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Authors
Denizer, Erce
Bode, Lars
Dorrestein, Pieter
et al.

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Transfer of antibiotics and their metabolites in human milk: Implications for infant health and microbiota

Sydney P. Thomas[1,2], **Erce Denizer**[1,2], **Simone Zuffa**[1,2], **Brookie M. Best**[1,3], **Lars Bode**[3,4], **Christina D. Chambers**[1,3,5], **Pieter C. Dorrestein**[1,2], **George Y. Liu**[3], **Jeremiah D. Momper**[1], **Victor Nizet**[1,3], **Shirley M. Tsunoda**[1], **Adriana H. Tremoulet**[3]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, UC San Diego, La Jolla, California, USA

[2]Collaborative Mass Spectrometry Innovation Center, UC San Diego, La Jolla, California, USA

[3]Pediatrics Department-Rady Children's Hospital San Diego, UC San Diego School of Medicine, La Jolla, California, USA

[4]Mother-Milk-Infant Center of Research Excellence (MOMI CORE), UC San Diego, La Jolla, California, USA

[5]Hebert Wertheim School of Public Health and Human Longevity Science, UC San Diego, La Jolla, California, USA

Abstract

Antibiotics are an essential tool for perinatal care. While antibiotics can play a life-saving role for both parents and infants, they also cause collateral damage to the beneficial bacteria that make up the host gut microbiota. This is especially true for infants, whose developing gut microbiota is uniquely sensitive to antibiotic perturbation. Emerging evidence suggests that disruption of these bacterial populations during this crucial developmental window can have long-term effects on infant health and development. Although most current studies have focused on microbial disruptions caused by direct antibiotic administration to infants or prenatal exposure to antibiotics administered to the mother, little is known about whether antibiotics in human milk may pose similar risks to the infant. This review surveys current data on antibiotic transfer during lactation and highlights new methodologies to assess drug transfer in human milk. Finally, we provide recommendations for future work to ensure antibiotic use in lactating parents is safe and effective for both parents and infants.

Correspondence Sydney P. Thomas, University of California San Diego, 9500 Gilman Drive, MC 0751, La Jolla, CA, USA. spthomas@health.ucsd.edu.

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Keywords

antibiotics; breastmilk; human milk; metabolomics

1 | INTRODUCTION

Antibiotics are an indispensable component of modern perinatal care. The practice of reducing bacterial infection during childbirth was pioneered by the physician Ignaz Semmelweis, who in 1847 achieved a 90% reduction in maternal mortality from postpartum infection after instituting mandatory handwashing among the medical students working in the First Obstetrical Clinic of the Vienna General Hospital.[1] Today, antibiotics are prescribed to 30–50% of pregnant or lactating parents, depending on their geographical location.[2-5] Current World Health Organization (WHO) guidelines only recommend antibiotic administration to parents with preterm premature rupture of membranes (PPROM), manual removal of the placenta, third- or fourth-degree perineal tear, cesarean section, chorioamnionitis, group B *Streptococcus* (GBS) colonization, or postpartum endometritis, but does not give specific guidance on antibiotic treatment of disorders that may be related to childbirth, such as urinary tract infections.[6] However, routine antibiotic prophylaxis for uncomplicated vaginal births is still common, especially in low- to middle-income countries.[6,7]

Although antibiotics can serve a life-saving role, their incorrect use — including overuse, sporadic use, wrong dosage, or incomplete adherence — not only promotes antimicrobial resistance but may also negatively affect long-term health.[8-10] In general, many of these negative consequences are associated with disruption of the gut microbiota. This community of bacteria, fungi, archaea, protists, and viruses plays essential roles in human health — metabolizing indigestible dietary substrates, supplying energy metabolites, vitamins, and neurotransmitters, and protecting against pathogen colonization.[11] Broad-spectrum antibiotics kill these commensal bacteria along with pathogenic strains, leading to altered gut microbial profiles, which have been associated with a wide array of non-communicable diseases, from atopy to irritable bowel syndrome (IBS) to Alzheimer's disease.[12,13] Although the exact mechanisms behind these associations are still unclear, current evidence suggests that microbial dysbiosis is both a driver and marker of chronic diseases, and that disruption of the gut microbial community can have significant long-term impacts on human health. This presents a unique challenge for clinicians, who must weigh the short-term benefits of antibiotic use with long-term risks that are not yet well defined.

