	**campesterol**	**stigmasterol**	**fusosterol**	**beta-sitosterol**	**sitostanol**
161	FMF58-0	0,6	1,0	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,3
162	FMF58-20	0,0	0,8	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,3
163	FMF58-60	3,5	0,8	0,2	0,0	0,0	0,3	0,2	0,0	0,7	1,0
164	FMF58-120	0,5	1,1	0,1	0,1	0,0	0,5	0,2	0,1	1,2	1,0
165	FMF58-300	0,7	0,7	0,1	0,0	0,0	0,3	0,1	0,0	0,7	0,6
166	FMF59-0	0,0	0,8	0,1	0,0	0,0	0,1	0,1	0,0	0,4	0,2
167	FMF59-28	0,2	0,7	0,1	0,0	0,0	0,1	0,1	0,0	0,4	0,2
168	FMF59-60	1,8	0,7	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,3
169	FMF59-120	2,6	1,3	0,2	0,0	0,0	0,2	0,1	0,0	0,5	0,5
170	FMF59-300	0,2	1,6	0,2	0,0	0,0	0,6	0,2	0,1	1,4	0,9
171	FMF61-0	0,0	1,2	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,1
172	FMF61-28	0,1	1,1	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,1
173	FMF61-60	0,7	2,0	0,1	0,0	0,0	0,5	0,2	0,1	1,2	0,8
174	FMF61-120	0,5	1,2	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,5
175	FMF61-300	0,3	0,8	0,1	0,0	0,0	0,4	0,2	0,1	1,0	0,9
176	FMF62-0	0,2	1,6	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,1
177	FMF62-28	1,4	0,5	0,1	0,0	0,0	0,1	0,1	0,0	0,2	0,2
178	FMF62-60	1,3	1,3	0,1	0,0	0,0	0,4	0,2	0,1	1,1	0,9
179	FMF62-120	0,9	1,9	0,1	0,0	0,0	0,4	0,2	0,0	0,8	0,7
180	FMF62-300	0,6	2,3	0,2	0,0	0,0	0,7	0,3	0,1	1,4	1,1
181	FMF63-0	0,0	1,3	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,1
182	FMF63-28	0,5	0,5	0,1	0,0	0,0	0,1	0,1	0,0	0,2	0,1
183	FMF63-60	2,0	0,7	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,2
184	FMF63-120	3,4	1,7	0,2	0,1	0,0	0,5	0,2	0,1	1,0	1,2
185	FMF63-300	1,2	2,3	0,2	0,1	0,0	0,7	0,3	0,1	1,6	1,1
186	FMF64-0	0,0	1,2	0,2	0,0	0,0	0,4	0,2	0,1	0,8	0,6
187	FMF64-28	0,0	1,1	0,1	0,1	0,0	0,2	0,2	0,0	0,6	0,4
188	FMF64-60	0,0	1,4	0,1	0,0	0,0	0,3	0,1	0,0	0,6	0,4
189	FMF64-120	0,0	3,3	0,2	0,0	0,0	0,5	0,2	0,1	1,1	0,7
190	FMF64-300	0,0	1,4	0,1	0,1	0,0	0,5	0,3	0,1	1,7	1,2
191	FMF66-0	0,0	2,6	0,1	0,0	0,0	0,1	0,0	0,0	0,2	0,0
192	FMF66-28	0,0	1,4	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
193	FMF66-60	0,0	0,9	0,1	0,0	0,0	0,2	0,1	0,0	0,6	0,4
194	FMF66-120	0,1	1,1	0,1	0,0	0,0	0,3	0,1	0,0	0,6	0,4
195	FMF66-300	2,5	1,4	0,2	0,1	0,0	0,5	0,2	0,1	1,3	1,2
196	FMF67-0	0,0	1,5	0,0	0,0	0,0	0,1	0,0	0,0	0,2	0,0
197	FMF67-20	0,0	0,6	0,1	0,0	0,0	0,2	0,1	0,0	0,7	0,4
198	FMF67-60	0,0	1,4	0,3	0,1	0,0	0,7	0,3	0,4	2,0	1,1
199	FMF67-120	0,3	0,8	0,1	0,0	0,0	0,3	0,2	0,0	0,8	0,7
200	FMF67-300	0,0	1,4	0,1	0,0	0,0	0,5	0,2	0,1	1,6	1,0
201	FMF68-0	0,0	1,3	0,0	0,0	0,0	0,1	0,0	0,0	0,2	0,0
202	FMF68-20	0,1	1,3	0,1	0,0	0,0	0,5	0,3	0,1	1,6	1,1
203	FMF68-60	0,1	1,6	0,1	0,0	0,0	0,4	0,2	0,1	1,3	0,9
204	FMF68-120	3,2	2,2	0,2	0,0	0,0	0,3	0,1	0,0	0,6	0,5
205	FMF68-300	0,0	1,1	0,1	0,0	0,0	0,4	0,2	0,1	1,2	0,8
206	FMF70-0	0,0	1,1	0,1	0,1	0,0	0,5	0,2	0,1	1,4	0,9
207	FMF70-20	0,6	3,8	0,1	0,0	0,0	0,1	0,1	0,0	0,3	0,0
208	FMF70-60	0,0	1,1	0,1	0,0	0,0	0,4	0,2	0,1	1,0	0,6
209	FMF70-120	0,0	0,7	0,1	0,0	0,0	0,3	0,1	0,0	0,8	0,5
210	FMF70-300	0,0	1,1	0,1	0,0	0,0	0,4	0,2	0,1	1,1	0,7
211	FMF71-0	0,9	8,1	0,2	0,1	0,0	0,2	0,1	0,0	0,3	0,0
212	FMF71-28	0,0	1,0	0,1	0,0	0,0	0,4	0,2	0,1	1,0	0,7
213	FMF71-60	0,1	1,6	0,1	0,0	0,0	0,5	0,2	0,1	1,2	0,9
214	FMF71-120	0,4	0,9	0,1	0,1	0,0	0,3	0,2	0,0	0,8	0,7
215	FMF71-300	0,2	1,1	0,1	0,0	0,0	0,3	0,1	0,0	0,8	0,6
216	FMF74-0	2,7	4,4	0,2	0,0	0,0	0,2	0,1	0,0	0,4	0,1
217	FMF74-20	0,4	1,1	0,1	0,0	0,0	0,2	0,1	0,0	0,4	0,3
218	FMF74-60	0,1	0,9	0,1	0,0	0,0	0,3	0,1	0,0	0,7	0,4
219	FMF74-120	1,3	1,3	0,1	0,0	0,0	0,3	0,1	0,0	0,6	0,6
220	FMF74-300	1,2	1,1	0,1	0,0	0,0	0,5	0,3	0,1	1,5	1,3
221	FMF75-0	0,0	3,3	0,1	0,1	0,0	0,1	0,1	0,0	0,2	0,0
222	FMF75-28	0,0	0,7	0,1	0,0	0,0	0,2	0,1	0,0	0,5	0,3
223	FMF75-60	0,0	2,5	0,1	0,0	0,0	0,4	0,1	0,1	0,8	0,5
224	FMF75-120	1,7	3,7	0,2	0,1	0,0	0,7	0,3	0,1	1,6	1,1
225	FMF75-300	0,0	2,0	0,1	0,0	0,0	0,6	0,3	0,1	1,7	1,3