Although antibiotics can disrupt microbial communities at any age, there is evidence that antibiotics have an outsized influence on the gut microbiota in early life.[14] Research over the past decades has highlighted the critical importance of the developing gut microbiota on infant health.[15,16] Development of the gut microbiota begins at birth, and is highly dynamic over the first 3 years of life before becoming more stable during adulthood.[10,17] Thus, antibiotic administration early in life can disrupt this crucial window of microbiome development, and potentially lead to long-term changes in the gut microbial community.[9,18-21] Early life antibiotic administration is associated with increased risk of obesity,[22,23] type 1 diabetes,[24] asthma,[25] and other metabolic, neurological, and immunological disorders.[26] With growing evidence that the gut microbiota influences both immune development and neurodevelopment, this list will likely increase.[15,27] Although it is clear that antibiotics can negatively impact gut microbiota development in infants, most studies have focused on direct infant administration of antibiotics[17,23-25,28,29] or prenatal exposure in utero.[30] However, there are few clinical data on one of the most common routes of infant antibiotic exposure — human milk.

Transfer of drugs to infants via human milk is an area of critical research need. Historically, pregnant and lactating parents were routinely excluded from clinical research due to ethical and safety concerns. Unfortunately, this contributed to a major knowledge gap in the safety of medications in lactating parents, as there was little to no incentive or requirement to assess the safety of drugs during lactation after registrational clinical trials were completed.[31] Although some groups are beginning to encourage inclusion of pregnant and lactating parents in clinical trials, most marketed drugs still do not have appropriate labeling for lactating parents.[32] Several federal efforts have aimed to address this gap, including the Pregnancy and Lactation Labeling Rule, the Best Pharmaceuticals for Children Act (BPCA), the Pediatric Research Equity Act (PREA), the Pediatric Trials Network (PTN), and the United States Food and Drug Administration (FDA)'s Clinical Lactation Studies guidance document.[33-35] Even so, our understanding of the safety of drugs during lactation is still inadequate.

2 | ANTIBIOTIC TRANSFER IN HUMAN MILK

Human milk is a complex nutritive and bioactive fluid that is in a constant state of flux.[36] Milk composition varies both between and within individuals based on a variety of factors such as lactation stage, length of feeding, time of day, and diet. In general, milk can be divided into three major stages: colostrum, which occurs after 24 weeks of gestation; transitional, which begins between days 2 and 3 postpartum; and mature, which appears 10–14 days postpartum. Colostrum is enriched in a variety of immune-related factors such as immunoglobulins and macrophages, whereas transitional and mature milk contain more calorie-rich lactose, protein, and fat.[37] Many of these components play roles beyond nutritional value — many interact with host microbes and can have either prebiotic or antimicrobial properties.[38,39] In fact, human milk is the most significant driver of gut microbiota development during the first year of life.[10] Human milk components may also interact with antibiotics themselves, as breastfed and formula-fed infants show different microbial responses to antibiotic exposure.[40] However, the mechanisms behind these interactions and the extent to which they determine the effects of drug transfer are not yet well understood.