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		BA											
NO	**ID**	**Total Primary Bile Acids (ng/mg)**	**Total Secondary Bile Acids (ng/mg)**	**Total Bile Acids (ng/mg)**	**Secondary BA (% Total)**	**Primary BA (% Total)**	**Cholic Acid (% Total)**	**Chenodeoxycholic Acid (% Total)**	**Lithocholic Acid (% Total)**	**Deoxycholic Acid (% Total)**	**Ursodeoxycholic Acid (% Total)**	**2° to 1° % of Total (Ratio)**	**1° to 2° % of Total (Ratio)**
1	FMF4-0	71,7	1538,1	1609,8	95,5	4,5	1,1	3,3	17,1	78,3	0,1	21,5	0,0
2	FMF4-28	108,6	2098,9	2207,5	95,1	4,9	2,4	2,6	8,8	86,3	0,1	19,3	0,1
3	FMF4-60	742,9	519,3	1262,1	41,1	58,9	47,4	11,5	0,1	40,9	0,1	0,7	1,4
4	FMF4-120	371,2	2857,2	3228,4	88,5	11,5	7,8	3,7	12,0	76,0	0,5	7,7	0,1
5	FMF4-300	937,1	2258,5	3195,6	70,7	29,3	24,7	4,6	6,9	63,7	0,0	2,4	0,4
6	FMF6-0	95,1	976,8	1071,9	91,1	8,9	4,3	4,5	7,3	83,7	0,1	10,3	0,1
7	FMF6-28	2378,5	3609,2	5987,7	60,3	39,7	33,0	6,7	7,7	52,5	0,0	1,5	0,7
8	FMF6-60	1100,7	3608,1	4708,8	76,6	23,4	18,4	5,0	11,8	64,2	0,6	3,3	0,3
9	FMF6-120	3141,3	3576,4	6717,7	53,2	46,8	39,8	7,0	6,0	44,7	2,6	1,1	0,9
10	FMF6-300	428,3	5298,9	5727,3	92,5	7,5	4,3	3,2	13,6	78,9	0,0	12,4	0,1
11	FMF7-0	107,6	5910,8	6018,4	98,2	1,8	0,6	1,1	19,2	77,5	1,5	54,9	0,0
12	FMF7-20	424,3	1621,4	2045,7	79,3	20,7	14,2	6,6	9,0	70,2	0,1	3,8	0,3
13	FMF7-60	98,5	2930,9	3029,4	96,7	3,3	1,4	1,9	13,0	83,7	0,0	29,7	0,0
14	FMF7-120	186,1	5124,3	5310,4	96,5	3,5	1,7	1,8	14,4	81,6	0,6	27,5	0,0
15	FMF7-300	823,8	1280,9	2104,7	60,9	39,1	29,5	9,6	3,2	54,4	3,2	1,6	0,6
16	FMF8-0	2897,1	282,7	3179,8	8,9	91,1	79,3	11,8	0,0	8,8	0,0	0,1	10,2
17	FMF8-28	877,3	1412,4	2289,7	61,7	38,3	28,7	9,7	5,4	56,3	0,1	1,6	0,6
18	FMF8-60	1131,0	2435,8	3566,8	68,3	31,7	20,8	10,9	11,0	48,0	9,3	2,2	0,5
19	FMF8-120	91,4	2171,9	2263,3	96,0	4,0	1,7	2,4	18,0	73,2	4,7	23,8	0,0
20	FMF8-300	74,9	3349,6	3424,5	97,8	2,2	0,4	1,8	20,0	71,6	6,2	44,7	0,0
21	FMF9-0	196,2	2272,1	2468,3	92,1	7,9	3,7	4,2	15,3	61,6	15,1	11,6	0,1
22	FMF9-28	119,5	1603,4	1722,9	93,1	6,9	3,1	3,8	24,5	63,3	5,2	13,4	0,1
23	FMF9-60	141,2	6090,0	6231,2	97,7	2,3	0,9	1,3	21,3	73,5	2,9	43,1	0,0
24	FMF9-120	133,6	3559,1	3692,7	96,4	3,6	1,6	2,0	17,3	75,6	3,4	26,6	0,0
25	FMF9-300	470,3	1768,1	2238,4	79,0	21,0	12,6	8,4	4,9	66,5	7,6	3,8	0,3
26	FMF13-0	69,1	1529,5	1598,6	95,7	4,3	1,2	3,1	14,4	81,1	0,1	22,1	0,0
27	FMF13-20	2772,4	99,0	2871,5	3,4	96,6	81,6	14,9	0,0	0,6	2,8	0,0	28,0
28	FMF13-60	4105,1	1826,2	5931,4	30,8	69,2	57,4	11,8	1,3	27,2	2,2	0,4	2,2
29	FMF13-120	1097,3	2764,6	3861,9	71,6	28,4	23,0	5,4	7,1	60,0	4,5	2,5	0,4
30	FMF13-300	384,9	2395,9	2780,8	86,2	13,8	10,0	3,9	6,2	74,0	6,0	6,2	0,2
31	FMF14-0	133,4	4155,1	4288,5	96,9	3,1	1,5	1,6	13,9	81,0	2,0	31,1	0,0
32	FMF14-28	182,2	2844,3	3026,5	94,0	6,0	3,2	2,9	15,3	71,9	6,8	15,6	0,1
33	FMF14-60	370,7	2139,0	2509,8	85,2	14,8	7,1	7,6	11,5	67,6	6,1	5,8	0,2
34	FMF14-120	3138,7	1852,3	4990,9	37,1	62,9	52,9	10,0	0,5	30,7	5,9	0,6	1,7
35	FMF14-300	96,3	1354,7	1451,0	93,4	6,6	3,1	3,5	16,2	73,1	4,0	14,1	0,1
36	FMF15-0	173,5	2148,8	2322,3	92,5	7,5	2,4	5,1	18,3	74,1	0,1	12,4	0,1
37	FMF15-28	678,1	1141,2	1819,3	62,7	37,3	26,5	10,7	5,3	54,8	2,6	1,7	0,6
38	FMF15-60	436,4	3572,5	4008,9	89,1	10,9	7,4	3,5	11,8	75,9	1,4	8,2	0,1
39	FMF15-120	317,0	4446,9	4763,9	93,3	6,7	3,8	2,8	12,1	70,9	10,3	14,0	0,1
40	FMF15-300	155,5	3252,8	3408,3	95,4	4,6	2,3	2,3	14,9	75,6	4,9	20,9	0,0
41	FMF16-0	338,4	2423,2	2761,6	87,7	12,3	7,6	4,6	11,4	75,8	0,5	7,2	0,1
42	FMF16-28	1231,9	1552,3	2784,2	55,8	44,2	34,8	9,4	3,7	52,0	0,1	1,3	0,8
43	FMF16-60	69,3	1418,6	1487,9	95,3	4,7	1,0	3,7	20,0	70,6	4,7	20,5	0,0
44	FMF16-120	207,0	3077,3	3284,3	93,7	6,3	3,4	2,9	20,8	69,7	3,2	14,9	0,1
45	FMF16-300	151,8	4060,2	4212,0	96,4	3,6	1,7	1,9	16,6	76,3	3,5	26,7	0,0
46	FMF18-0	97,0	5902,0	5999,1	98,4	1,6	0,7	0,9	12,0	84,5	1,9	60,8	0,0
47	FMF18-20	1463,3	1346,0	2809,3	47,9	52,1	41,2	10,9	2,4	41,0	4,5	0,9	1,1
48	FMF18-60	124,5	2902,8	3027,3	95,9	4,1	2,4	1,7	11,7	82,5	1,7	23,3	0,0
49	FMF18-120	730,6	4299,7	5030,3	85,5	14,5	12,0	2,6	13,5	69,9	2,0	5,9	0,2
50	FMF18-300	136,1	2780,0	2916,1	95,3	4,7	1,6	3,0	18,0	73,3	4,1	20,4	0,0
51	FMF20-0	800,2	1942,8	2743,0	70,8	29,2	17,6	11,6	7,4	52,7	10,8	2,4	0,4
52	FMF20-20	65,1	2328,2	2393,3	97,3	2,7	0,8	2,0	15,2	77,7	4,4	35,7	0,0
53	FMF20-60	140,6	3505,6	3646,3	96,1	3,9	1,9	2,0	17,6	73,5	5,1	24,9	0,0
54	FMF20-120	426,2	5529,1	5955,3	92,8	7,2	4,3	2,8	6,9	75,6	10,3	13,0	0,1
55	FMF20-300	215,9	3471,5	3687,5	94,1	5,9	3,7	2,2	9,6	76,4	8,2	16,1	0,1
56	FMF22-0	657,9	5382,5	6040,4	89,1	10,9	7,1	3,8	17,6	70,2	1,3	8,2	0,1
57	FMF22-20	459,4	6337,0	6796,4	93,2	6,8	2,9	3,9	17,6	74,5	1,1	13,8	0,1
58	FMF22-60	109,6	3425,4	3535,0	96,9	3,1	1,2	1,9	13,3	82,9	0,8	31,3	0,0
59	FMF22-120	6760,9	2378,2	9139,1	26,0	74,0	62,4	11,6	2,4	21,5	2,1	0,4	2,8
60	FMF22-300	803,8	5903,4	6707,2	88,0	12,0	8,9	3,1	10,4	74,6	3,0	7,3	0,1
61	FMF23-0	773,2	7233,0	8006,1	90,3	9,7	6,7	2,9	12,1	73,1	5,1	9,4	0,1
62	FMF23-28	90,1	5108,3	5198,4	98,3	1,7	0,7	1,1	16,8	78,2	3,3	56,7	0,0
63	FMF23-60	284,1	3554,1	3838,2	92,6	7,4	3,4	4,0	13,9	67,0	11,7	12,5	0,1
64	FMF23-120	74,4	2011,8	2086,2	96,4	3,6	0,7	2,8	18,4	73,5	4,5	27,0	0,0
65	FMF23-300	1304,7	2830,7	4135,5	68,5	31,5	26,0	5,6	5,6	58,4	4,5	2,2	0,5
66	FMF24-0	629,6	2063,2	2692,8	76,6	23,4	15,3	8,0	7,1	67,9	1,5	3,3	0,3
67	FMF24-20	1020,2	128,1	1148,3	11,2	88,8	43,2	45,6	0,1	1,6	9,4	0,1	8,0
68	FMF24-60	170,8	3287,3	3458,1	95,1	4,9	1,9	3,0	17,5	70,4	7,2	19,3	0,1
69	FMF24-120	847,8	2830,7	3678,5	77,0	23,0	16,6	6,4	6,9	59,8	10,2	3,3	0,3
70	FMF24-300	301,6	3931,9	4233,5	92,9	7,1	3,2	3,9	10,6	76,3	6,0	13,0	0,1
71	FMF26-0	67,9	17,3	85,2	20,3	79,7	17,6	62,1	1,3	17,6	1,5	0,3	3,9
72	FMF26-28	725,7	1391,0	2116,7	65,7	34,3	22,1	12,2	5,5	58,8	1,5	1,9	0,5
73	FMF26-60	183,1	2418,7	2601,7	93,0	7,0	2,2	4,8	11,4	73,6	7,9	13,2	0,1
74	FMF26-120	312,6	5328,8	5641,3	94,5	5,5	2,8	2,7	15,4	71,4	7,7	17,0	0,1
75	FMF26-300	94,8	4156,9	4251,7	97,8	2,2	0,4	1,8	17,2	78,6	1,9	43,8	0,0
76	FMF29-0	103,6	1129,5	1233,1	91,6	8,4	1,4	7,0	45,9	42,3	3,3	10,9	0,1
77	FMF29-20	3298,2	446,0	3744,2	11,9	88,1	65,5	22,6	0,0	0,5	11,4	0,1	7,4
78	FMF29-60	1230,8	2658,1	3888,9	68,4	31,6	22,6	9,0	4,7	59,6	4,0	2,2	0,5
79	FMF29-120	609,0	4071,8	4680,8	87,0	13,0	8,9	4,1	7,2	73,3	6,4	6,7	0,1
80	FMF29-300	289,9	2432,6	2722,6	89,4	10,6	4,8	5,9	16,6	62,2	10,5	8,4	0,1