Traditionally, drug exposure in milk is represented as a milk-to-plasma (M/P) ratio, which is defined as the ratio of drug concentration in milk over its concentration in parental serum/plasma at a simultaneous point in time. Drugs generally enter milk through diffusion from maternal serum and their mode and efficiency of transfer depends on a variety of factors, such as molecular weight, solubility, pKa, and protein binding (Figure 1).[41] Drugs that undergo passive diffusion are expected to have a M/P ratio approaching 1.0. As milk pH is often lower than that of serum, weak acids are expected to have a M/P ratio <1.0 and weak bases >1.0. Finally, lipophilic drugs can accumulate in milk fat and thus have a M/P ratio >1.0. Although heavily used in the field, M/P ratios are biased by several overarching assumptions, and thus may not accurately estimate infant drug exposure.[42] For one, single-point M/P ratios assume that drug concentrations in milk and plasma are at equilibrium at the time of dosing and that their concentrations will change in parallel to one another. Because drug transfer to milk is a time-dependent process, milk and serum concentrations often peak at different time points, leading to vastly different M/P values depending on the time of sampling.[42] To account for these limitations, area-under-the-curve (AUC) measurements have been used to create M/P AUC ratios.[43] However, although M/P AUC ratios provide an improvement over single-point M/P ratios, neither measure fully accounts for the many interdependent variables that determine drug concentrations in human milk and their actual infant dose. These variables include pharmacokinetic and physicochemical properties of the drug, as well as maternal and infant health, milk composition, and drug metabolism (Figure 1).

Many commonly prescribed antibiotics can be transferred from the parent to infant via milk. Commonly prescribed antibiotics used during lactation are summarized in Table 1. The safety of each of these antibiotics during lactation has been extensively reviewed elsewhere,[41,44-47] and is also available from medical references.[48, 49] The safety of drugs in human milk is often described in terms of the relative infant dose (RID), which is the percent ratio of the daily infant dosage over the daily parental dosage.[50] RID can be calculated by first calculating daily infant dosage by one of the two following equations. Both equations set the average value of milk intake by a fully breastfed infant to 150 ml/kg/day, although this value does vary between individuals.[50]

1. Daily infant dosage (mg/kg) = Average concentration in milk (mg/ml) × 150 ml/kg/day
2. Daily infant dosage (mg/kg) = M/P x average concentration in parental plasma (mg/ml) × 150 ml/kg/day.

The RID is then calculated as a percentage of the infant dosage over the parental dosage. The WHO has categorized drugs with an RID value <10% as acceptable during lactation, with those between 10 and 25% labeled as caution and > 25% labeled as unacceptable.[50] Existing studies estimate that 87–90% of drugs have RID values below 10%, which would indicate that most medications are safe during lactation.[51,52] However, although these categories are useful, they do not account for drug toxicity and thus do not fully represent drug safety. For instance, an acutely toxic drug may prove harmful to the infant at RID values far less than 10%, whereas a drug with low toxicity may be easily tolerated at RID values above 25%.

Thus, some have suggested that the antibiotic dose in milk is safe as long as it is lower than the therapeutic dose that would be administered directly to the infant.[47,53,54] Aside from the fact that the doses extrapolated from RID and M/P ratios may be inaccurate, research in model organisms suggests that even low doses of antibiotics in milk can have deleterious effects on the infant.[9,20,55,56] These include disruption of the microbiome and increases in antibiotic-resistant genes, which can be selected at very low doses of antibiotics.[56,57] Although the effects of low-dose antibiotic exposure in human milk have not been systematically investigated, it is possible that even those antibiotics which exhibit low concentrations in milk could still negatively affect the infant. One worrying observation is that low doses of multiple antibiotics are present in the milk of most lactating parents, whether or not they were prescribed antibiotics.[58] These antibiotic residues are likely derived from the diet, and with widespread antibiotic use in agriculture and aquaculture, it is possible that most human milk (as well as cow's milk and infant formula) may contain some baseline level of antibiotics.[59] Thus, the real antibiotic exposure to a breastfeeding infant may be significantly more complex than our current recommendations assume.