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		BA											
NO	**ID**	**Total Primary Bile Acids (ng/mg)**	**Total Secondary Bile Acids (ng/mg)**	**Total Bile Acids (ng/mg)**	**Secondary BA (% Total)**	**Primary BA (% Total)**	**Cholic Acid (% Total)**	**Chenodeoxycholic Acid (% Total)**	**Lithocholic Acid (% Total)**	**Deoxycholic Acid (% Total)**	**Ursodeoxycholic Acid (% Total)**	**2° to 1° % of Total (Ratio)**	**1° to 2° % of Total (Ratio)**
81	FMF31-0	746,1	3325,8	4072,0	81,7	18,3	7,8	10,5	12,0	56,1	13,5	4,5	0,2
82	FMF31-28	449,8	3487,3	3937,1	88,6	11,4	4,5	6,9	9,7	70,5	8,4	7,8	0,1
83	FMF31-60	1515,9	1887,8	3403,7	55,5	44,5	30,8	13,7	4,2	42,2	9,0	1,2	0,8
84	FMF31-120	624,8	3740,3	4365,1	85,7	14,3	9,2	5,1	8,2	73,2	4,3	6,0	0,2
85	FMF31-300	340,3	2559,7	2900,0	88,3	11,7	3,6	8,1	10,3	75,2	2,7	7,5	0,1
86	FMF32-0	4415,8	3515,8	7931,6	44,3	55,7	42,7	12,9	3,0	30,7	10,7	0,8	1,3
87	FMF32-20	586,8	19,8	606,7	3,3	96,7	69,7	27,0	0,2	2,8	0,2	0,0	29,6
88	FMF32-60	2633,4	3170,8	5804,2	54,6	45,4	35,9	9,4	2,2	39,6	12,9	1,2	0,8
89	FMF32-120	1591,2	2566,9	4158,1	61,7	38,3	26,4	11,9	4,9	47,1	9,8	1,6	0,6
90	FMF32-300	225,7	9245,0	9470,7	97,6	2,4	0,9	1,5	16,5	76,7	4,4	41,0	0,0
91	FMF33-0	106,4	5159,5	5265,9	98,0	2,0	0,6	1,4	18,6	78,2	1,1	48,5	0,0
92	FMF33-28	8987,7	1030,3	10017,9	10,3	89,7	76,1	13,6	0,4	7,3	2,6	0,1	8,7
93	FMF33-60	2628,4	3076,0	5704,4	53,9	46,1	36,2	9,9	4,2	43,2	6,5	1,2	0,9
94	FMF33-120	819,5	2434,6	3254,1	74,8	25,2	15,5	9,7	7,6	63,0	4,2	3,0	0,3
95	FMF33-300	147,4	2459,7	2607,1	94,3	5,7	2,4	3,3	12,5	78,7	3,1	16,7	0,1
96	FMF34-0	31,6	1748,7	1780,3	98,2	1,8	0,8	0,9	11,6	86,5	0,1	55,4	0,0
97	FMF34-20	9847,6	169,1	10016,7	1,7	98,3	86,3	12,0	0,5	0,2	1,0	0,0	58,2
98	FMF34-60	276,9	2420,4	2697,3	89,7	10,3	5,1	5,2	19,1	70,6	0,1	8,7	0,1
99	FMF34-120	2362,4	4048,8	6411,2	63,2	36,8	29,7	7,2	6,1	56,1	0,9	1,7	0,6
100	FMF34-300	327,4	3312,3	3639,7	91,0	9,0	3,5	5,5	15,4	75,1	0,5	10,1	0,1
101	FMF35-0	57,2	6258,3	6315,5	99,1	0,9	0,3	0,6	22,0	75,9	1,3	109,5	0,0
102	FMF35-28	5341,5	110,9	5452,4	2,0	98,0	84,6	13,3	0,4	0,3	1,3	0,0	48,2
103	FMF35-60	288,4	2428,6	2717,0	89,4	10,6	4,4	6,2	15,6	72,4	1,3	8,4	0,1
104	FMF35-120	371,4	307,6	679,0	45,3	54,7	39,5	15,2	0,2	44,9	0,2	0,8	1,2
105	FMF35-300	452,5	2710,3	3162,8	85,7	14,3	12,2	2,1	12,2	73,5	0,0	6,0	0,2
106	FMF36-0	45,2	2799,2	2844,4	98,4	1,6	0,5	1,0	25,5	69,1	3,8	61,9	0,0
107	FMF36-28	1596,8	4304,9	5901,7	72,9	27,1	22,6	4,5	7,9	58,2	6,9	2,7	0,4
108	FMF36-60	162,5	4092,3	4254,8	96,2	3,8	2,5	1,4	15,7	75,4	5,2	25,2	0,0
109	FMF36-120	329,9	3163,6	3493,5	90,6	9,4	6,5	3,0	14,9	68,6	7,1	9,6	0,1
110	FMF36-300	85,7	1911,1	1996,8	95,7	4,3	2,3	2,0	13,0	78,5	4,2	22,3	0,0
111	FMF37-0	73,2	3843,1	3916,3	98,1	1,9	0,4	1,5	16,0	81,3	0,8	52,5	0,0
112	FMF37-28	2345,8	4921,6	7267,4	67,7	32,3	26,9	5,4	7,1	46,9	13,7	2,1	0,5
113	FMF37-60	121,0	1522,1	1643,1	92,6	7,4	3,2	4,1	14,2	72,6	5,8	12,6	0,1
114	FMF37-120	274,3	4036,9	4311,2	93,6	6,4	4,2	2,1	14,0	71,1	8,6	14,7	0,1
115	FMF37-300	4547,7	4811,7	9359,4	51,4	48,6	43,5	5,1	6,6	41,1	3,7	1,1	0,9
116	FMF38-0	65,2	2238,2	2303,4	97,2	2,8	0,7	2,2	6,9	89,1	1,2	34,3	0,0
117	FMF38-28	55,0	3260,8	3315,8	98,3	1,7	0,5	1,1	20,4	75,0	2,9	59,2	0,0
118	FMF38-60	553,3	2677,1	3230,4	82,9	17,1	13,8	3,4	7,4	68,6	6,9	4,8	0,2
119	FMF38-120	87,8	2177,3	2265,1	96,1	3,9	2,6	1,3	18,8	71,9	5,4	24,8	0,0
120	FMF38-300	188,1	6707,1	6895,2	97,3	2,7	1,4	1,3	16,5	78,6	2,1	35,7	0,0
121	FMF41-0	1867,7	486,7	2354,5	20,7	79,3	71,1	8,2	0,1	18,9	1,7	0,3	3,8
122	FMF41-28	819,5	199,2	1018,7	19,6	80,4	61,1	19,4	0,1	1,5	18,0	0,2	4,1
123	FMF41-60	70,9	1874,5	1945,4	96,4	3,6	0,8	2,8	18,5	77,8	0,1	26,4	0,0
124	FMF41-120	163,0	1134,0	1297,0	87,4	12,6	6,8	5,8	25,1	62,2	0,1	7,0	0,1
125	FMF41-300	427,0	4566,1	4993,1	91,4	8,6	4,7	3,9	21,7	69,1	0,6	10,7	0,1
126	FMF43-0	2265,7	21,6	2287,3	0,9	99,1	89,5	9,5	0,1	0,8	0,1	0,0	105,0
127	FMF43-28	3636,0	22,0	3658,0	0,6	99,4	86,3	13,1	0,0	0,5	0,0	0,0	165,3
128	FMF43-60	4052,0	295,7	4347,7	6,8	93,2	83,2	10,0	0,0	0,4	6,4	0,1	13,7
129	FMF43-120	3975,9	2186,8	6162,7	35,5	64,5	57,5	7,0	0,0	35,1	0,4	0,6	1,8
130	FMF43-300	237,2	2964,5	3201,7	92,6	7,4	5,3	2,1	8,3	82,8	1,6	12,5	0,1
131	FMF45-0	1991,6	20,6	2012,1	1,0	99,0	83,8	15,1	0,1	0,9	0,1	0,0	96,9
132	FMF45-28	7318,3	277,0	7595,3	3,6	96,4	86,0	10,3	0,0	0,2	3,4	0,0	26,4
133	FMF45-60	1589,4	18,5	1607,9	1,1	98,9	84,9	13,9	0,1	1,0	0,1	0,0	86,0
134	FMF45-120	1783,8	149,0	1932,9	7,7	92,3	75,6	16,7	0,1	0,9	6,7	0,1	12,0
135	FMF45-300	109,2	31,1	140,3	22,2	77,8	51,0	26,8	0,8	11,4	9,9	0,3	3,5
136	FMF47-0	3165,5	123,8	3289,3	3,8	96,2	70,8	25,5	0,0	0,6	3,2	0,0	25,6
137	FMF47-28	183,5	2144,8	2328,3	92,1	7,9	2,6	5,3	13,7	78,4	0,1	11,7	0,1
138	FMF47-60	156,5	2550,7	2707,3	94,2	5,8	2,6	3,2	19,3	71,2	3,6	16,3	0,1
139	FMF47-120	117,1	1512,9	1630,0	92,8	7,2	3,3	3,9	7,3	82,7	2,8	12,9	0,1
140	FMF47-300	129,1	2793,9	2923,0	95,6	4,4	2,2	2,2	15,4	78,3	1,8	21,6	0,0
141	FMF48-0	1442,2	22,0	1464,2	1,5	98,5	81,0	17,5	0,1	1,3	0,1	0,0	65,6
142	FMF48-28	350,9	3391,2	3742,1	90,6	9,4	3,6	5,8	16,0	74,6	0,0	9,7	0,1
143	FMF48-60	145,6	3813,3	3958,9	96,3	3,7	1,7	2,0	16,1	80,2	0,0	26,2	0,0
144	FMF48-120	99,8	1432,9	1532,7	93,5	6,5	2,4	4,1	13,6	76,2	3,7	14,4	0,1
145	FMF48-300	424,7	2526,1	2950,8	85,6	14,4	10,1	4,3	11,8	70,2	3,6	5,9	0,2
146	FMF49-0	142,4	3679,8	3822,2	96,3	3,7	1,4	2,4	22,8	70,1	3,3	25,8	0,0
147	FMF49-28	123,5	2591,5	2715,0	95,4	4,6	1,9	2,6	14,6	75,5	5,4	21,0	0,0
148	FMF49-60	158,8	2520,7	2679,5	94,1	5,9	3,0	3,0	22,1	67,9	4,1	15,9	0,1
149	FMF49-120	139,6	2189,8	2329,4	94,0	6,0	3,1	2,9	12,3	80,4	1,3	15,7	0,1
150	FMF49-300	297,9	9525,3	9823,3	97,0	3,0	2,1	0,9	14,8	80,2	2,0	32,0	0,0
151	FMF55-0	1536,8	2801,7	4338,5	64,6	35,4	22,9	12,5	11,4	47,5	5,6	1,8	0,5
152	FMF55-28	69,0	1624,4	1693,5	95,9	4,1	1,0	3,1	15,9	79,9	0,1	23,5	0,0
153	FMF55-60	107,0	2412,8	2519,8	95,8	4,2	2,0	2,3	16,5	77,0	2,2	22,6	0,0
154	FMF55-120	135,8	3101,1	3237,0	95,8	4,2	1,9	2,3	14,0	79,0	2,8	22,8	0,0
155	FMF55-300	582,7	3771,8	4354,5	86,6	13,4	10,2	3,1	10,2	72,4	4,0	6,5	0,2
156	FMF56-0	524,0	1797,7	2321,7	77,4	22,6	13,4	9,2	12,4	58,9	6,1	3,4	0,3
157	FMF56-20	154,0	1671,7	1825,7	91,6	8,4	2,4	6,0	25,3	62,1	4,2	10,9	0,1
158	FMF56-60	205,1	3392,5	3597,5	94,3	5,7	3,0	2,7	15,4	74,3	4,6	16,5	0,1
159	FMF56-120	113,9	2986,8	3100,7	96,3	3,7	1,8	1,8	19,6	76,6	0,0	26,2	0,0
160	FMF56-300	202,3	2827,3	3029,7	93,3	6,7	4,5	2,1	15,2	78,0	0,0	14,0	0,1

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		BA											
NO	**ID**	**Total Primary Bile Acids (ng/mg)**	**Total Secondary Bile Acids (ng/mg)**	**Total Bile Acids (ng/mg)**	**Secondary BA (% Total)**	**Primary BA (% Total)**	**Cholic Acid (% Total)**	**Chenodeoxycholic Acid (% Total)**	**Lithocholic Acid (% Total)**	**Deoxycholic Acid (% Total)**	**Ursodeoxycholic Acid (% Total)**	**2° to 1° % of Total (Ratio)**	**1° to 2° % of Total (Ratio)**
161	FMF58-0	1569,4	3574,7	5144,0	69,5	30,5	24,1	6,4	8,6	59,6	1,3	2,3	0,4
162	FMF58-20	472,5	3189,1	3661,6	87,1	12,9	7,2	5,7	9,1	73,9	4,1	6,7	0,1
163	FMF58-60	274,6	2711,0	2985,6	90,8	9,2	5,5	3,7	10,3	71,8	8,7	9,9	0,1
164	FMF58-120	444,8	3005,0	3449,8	87,1	12,9	9,6	3,3	8,8	74,2	4,0	6,8	0,1
165	FMF58-300	104,4	2595,0	2699,4	96,1	3,9	2,0	1,8	6,4	89,1	0,7	24,9	0,0
166	FMF59-0	1440,2	44,8	1485,0	3,0	97,0	74,4	22,6	0,1	1,1	1,8	0,0	32,2
167	FMF59-28	77,9	892,5	970,4	92,0	8,0	1,9	6,1	9,3	82,5	0,2	11,5	0,1
168	FMF59-60	117,5	1767,9	1885,4	93,8	6,2	2,5	3,7	9,0	82,4	2,4	15,0	0,1
169	FMF59-120	219,3	3695,3	3914,6	94,4	5,6	3,3	2,3	16,5	76,3	1,6	16,9	0,1
170	FMF59-300	139,3	3113,9	3253,2	95,7	4,3	2,2	2,1	15,6	76,6	3,5	22,4	0,0
171	FMF61-0	1044,1	1062,9	2107,0	50,4	49,6	41,1	8,4	0,1	49,1	1,3	1,0	1,0
172	FMF61-28	374,6	560,8	935,4	60,0	40,0	28,4	11,6	0,1	53,5	6,3	1,5	0,7
173	FMF61-60	1085,8	3389,0	4474,8	75,7	24,3	19,8	4,5	4,5	65,4	5,8	3,1	0,3
174	FMF61-120	707,6	2681,2	3388,7	79,1	20,9	16,6	4,3	3,3	70,3	5,4	3,8	0,3
175	FMF61-300	347,4	3015,0	3362,4	89,7	10,3	7,1	3,2	7,1	81,6	1,0	8,7	0,1
176	FMF62-0	62,4	1185,0	1247,3	95,0	5,0	1,4	3,6	7,1	87,7	0,1	19,0	0,1
177	FMF62-28	71,1	1329,1	1400,2	94,9	5,1	1,1	4,0	9,4	83,4	2,1	18,7	0,1
178	FMF62-60	573,7	1709,1	2282,8	74,9	25,1	18,5	6,6	6,9	62,6	5,3	3,0	0,3
179	FMF62-120	871,5	1976,7	2848,2	69,4	30,6	24,0	6,6	3,6	60,0	5,8	2,3	0,4
180	FMF62-300	1314,8	1708,6	3023,4	56,5	43,5	36,2	7,3	4,4	48,1	4,0	1,3	0,8
181	FMF63-0	58,9	884,8	943,8	93,8	6,2	1,6	4,7	2,5	91,1	0,1	15,0	0,1
182	FMF63-28	59,5	351,3	410,8	85,5	14,5	3,7	10,8	0,3	84,9	0,3	5,9	0,2
183	FMF63-60	62,2	1721,9	1784,1	96,5	3,5	0,9	2,6	11,9	84,5	0,1	27,7	0,0
184	FMF63-120	118,7	2934,5	3053,1	96,1	3,9	1,8	2,1	19,8	74,0	2,3	24,7	0,0
185	FMF63-300	178,2	3543,7	3721,8	95,2	4,8	2,8	2,0	12,6	81,2	1,4	19,9	0,1
186	FMF64-0	3803,9	63,4	3867,3	1,6	98,4	79,2	19,2	0,0	0,4	1,2	0,0	60,0
187	FMF64-28	1369,5	45,0	1414,5	3,2	96,8	74,4	22,5	0,1	1,3	1,7	0,0	30,5
188	FMF64-60	236,3	3303,5	3539,8	93,3	6,7	4,3	2,4	17,6	75,1	0,6	14,0	0,1
189	FMF64-120	90,8	2896,0	2986,8	97,0	3,0	0,6	2,4	16,7	79,0	1,2	31,9	0,0
190	FMF64-300	255,4	3066,1	3321,5	92,3	7,7	3,6	4,1	16,6	70,1	5,6	12,0	0,1
191	FMF66-0	325,5	2465,3	2790,8	88,3	11,7	7,9	3,7	3,3	85,0	0,1	7,6	0,1
192	FMF66-28	267,9	2359,7	2627,6	89,8	10,2	3,5	6,7	17,0	70,6	2,2	8,8	0,1
193	FMF66-60	316,9	1897,4	2214,3	85,7	14,3	3,8	10,5	14,7	69,8	1,2	6,0	0,2
194	FMF66-120	135,2	1863,3	1998,5	93,2	6,8	2,4	4,3	16,8	76,4	0,1	13,8	0,1
195	FMF66-300	294,6	5508,9	5803,5	94,9	5,1	3,5	1,6	10,9	84,0	0,0	18,7	0,1
196	FMF67-0	876,5	20,4	896,9	2,3	97,7	77,3	20,4	0,1	2,0	0,2	0,0	43,0
197	FMF67-20	1975,8	21,0	1996,8	1,0	99,0	84,3	14,6	0,1	0,9	0,1	0,0	94,3
198	FMF67-60	1827,2	2583,5	4410,7	58,6	41,4	27,3	14,2	6,9	51,1	0,6	1,4	0,7
199	FMF67-120	137,4	1888,3	2025,8	93,2	6,8	2,4	4,4	13,0	80,2	0,1	13,7	0,1
200	FMF67-300	252,0	3767,0	4018,9	93,7	6,3	3,2	3,1	16,4	76,8	0,5	15,0	0,1
201	FMF68-0	334,3	20,4	354,6	5,7	94,3	71,5	22,8	0,4	5,0	0,4	0,1	16,4
202	FMF68-20	1531,5	71,3	1602,8	4,4	95,6	71,7	23,9	0,1	1,0	3,4	0,0	21,5
203	FMF68-60	453,6	1425,4	1878,9	75,9	24,1	12,2	11,9	9,0	56,9	10,0	3,1	0,3
204	FMF68-120	160,0	2956,0	3116,0	94,9	5,1	2,6	2,6	8,9	83,3	2,7	18,5	0,1
205	FMF68-300	637,3	2317,0	2954,2	78,4	21,6	15,0	6,6	8,8	65,9	3,7	3,6	0,3
206	FMF70-0	2835,8	102,0	2937,8	3,5	96,5	71,6	25,0	0,0	0,6	2,8	0,0	27,8
207	FMF70-20	415,6	1243,3	1658,9	74,9	25,1	19,1	5,9	3,0	68,8	3,2	3,0	0,3
208	FMF70-60	1380,6	315,8	1696,5	18,6	81,4	62,7	18,7	0,1	0,9	17,7	0,2	4,4
209	FMF70-120	1888,6	52,9	1941,4	2,7	97,3	72,9	24,4	0,1	0,9	1,8	0,0	35,7
210	FMF70-300	1047,4	1362,6	2410,1	56,5	43,5	30,4	13,1	2,4	51,0	3,2	1,3	0,8
211	FMF71-0	3959,1	936,5	4895,6	19,1	80,9	69,9	10,9	0,0	0,3	18,8	0,2	4,2
212	FMF71-28	2398,3	168,4	2566,7	6,6	93,4	73,8	19,6	0,0	0,6	5,9	0,1	14,2
213	FMF71-60	3836,3	338,4	4174,8	8,1	91,9	79,9	12,0	0,0	0,4	7,7	0,1	11,3
214	FMF71-120	211,6	3438,4	3650,0	94,2	5,8	2,0	3,8	6,7	87,1	0,4	16,2	0,1
215	FMF71-300	175,5	3321,8	3497,3	95,0	5,0	2,4	2,6	5,8	87,9	1,3	18,9	0,1
216	FMF74-0	144,0	2309,0	2453,0	94,1	5,9	1,7	4,1	12,3	81,8	0,1	16,0	0,1
217	FMF74-20	83,2	1055,1	1138,3	92,7	7,3	1,6	5,7	3,9	88,6	0,1	12,7	0,1
218	FMF74-60	237,4	1930,7	2168,0	89,1	10,9	5,2	5,8	8,5	80,4	0,1	8,1	0,1
219	FMF74-120	177,6	2138,9	2316,5	92,3	7,7	3,3	4,3	10,6	76,5	5,2	12,0	0,1
220	FMF74-300	316,4	3185,1	3501,5	91,0	9,0	5,5	3,6	12,0	75,4	3,5	10,1	0,1
221	FMF75-0	2873,1	20,6	2893,6	0,7	99,3	82,6	16,7	0,0	0,6	0,1	0,0	139,7
222	FMF75-28	2105,7	18,3	2124,0	0,9	99,1	81,3	17,8	0,1	0,7	0,1	0,0	114,9
223	FMF75-60	165,4	2240,8	2406,2	93,1	6,9	1,9	5,0	12,5	77,0	3,6	13,5	0,1
224	FMF75-120	963,8	4382,8	5346,6	82,0	18,0	13,0	5,1	8,5	66,8	6,7	4,5	0,2
225	FMF75-300	401,4	4981,8	5383,2	92,5	7,5	4,2	3,2	13,1	73,2	6,3	12,4	0,1