Beyond antibiotics derived from the diet, infants may be exposed to a large array of antibiotic metabolites and antimicrobial compounds. Milk itself contains components with antimicrobial properties such as human milk oligosaccharides (HMOs), which can protect against GBS colonization and necrotizing enterocolitis.[38,60] Clinical pharmacokinetic studies typically assess systemic concentrations of a parent compound and a limited number of known metabolites derived from human drug metabolizing enzymes.[61-63] However, mounting evidence suggests that drugs will yield a significant number of metabolites in the host, many of which are produced by microbial enzymes that are capable of chemical transformations which do not exist in known human pathways.[64] This opens the door to a wide variety of drug transformations, including many novel metabolites whose activities are unknown. While any of these metabolites could theoretically diffuse into milk in a similar manner to their parent compounds, the presence of microbes in milk raises the possibility of further drug metabolism in milk itself. Thus, it may be more accurate to view any pharmacokinetic target not as a single drug, but as a constellation of a drug and its human and microbial drug metabolites, whose composition may vary between individuals. This perspective presents obvious technical challenges: how does one measure a drug and its metabolites if the full extent of the drug's metabolism is unknown? Fortunately, new advances in untargeted metabolomics may provide a rapid and unbiased method that has the potential to measure the entire constellation of a drug's metabolites without prior knowledge of all possible drug transformations.[65]

3 | UNTARGETED METABOLOMICS IN DRUG METABOLISM

Untargeted metabolomics uses mass spectrometry to survey a range of small molecules (<1500 Da) in a biological sample. Experiments often measure thousands of molecules in a single sample and can be run in minutes. Although this amount of data is incredibly powerful, it has also proved to be one of the method's major drawbacks. Determining the chemical identity of all of these compounds is an enormous technical and computational challenge, and traditionally results in the chemical identification of 5–10% of the total compounds in a sample.[66] However, recent computational tools have enabled the clustering of structurally related compounds whether or not their exact chemical identity is known. This method — called molecular networking — can routinely uncover novel drug metabolites by identifying networks of compounds that are chemically related to a known drug of interest.[65,67] Molecular networking was pioneered by the Global Natural Products Social Molecular Networking (GNPS) platform, whose publicly available repository of over a billion mass spectra allows for drug searches on both newly acquired and existing metabolomic data.[66] For example, Figure 2 shows a molecular network containing sulfonamide antibiotics in public data from approximately 1000 human milk samples. The network contains not only known drugs such as sulfamethazine and sulfapyridine but also a range of novel metabolites. The structures of these novel metabolites can often be deduced by manual comparison to spectra of known compounds (Figure 2B). Thus, untargeted metabolomics and molecular networking are uniquely positioned to resolve the challenges of identifying novel drug metabolites, as these tools provide both an unbiased survey of compounds in a biological sample and a method to visualize structurally related metabolites.

One drawback of untargeted methods is that they tend to be qualitative or semiquantitative. Thus, an ideal pharmacokinetic study would combine unbiased discoveries of drug metabolism using untargeted methods with accurate quantitative measurements of active metabolites using a targeted assay. This also raises the issue that while untargeted methods can identify novel metabolites, they do not report on the activity of said compounds. Synthesizing novel metabolites and measuring their activity in vitro and in vivo is currently both labor-intensive and low-throughput. Thus, new methods to prioritize novel metabolites based on their expected activity or increase throughput of current activity assays are necessary to make the most of the information provided by untargeted metabolomics.

Although untargeted metabolomics can resolve issues of novel drug metabolism in milk, extrapolation of actual infant antibiotic dose from drug levels in milk will still fail to account for the full range of variables that affect drug transfer from parent to infant (Figure 1). Ideally, one would directly measure the actual infant dose of an antibiotic by monitoring drug levels in the infant rather than estimating based on drug levels in milk. Unfortunately, the technical and ethical challenges of performing blood draws in infants has made this approach difficult when performing timed pharmacokinetic studies. Physiologically based pharmacokinetic (PBPK) modeling can bypass the need for infant sampling by providing in silico, mechanistic predictions of drug transfer using known parameters encompassing anatomy, physiology, drug transport, biotransformation, and physicochemical properties.[68] Existing PBPK modeling of drugs in human milk have predicted milk AUC within 50% of observed values, and can also be used to simulate infant exposure by integration of whole body parental and infant PBPK models.[69-71] The ability of PBPK models to be performed in silico may prove especially useful in prioritizing drugs with high estimated RID ratios for further clinical studies.

Despite these advantages, PBPK models can be limited by the availability of accurate information on factors such as drug M/P ratios, inter-individual variability, and altered drug disposition during the perinatal period.[68] Thus, there is always a chance that these in silico models will not accurately predict drug transfer to the infant. New sampling methods, however, may provide an opportunity to directly measure infant drug levels in a rapid and non-invasive manner. Recent work describing drug measurements from skin and sweat using both targeted and untargeted metabolomics opens the door to non-invasively sample drug levels on infant skin over time.[72-74] These methods are dependent on drug transfer from systemic circulation to skin and sweat, which does not occur for every drug.[75] However, preliminary analyses in adults suggest that skin drug levels show similar concentration curves to corresponding serum levels, although their peaks may occur at different points in time.[73,74] Although still developing, these methods hold promise in improving our knowledge of systemic exposure of drugs acquired through human milk.

Ultimately, to fully understand the safety of antibiotics in infants, one must measure the actual perturbations to the gut microbiota caused by a specific drug exposure.[76] This objective can be achieved through gut bacterial sequencing of infant fecal samples, ideally with longitudinal sampling to assess gut microbiota composition before, during, and after antibiotic exposure. Since antibiotics of differing spectrum and potency will differentially affect commensal bacteria, it is possible that certain antibiotics will have a larger effect on gut microbiota development despite being present at a lower dose in the infant.[77] Thus, antibiotics should be prioritized that cause the least disruption to gut microbial development. This goal may require long-term longitudinal follow-up, as many of the potential risks of early life antibiotic exposure may not occur until much later in life. The ability to pair early life antibiotic exposure information from banked samples available in human milk biorepositories with electronic health records is a promising method to reduce both the cost and time necessary to perform these large cohort longitudinal studies. For example, the Mommy's Milk biorepository has collected over 80,000 milk aliquots, including many longitudinal samples, paired infant biospecimens, and clinical data.[78] Even so, clinical data gathered from electronic health records may not always be complete – for example, the records may report antibiotics prescribed directly to the infant but not those prescribed to the lactating parent.[79,80] Medical records also do not consistently include the use of over-the-counter medications and supplements, such as probiotics, which could affect microbiome development. Some of these issues can be mitigated by linking parent and infant health records – something that has been implemented within specific health systems.[81] However, harmonizing medical records from different medical systems and providers still presents a significant hurdle. Thus, accurate reporting of lactation and drug information for both parents and infants in medical records is crucial to fully utilize this new technology in understanding antibiotic safety in lactation.

Although the studies described above will aid in prioritizing antibiotics that exert the least collateral damage to the developing infant gut microbiota, it is possible that all broad-spectrum antibiotics currently prescribed to lactating parents will have some effect on the infant. However, these medications are and will continue to be crucial tools for clinicians to prevent parent and infant mortality as well as long-term disability and birth defects. Fortunately, several recent developments may allow clinicians to minimize these effects on the infant gut microbiota. Currently, probiotics are the most widely used product to stabilize or restore gut microbiota diversity, and a wide array of “baby probiotics” are marketed to parents to boost infant gut bacterial communities. However, the quality and effectiveness of probiotic products vary widely, and very little clinical data exists on probiotic supplementation in infants.[82,83] A more targeted approach could involve a new class of drugs aimed at minimizing the effect of antibiotics on beneficial gut bacteria.[84,85] Current iterations work by absorbing or degrading antibiotic residues in the colon, and have not yet been shown to reduce antibiotic concentrations in milk. However, it is possible that direct infant administration of these drugs could protect the infant gut microbiota from antibiotics introduced by lactation. In addition to these drugs, a renewed prioritization of narrow-spectrum antibiotics may result in more tailored therapies that do less damage to other gut bacteria.[86] Finally, certain components in milk, such as HMOs, are already known to interact with antibiotics.[39] It may be possible to harness these naturally produced molecules to reduce the effects of antibiotics in milk either by direct supplementation to infants or by changing parental diet to boost specific HMO production.[87] Although all of these developments have the potential to reduce the collateral damage of antibiotics in the infant, the vast majority of research in these areas has focused on non-lactating adults. Since infants are especially vulnerable to perturbations caused by antibiotics, it is imperative that lactating parents and infants are included in clinical trials of these new drugs.