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Supplementary-Table S4: List of metabolites identified in fecal samples by targeted metabolomics. Mean and standard deviation by group and time point.

		Day 0						Day 20/28						Day 60					
		CON		AMC		DOX		CON		AMC		DOX		CON		AMC		DOX	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
cholic_acid	**BA**	775,28	990,84	632,57	951,39	894,66	1151,10	587,67	922,70	1299,56	2188,66	1823,78	2459,68	524,01	902,66	645,15	970,78	562,41	970,95
chenodeoxycholic_acid	**BA**	240,10	254,28	247,18	280,19	211,21	185,48	185,11	142,00	338,44	318,68	363,04	359,14	162,58	119,83	239,44	220,05	193,23	166,90
lithocholic_acid	**BA**	244,49	346,89	374,02	359,35	355,18	415,74	313,90	268,80	184,22	319,26	166,59	198,14	379,58	236,01	325,92	200,39	352,78	302,10
deoxycholic_acid	**BA**	1282,12	1576,14	1968,80	1652,68	1798,30	1562,41	1881,44	1245,42	1041,82	1392,45	985,90	988,27	2082,72	934,32	2073,51	742,63	1740,28	1110,62
ursodeoxycholic_acid	**BA**	95,50	164,05	120,44	215,12	123,77	243,97	87,14	127,46	90,37	104,44	155,15	250,94	174,05	163,65	166,33	190,30	119,40	126,44
myristic acid	**FA**	0,47	0,28	0,69	0,94	0,54	0,28	0,29	0,09	0,47	0,93	0,25	0,07	0,44	0,36	0,26	0,11	0,25	0,09
alpha_linolenic acid	**FA**	0,21	0,09	0,84	1,59	0,25	0,18	0,33	0,16	0,62	1,16	0,33	0,14	0,38	0,18	0,32	0,10	0,27	0,13
cis_vaccenic acid	**FA**	1,84	1,17	2,49	1,89	2,34	1,64	1,25	0,69	0,99	1,14	1,28	0,83	2,10	1,49	1,25	0,93	1,45	1,33
palmitic acid	**FA**	13,15	4,91	12,62	5,95	14,65	4,60	9,01	3,66	9,15	3,73	9,61	4,35	11,91	5,01	7,49	3,11	8,49	4,17
oleic acid	**FA**	12,13	5,59	13,50	6,28	14,28	5,04	10,95	4,68	11,56	5,53	11,73	5,17	13,82	4,77	9,84	3,99	9,56	4,48
linoleic acid	**FA**	6,54	3,88	7,82	5,58	7,27	4,87	7,92	3,81	8,05	4,35	8,35	3,95	10,20	4,80	6,79	2,06	6,86	3,42
stearic acid	**FA**	8,49	4,74	9,94	6,35	11,73	6,10	5,27	3,62	4,20	1,20	4,34	1,67	7,25	4,24	4,17	1,60	4,71	2,67
arachidonic acid	**FA**	0,80	0,41	1,38	1,65	1,20	0,67	0,90	0,50	2,06	4,71	0,75	0,20	1,25	1,10	0,79	0,29	0,88	0,42
gondoic acid	**FA**	0,44	0,25	0,64	0,58	0,60	0,44	0,37	0,32	0,36	0,44	0,26	0,08	0,49	0,40	0,29	0,15	0,27	0,14
erucic acid	**FA**	0,08	0,05	0,17	0,26	0,11	0,09	0,07	0,03	0,12	0,24	0,06	0,02	0,11	0,10	0,07	0,06	0,06	0,03
docosanoic acid	**FA**	0,17	0,09	0,38	0,57	0,29	0,21	0,13	0,03	0,23	0,47	0,12	0,03	0,19	0,10	0,12	0,05	0,13	0,04
nervonic acid	**FA**	0,23	0,14	0,49	0,62	0,45	0,38	0,18	0,06	0,28	0,46	0,15	0,05	0,29	0,20	0,16	0,05	0,17	0,06
coprostanol	**Sterols**	0,42	0,99	0,89	1,31	0,69	1,03	0,43	0,75	0,35	0,97	0,37	0,52	0,91	1,21	0,62	0,96	0,39	0,58
cholesterol	**Sterols**	1,75	0,81	1,95	1,27	3,15	2,28	1,51	0,91	1,44	0,96	1,05	0,47	1,96	0,98	1,11	0,47	1,26	0,69
cholestanol	**Sterols**	0,17	0,12	0,12	0,09	0,15	0,11	0,12	0,04	0,13	0,06	0,13	0,05	0,15	0,06	0,13	0,06	0,11	0,03
brassicasterol	**Sterols**	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,00
lathosterol	**Sterols**	0,02	0,00	0,03	0,02	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00
campesterol	**Sterols**	0,24	0,15	0,19	0,11	0,26	0,13	0,34	0,17	0,30	0,15	0,36	0,19	0,42	0,19	0,34	0,15	0,33	0,11
stigmasterol	**Sterols**	0,12	0,07	0,11	0,07	0,12	0,08	0,18	0,08	0,18	0,08	0,21	0,11	0,20	0,06	0,19	0,06	0,17	0,06
fusosterol	**Sterols**	0,03	0,04	0,02	0,03	0,03	0,03	0,06	0,04	0,06	0,06	0,07	0,05	0,07	0,04	0,09	0,10	0,05	0,03
beta_sitosterol	**Sterols**	0,66	0,38	0,49	0,35	0,62	0,38	0,92	0,47	0,92	0,53	1,02	0,58	1,05	0,43	1,00	0,42	0,88	0,32
sitostanol	**Sterols**	0,37	0,27	0,29	0,33	0,34	0,37	0,63	0,33	0,61	0,34	0,75	0,43	0,78	0,28	0,77	0,19	0,63	0,24
Tot_Prim_BA	**BA**	1015,38	1213,22	879,74	1226,98	1105,87	1312,71	772,77	1049,53	1638,00	2476,92	2186,81	2807,76	686,59	991,49	884,58	1175,70	755,64	1116,92
Tot_Sec_BA	**BA**	1622,11	2003,05	2463,26	2002,60	2277,26	1919,60	2282,48	1566,12	1316,41	1688,37	1307,65	1322,59	2636,36	1147,14	2565,75	878,44	2212,47	1405,61
Tot_BA	**BA**	2637,49	1879,18	3343,00	2290,04	3383,13	1422,18	3055,25	1679,52	2954,41	2459,64	3494,46	2776,59	3322,95	1040,63	3450,34	1230,77	2968,11	1479,27
Sec_BA_%	**BA**	55,15	43,96	67,70	36,15	64,10	40,69	73,87	32,21	46,73	41,81	49,94	38,40	79,54	24,72	76,76	25,48	76,56	31,54
Prim_BA_%	**BA**	44,85	43,96	32,30	36,15	35,90	40,69	26,13	32,21	53,27	41,81	50,06	38,40	20,46	24,72	23,24	25,48	23,44	31,54
Cholic_Acid_%	**BA**	31,83	36,17	23,15	28,49	29,06	35,96	19,06	27,35	39,44	34,19	39,63	33,92	15,40	22,36	16,37	20,71	17,01	28,22
Chenodeoxycholic_Acid_%	**BA**	13,03	15,78	9,15	7,95	6,84	5,30	7,07	5,70	13,83	11,72	10,43	5,56	5,06	3,19	6,86	5,35	6,43	4,08
Lithocholic_Acid_%	**BA**	7,51	8,72	11,48	11,32	8,87	8,23	9,33	6,24	5,77	7,90	6,36	7,98	11,20	6,60	10,04	6,11	12,26	6,47
Deoxycholic_Acid_%	**BA**	45,22	36,86	53,42	30,70	52,07	35,48	61,93	27,03	37,64	36,72	39,43	33,36	63,40	20,14	61,68	23,59	60,77	26,68
Ursodeoxycholic_Acid_%	**BA**	2,42	3,45	2,80	3,59	3,16	5,82	2,60	2,87	3,32	3,35	4,15	5,29	4,94	4,05	5,04	5,32	3,54	3,00
Tot_Phytosterols	**Sterols**	2,36	1,25	2,98	1,76	4,02	2,78	2,08	1,03	1,94	1,66	1,57	0,74	3,05	1,76	1,87	0,92	1,78	0,73
Total_Zoosterols	**Sterols**	1,43	0,86	1,10	0,86	1,37	0,97	2,13	1,08	2,07	1,13	2,40	1,31	2,53	0,97	2,38	0,85	2,07	0,74
Total_Sterols	**Sterols**	3,83	1,76	4,13	1,81	5,44	2,62	4,26	1,57	4,07	1,97	4,02	1,97	5,63	2,20	4,30	1,28	3,90	1,13
Tot_FAs	**FA**	44,55	17,81	50,96	27,08	53,71	18,75	36,66	15,56	38,10	20,56	37,24	15,43	48,44	19,81	31,55	11,05	33,12	15,60