Finally, new methods to improve the detection and health effects of antibiotics in milk hold great promise in improving our understanding of drug safety, but none of these advances will prove useful if they are not made clear and accessible to both clinicians and parents. Many parents stop taking important medications during lactation due to safety concerns, and may even be incorrectly advised by their health professionals to do so.[88] The development of the Drugs and Lactation Database (LactMed), a publicly available database on medication use during lactation, is a step in the right direction.[48] In addition, the Maternal and Pediatric Precision in Therapeutics (MPRINT) knowledge portal is working to provide a repository of pharmacokinetic parameters mined from all published studies in maternal and pediatric patients (https://mprint.org/). However, these databases contain a large amount of technical language, making them more useful for healthcare professionals and researchers than for parents. MotherToBaby has translated information from LactMed into consumer summaries offered free of charge to parents. These fact sheets are currently available on the MotherToBaby website (https://mothertobaby.org/fact-sheets/) and will soon be available in the National Library of Medicine. The Infant Risk Center has also created other user-friendly tools, including the MommyMeds app, although much of this information is currently behind a paywall.[89] These improvements are encouraging, but are too often buried in the vast amount of information available online. Thus, investing in and promoting free, evidence-based, and user-friendly tools for parents should remain a priority.[90]

4 | CONCLUSIONS

Current knowledge of antibiotic safety in lactation too often relies on simplistic models of drug transfer from serum to milk, and an outdated assessment of the risks of antibiotics for the developing infant gut microbiota. Optimizing antibiotic use during lactation will require deeper understanding of the wide variety of factors that affect the actual infant dosing. These include pharmacokinetic and physical properties of drugs, novel drug metabolism by host bacteria (including microbes in milk), and direct measurement of perturbations to the infant gut microbiota. New methods to rapidly assess the full range of drug metabolites and non-invasively measure levels of those compounds in infants have the potential to revolutionize pharmacokinetic studies in lactation. Together with responsible use of electronic medical records, new technologies to reduce collateral damage to gut bacteria, and appropriate public engagement, we can achieve optimized antibiotic doses that are safe and effective for both parents and infants.

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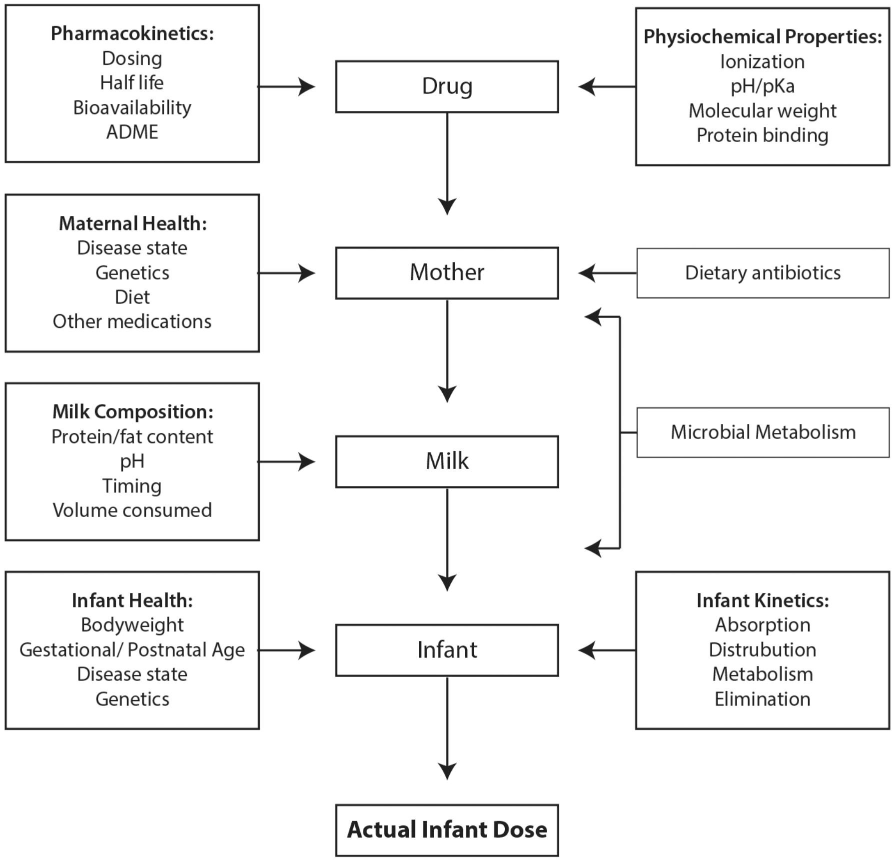

FIGURE 1.
Variables that affect actual infant dose of antibiotics in human milk.

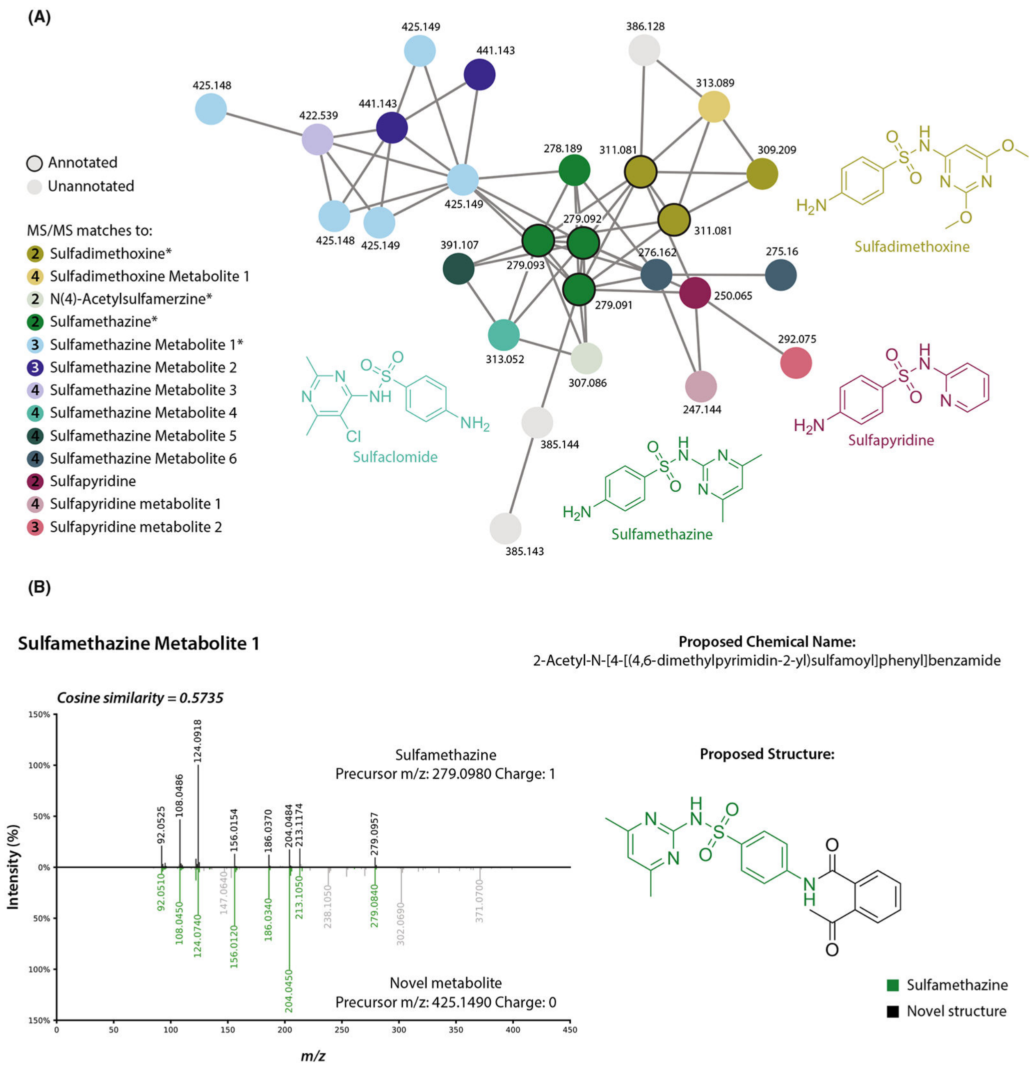

FIGURE 2.

Molecular networking allows for identification of novel antibiotic metabolites. (A) Molecular network containing sulfonamide antibiotics and their metabolites in human milk. Reproduced with permission from Thomas et al.[102] Network nodes with chemical identifications from basic computational analysis are shown with black outlines. Numbers next to each node correspond to *m/z* (or mass-to-charge ratio) of each molecule. Asterisks (*) mark compounds that were identified in solvent controls in at least one dataset; number in circle indicates MS/MS match level (a measure of match certainty).[103] All colored nodes in these networks have been manually annotated by spectral comparison to library compounds and other related spectra. (B) Proposed structure of novel sulfamethazine metabolite. Structures can be proposed by comparing spectra of known compounds (black, top) with the unknown metabolites of interest (green and gray, bottom). Matching peaks (green) indicate where the two structures are identical, unmatched peaks (gray) indicate where they differ.

TABLE 1

Summary of commonly prescribed antibiotics used during lactation

Drug Class	In milk?	Safety	M/P Ratio	Comments	Ref.
Aminoglycosides					
Gentamicin	Yes	Likely safe	0.110–0.440	May cause skin rash	[91]