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		Day 120						Day 300					
		CON		AMC		DOX		CON		AMC		DOX	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
cholic_acid	**BA**	591,95	1053,57	905,09	1438,44	431,40	718,71	309,24	365,07	256,10	226,32	425,59	1016,72
chenodeoxycholic_acid	**BA**	152,29	132,95	263,82	265,40	159,58	130,54	125,76	64,84	148,49	69,49	125,41	108,99
lithocholic_acid	**BA**	354,57	229,09	349,37	198,88	373,69	233,11	507,57	377,18	458,13	364,06	474,01	278,49
deoxycholic_acid	**BA**	2281,85	781,83	2584,47	1151,55	2065,94	1092,01	3025,62	1705,13	2783,56	1549,03	2702,98	1219,98
ursodeoxycholic_acid	**BA**	125,37	112,49	175,63	176,26	153,02	153,10	95,90	62,81	145,48	124,23	122,50	112,61
myristic acid	**FA**	0,41	0,31	0,31	0,16	0,32	0,15	0,30	0,11	0,32	0,20	0,39	0,25
alpha_linolenic acid	**FA**	0,35	0,15	0,36	0,18	0,33	0,09	0,37	0,17	0,32	0,09	0,37	0,14
cis_vaccenic acid	**FA**	1,90	1,57	1,47	1,09	1,37	0,96	1,14	0,63	1,51	1,21	1,73	1,13
palmitic acid	**FA**	10,99	5,32	10,00	4,90	8,87	2,72	9,32	4,11	9,81	4,16	10,69	5,05
oleic acid	**FA**	12,33	5,04	12,11	4,81	11,92	4,60	12,24	4,76	12,06	4,71	12,43	5,64
linoleic acid	**FA**	9,08	4,69	8,99	4,43	7,70	2,27	7,95	2,90	8,07	2,80	8,89	4,14
stearic acid	**FA**	7,34	5,31	6,31	4,34	4,93	2,01	5,34	3,69	6,29	4,58	6,25	3,80
arachidonic acid	**FA**	1,08	0,63	0,92	0,41	1,01	0,48	1,07	0,51	2,00	3,98	1,05	0,57
gondoic acid	**FA**	0,38	0,29	0,33	0,23	0,33	0,17	0,29	0,18	0,40	0,40	0,37	0,25
erucic acid	**FA**	0,08	0,04	0,07	0,03	0,07	0,03	0,07	0,03	0,08	0,05	0,08	0,05
docosanoic acid	**FA**	0,18	0,10	0,14	0,06	0,16	0,08	0,15	0,06	0,15	0,09	0,16	0,07
nervonic acid	**FA**	0,24	0,15	0,19	0,09	0,22	0,11	0,18	0,06	0,20	0,13	0,21	0,09
coprostanol	**Sterols**	0,90	1,31	1,00	1,30	0,91	1,03	0,68	0,93	0,79	1,08	0,79	1,11
cholesterol	**Sterols**	1,57	0,96	1,70	1,24	1,40	0,77	1,33	0,59	1,67	1,34	1,51	0,58
cholestanol	**Sterols**	0,16	0,07	0,14	0,05	0,15	0,05	0,13	0,04	0,14	0,07	0,16	0,08
brassicasterol	**Sterols**	0,05	0,01	0,05	0,01	0,05	0,01	0,05	0,00	0,05	0,00	0,05	0,01
lathosterol	**Sterols**	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00	0,02	0,00
campesterol	**Sterols**	0,38	0,15	0,38	0,14	0,42	0,15	0,42	0,17	0,38	0,13	0,41	0,21
stigmasterol	**Sterols**	0,20	0,09	0,21	0,09	0,20	0,06	0,21	0,05	0,20	0,05	0,20	0,09
fusosterol	**Sterols**	0,06	0,04	0,07	0,05	0,06	0,03	0,07	0,04	0,07	0,03	0,06	0,04
beta_sitosterol	**Sterols**	0,97	0,40	1,04	0,45	1,04	0,36	1,17	0,43	1,03	0,35	1,03	0,53
sitostanol	**Sterols**	0,80	0,30	0,82	0,25	0,83	0,31	0,88	0,27	0,81	0,33	0,82	0,50
Tot_Prim_BA	**BA**	744,24	1179,44	1168,91	1695,04	590,98	840,91	435,00	411,37	404,59	284,65	551,00	1117,44
Tot_Sec_BA	**BA**	2761,79	1027,51	3109,46	1362,52	2592,65	1352,00	3629,09	2086,04	3387,17	1964,39	3299,49	1471,91
Tot_BA	**BA**	3506,03	1603,22	4278,38	1911,19	3183,63	1359,44	4064,09	2007,89	3791,76	1913,81	3850,49	2118,98
Sec_BA_%	**BA**	84,04	18,04	75,19	27,54	79,12	27,13	87,71	12,48	86,97	12,42	84,76	20,83
Prim_BA_%	**BA**	15,96	18,04	24,81	27,54	20,88	27,13	12,29	12,48	13,03	12,42	15,24	20,83
Cholic_Acid_%	**BA**	12,01	16,50	18,51	22,06	15,08	22,66	8,77	10,99	8,44	9,46	10,48	15,47
Chenodeoxycholic_Acid_%	**BA**	3,95	1,78	6,31	5,92	5,80	4,85	3,52	2,15	4,59	3,19	4,77	6,34
Lithocholic_Acid_%	**BA**	11,13	6,00	8,70	4,96	12,10	7,92	11,81	4,39	11,19	5,10	11,94	5,70
Deoxycholic_Acid_%	**BA**	69,29	13,23	62,44	23,54	63,05	22,05	73,32	9,75	71,94	9,74	69,04	19,09
Ursodeoxycholic_Acid_%	**BA**	3,62	2,36	4,04	3,64	3,97	3,19	2,58	1,64	3,83	2,94	3,77	2,88
Tot_Phytosterols	**Sterols**	2,66	1,50	2,86	1,87	2,48	1,43	2,17	1,18	2,63	2,18	2,49	1,41
Total_Zoosterols	**Sterols**	2,41	0,90	2,52	0,90	2,56	0,86	2,76	0,94	2,49	0,81	2,52	1,34
Total_Sterols	**Sterols**	5,12	1,80	5,43	2,12	5,09	2,07	4,98	1,43	5,16	2,53	5,06	2,62
Tot_FAs	**FA**	44,35	21,22	41,21	18,69	37,22	12,04	38,41	14,84	41,19	18,94	42,61	19,06

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CONCLUSIONS

The results of this study provide important information regarding the effects of antibiotics on the young feline GI microbiome and on the fecal and serum metabolomic profiles of young cats.

The GI microbiome of cats changed after 2 months of age and reached an adult-like state at around 6 months of age. The five most prevalent phyla of cats during the first year of life were Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, and Fusobacteria. The abundance of Proteobacteria, Enterobacteriales, Gammaproteobacteria, and Bacilli decreased, while the abundance of Erysipelotrichi increased from 2 to 4 months of age. This is in agreement with data from humans. Current knowledge suggests that the first microbes colonizing the GI tract are mainly facultative anaerobic bacteria that reduce oxygen concentrations in the gut and allow for successful colonization of the obligative anaerobic bacteria. The phylum Proteobacteria, which is comprised by facultative and obligative anaerobic bacteria, is among the first colonizers of the GI tract in humans. At the weaning period and after the introduction of a solid diet (i.e., around 5–6 months of age), the abundance of Proteobacteria gradually decreases. The concurrent increase in the abundance of taxa belonging to Firmicutes (i.e., Erysipelotrichales) reflects the introduction of dietary macronutrients that are utilized by these bacteria. The only taxonomical changes observed after 6 months of age was an increase in members of the order Aeromonadales.

Both antibiotics delayed the developmental progression of the feline GI microbiome resulting in a delay in its maturation. Amoxicillin/clavulanic acid caused immediate changes, while doxycycline effects appeared 1 month after its withdrawal. Amoxicillin/clavulanic acid resulted in a transient reduction in species richness lasting

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less than a month after treatment while doxycycline increased species richness 1 month after its withdrawal. Antibiotics, including amoxicillin and doxycycline are most commonly reported to either decrease or have no effect on species richness. Only a few studies have reported an increase in species richness indices. Members of Firmicutes (Erysipelotrichi, *Catenibacterium* spp., unclassified Lachnospiraceae), were decreased, while members of Actinobacteria (unclassified *Collinsella* spp.) and Proteobacteria (Enterobacteriales, *E.coli*) increased during and after treatment with both antibiotics. Erysipelotrichi contain bile salt hydrolase genes, and this enzyme is responsible for the deconjugation of primary bile acids. Thus, the decrease observed could potentially lead to increased concentrations of deconjugated primary BAs in the gut. Members of this family ferment carbohydrates leading to the production of butyrate. Butyrate is one of the main SCFAs in the gut and has anti-inflammatory properties, is a major energy source for colonocytes, and its absence causes autophagy of epithelial intestinal cells in germ-free mice. Early colonization with *Collinsella* spp. within the first 6 months of life is associated with increased adiposity in humans. The phylum Proteobacteria encompasses some of the most well-known pathogens and members of this phylum are commonly increased in dogs and cats with GI diseases, as well as during consumption of high-protein, canned and raw diets. The clinical consequences of the antibiotic-induced alterations in these bacteria remain to be determined.

Similar to the microbiome, the serum and fecal metabolomic profiles of cats were individualized at 2 months of age and changed towards the first year of life. Less interindividual variation was observed in the abundance of fecal metabolites in cats at 2 months of age compared to serum metabolites. Within the amino acids, tryptophan concentrations increased, and glycine concentrations decreased in serum after 3 months of age. Antioxidants (trans-4-hydroxyproline, methionine sulfoxide), polyamines

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(putrescine, phenylethylamine), and metabolites related to sugar metabolism (maltose, erythritol, arabitol, and threonic acid) decreased in serum after 3 months of age. Regarding the fecal metabolites, individual primary BAs (chenodeoxycholic acid), decreased and total secondary BAs increased after 2 months of age. Similarly, to young dogs, microbial converters of primary to secondary BAs in 2-month-old cats have not yet reached an adult plateau. In addition, total sterols, and individual fatty acids (linoleic acid) increased after 2 months of age.

Similar to the gastrointestinal microbiome, the fecal and serum metabolites were only temporarily affected by treatment with both antibiotics, and no changes were observed 10 months after their withdrawal. Indole-3-propionic acid, an antioxidant and inositol-4-monophosphate, an inositol lipid derivative, were detected at lower concentrations at the end of amoxicillin/clavulanic acid treatment compared to control cats. Indole-3-propionic acid is a tryptophan-derived microbial metabolite that exerts a protective role on the intestinal mucosal barrier through increasing mucin synthesis, and with other beneficial products produced by the intestinal goblet cells. Reduced indole 3-propionic acid concentrations have been found in mice treated with neomycin, which was significantly associated with weight gain. Exogenous indole-3-propionic acid administration led to a two-fold reduction in body weight gain in mice treated with neomycin compared to mice treated with neomycin alone, suggesting a potential link of antibiotic-induced alteration in the microbial metabolism of tryptophan and obesity. Uracil, a pyrimidine as well as guanine and hypoxanthine, which are classified as purines, increased at the end of doxycycline treatment compared to control cats. Nucleotide (purines and pyrimidines) biosynthesis pathways are suggested to be involved in antibiotic lethality. Bacterial nucleotide biosynthesis is stimulated during antibiotic treatment. The synthesis of nucleotides for ATP storage requires more energy,