Penicillins					
Amoxicillin	Yes	Likely safe	0.014–0.043	Occasional rash, disruption of gut microbiota, diarrhea, or thrush (mainly for amoxicillin)	[61,92-94]
Ampicillin			0.01–0.58		
Ticarcillin			N/A	Milk levels reported as 2–2.5 mg/dL	
Cephalosporins					
Cephalothin	Yes	Likely safe	0.073–0.500		[61]
Cephalexin			0.008–0.140		
Cefotaxime			0.029–0.160		
Cefadroxil			0.009–0.019		
Cephapirin			0.068–0.480		
Monobactam					
Aztreonam	Yes	Likely safe	0.005–0.009	IV and IM administration	[92,95]
Beta-lactamase inhibitors					
Sulbactam	Yes	Likely safe	N/A	Sulbactam reported at 0.5 mg/mL in human milk	[92]
Nitroimidazole					
Metronidazole	Yes	Likely safe	0.870–1.000	Major metabolite hydroxymetronidazole: M/P ratio = 0.700–0.880	[96]
Macrolides					
Azithromycin	Yes	Likely safe	2.490	Adverse events have included vomiting, diarrhea, candidiasis, and hypertrophic pyloric stenosis	[97]
Fluoroquinolones					
Ciprofloxacin	Yes	Likely safe	0.850–2.140	Pseudomembranous colitis and arthropathy have been reported Direct administration to neonates reported to be safe	[98,99]
Pefloxacin			0.750–1.040		
Ofloxacin			0.980–1.660		
Sulfonamides	Yes	Likely safe	0.016 - >1	Diarrhea and rash in healthy infants Should be avoided in parents of G6PD-deficient infants	[41,100]
Tetracycline Antibiotics	Yes	Likely safe	0.25–1.5	May contribute to dental staining and inhibition of bone growth	[41,101]