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followed by increasing cellular respiration, central carbon metabolism, and oxidative stress, and these metabolic disturbances eventually lead to bacterial cell death. However, this mechanism has been described with bactericidal and not with bacteriostatic antibiotics, such as doxycycline. Therefore, these data may suggest that doxycycline may alter bacterial nucleotide metabolism, an effect that was not observed with amoxicillin treatment. From the fecal metabolites, fecal secondary bile acids started to increase at the end of treatment with both antibiotics (i.e., after 3 months of age), whereas in control cats, secondary bile acids increased after 2 months of age. This suggests that antibiotics caused a transient suppression of microbial bile acid converters. Secondary BAs are commonly decreased after antibiotic treatments. Mounting evidence suggests that secondary BAs can suppress the proliferation of GI pathogens and maintain colonization resistance. During immune system maturation, the microbiome also matures and informs the immune system about which bacteria can be considered to be harmful or pathogenic. A reduction in secondary BAs at this critical developmental window of cats could therefore allow the proliferation of gastrointestinal pathogens and engender a lack of a proper immune response due to the immune system immaturity at this age. Cholesterol was significantly reduced only in doxycycline-treated cats compared to control cats with this effect also lasting for 3 months. The depletion of the GI microbiome by antibiotics is documented to cause a potential increase in the intestinal absorption of cholesterol, which could explain the reduced concentrations of cholesterol in feces in doxycycline-treated cats. In humans, it has been shown that particular antibiotics, including metronidazole, can have lipid-lowering effects.

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FUTURE STUDIES

Future studies could:

1. Investigate the effects of different antibiotic classes on the GI microbiome and metabolomic profiles of young cats and potentially identify antibiotics that affect the feline microbiome and metabolome to a lesser degree.
2. Follow-up cats with antibiotic-induced dysbiosis at a young age for a long period of time (years) to investigate whether they are predisposed to GI or other diseases.
3. Investigate the associations between changes in bacterial abundances with changes in the concentrations of metabolites.
4. Apply different -omic approaches, such as transcriptomics, proteomics, and resistomics to obtain a more thorough picture on the effects of antibiotics on bacterial gene expression, function, and resistance.
5. Investigate ways to facilitate the amelioration of the disruptive antibiotic effects on the microbiome and metabolome, such as next generation probiotics and FMT.
6. Investigate ways by which microbial members acquire resistance to antibiotics and to identify metabolic substances that increase antibiotic lethality and could be used to reduce antibiotic doses.

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SUMMARY

EVALUATION OF THE LONG-TERM EFFECTS OF ANTIBIOTIC USE ON GASTROINTESTINAL MICROBIOTA AND SERUM AND FECAL METABOLOMIC PROFILES IN GROWING CATS

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Doctoral Thesis 2022

Microbiome is the collective genome of microbial inhabitants in a certain environment while metabolome is defined as the complete set of small molecules present in a biological sample. Those small molecules can be metabolic products of the host, its microbiome or both. The term microbiome more commonly refers to the bacterial inhabitants of a community because bacteria play the most important role in host's metabolism and immune system development and response as well as during disease states.

Antibiotics have transformed the way of living since their discovery and introduction in clinical practice. However, numerous studies have shown that antibiotic treatment, results in a disruption of the normal microbial communities and their functions and increases antibiotic resistance genes. In addition, previous studies in humans have shown that antibiotic treatment during early life increases the risk of certain diseases such as inflammatory bowel disease, allergic diseases, obesity and potentially diabetes later in life. The term gastrointestinal dysbiosis is used to describe the compositional and functional alterations of the gastrointestinal microbiome in response to exogenous factors and/or the health status of the host. Antibiotic-induced dysbiosis in humans is characterized by a decrease in bacteria beneficial for the host ("health-

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associated bacteria"), allowing overgrowth of potentially pathogenic bacteria, and a shift in microbially derived metabolic products. No studies to date have investigated the effect of doxycycline and antibiotic treatment in general on the gastrointestinal microbiome and metabolome of young cats until they reach maturity.

The aim of this study was a) to describe and compare the fecal microbiota between kittens receiving antibiotics and kittens not receiving antibiotics over a time period of 10 months; b) to describe the normal fecal microbiota of healthy kittens and how the microbiota composition changes over time; c) to describe the fecal and serum metabolome, and how both of these are affected by antibiotics as well as their changes during development (from 2 months to one year of age).

A total of 72 eight-week-old rescue domestic shorthair (DSH) cats were enrolled in the study. Forty-four out of 72 cats were diagnosed with upper respiratory tract disease (URTD) based on the typical clinical presentation, including conjunctivitis, blepharospasm, ocular or nasal discharges, nasal congestion, sneezing, and coughing. The cats were randomly assigned to receive either amoxicillin/clavulanic acid for 20 days (AMC group) or doxycycline for 28 days (DOX group) as part of the standard treatment for this condition. In addition, 26 clinically healthy cats or cats with very mild URTD that did not require antibiotic treatment were enrolled as controls (CON group). All cats received the same diet and the same antiparasitic treatment during the study period. Fecal samples were collected on days 0, 20/28 (last day of antibiotic treatment on the AMC group and DOX group, respectively), 60, 120, and 300 while serum was collected on days 0, 20/28, and 300. Metagenomic analysis was performed on fecal samples with Illumina metagenomic sequencing and quantitative PCR was performed for quantification of bacterial groups commonly associated with dysbiosis in cats. Untargeted metabolomic analysis was performed on serum samples using a gas

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chromatography time-of-flight mass spectrometry method. Targeted metabolomic analysis was performed on fecal samples with a gas chromatography and mass spectrometry method.

A total of 45 cats, 15 in each group eventually completed the study. These included 25 males and 20 females. Bacterial abundances were characterized by high interindividual variation at 2 months of age in cats, indicating the immaturity of the microbiome at this age. However, no significant differences were identified in bacterial abundances at 2 months of age. AMC cats harbored a distinct microbial community composition on the last day of treatment and DOX cats 1 month after the end of treatment, compared to CON cats. In addition, DOX cats had increased species richness compared to CON cats on the last day of treatment. Abundance of Enterobacteriales was increased, and that of Erysipelotrichi was decreased in cats of the AMC group on the last day of treatment compared to CON cats. Nine months after amoxicillin/clavulanic acid withdrawal, higher abundances of unclassified *Collinsella* spp. were detected compared to CON cats. In cats of the DOX group, decreased *Catenibacterim* spp., and unclassified *Lachnospiraceae* spp. were identified compared to CON cats one month after doxycycline withdrawal. In addition, the abundance of the phylum Proteobacteria was increased in DOX cats compared to CON cats and this effect lasted for 3 months after doxycycline withdrawal. Nine months after doxycycline withdrawal, higher abundances of unclassified *Collinsella* spp., and unclassified *Bulleidia* spp. were detected compared to CON cats.

Regarding serum metabolites, AMC cats had reduced concentrations of inositol-4-monophosphate, and increased concentrations of indole-3-propionic acid on the last day of treatment compared to CON cats. Cats of the DOX group had increased serum concentrations of uracil, hypoxanthine, and guanine on the last day of treatment

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compared to control cats. Fecal nervonic acid was detected at significantly lower concentrations in both antibiotic-treated groups on the last day of treatment and this effect lasted for 3 months after antibiotic withdrawal. Fecal cholesterol was also persistently reduced in DOX cats compared to CON cats for 3 months after doxycycline discontinuation. When the pattern in the concentrations of metabolites was compared within each group, amino acids, antioxidants, metabolites related to carbohydrate metabolism, bile acids, sterols, and fatty acids where differentially expressed over time in each group.

In conclusion, our results indicate that the GI microbiome of cats changes after 2 months of age and reaches an adult-like state around 6 months. Similar to the microbiome, significant changes occur in the concentrations of fecal and serum metabolites in cats during the first year of life. Amoxicillin/clavulanic acid and doxycycline treatment early in life significantly affected the developing microbiome richness and composition. The abundance of Firmicutes members decreased, and that of members of Proteobacteria increased after 20 days of amoxicillin/clavulanic acid treatment and 3 months after a 28-day course of doxycycline. In addition, doxycycline had a delayed impact whereas amoxicillin/clavulanic acid had a more immediate impact on bacterial community composition, but only minor changes persisted 9 months after their discontinuation. Seven out of 208 fecal and serum metabolites differed significantly in antibiotic-treated cats compared to controls on day 20/28, 2 on day 60, and 2 on day 120. Amoxicillin/clavulanic acid affected serum metabolites classified as inositol phosphates and antioxidants while doxycycline affected serum metabolites classified as purines and pyrimidines at the end of treatment. Both antibiotics resulted in a reduction of metabolites belonging to fatty acids while doxycycline also affected sterols and these effects persisted 3 months after discontinuation. No changes were observed in

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metabolomic profiles 9 months after antibiotic withdrawal compared to CON cats. Similar to the developing microbiome, the concentrations of serum and fecal metabolites are characterized by high interindividual variability at 2 months of age and antibiotics appeared to delay the maturation of the serum and fecal metabolomic profiles in young cats.

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