It is not disputed that breastfeeding has many benefits for both mother and baby and is the optimal nutrition for infants. With an increase in education and support of breastfeeding mothers throughout the United States, the rate of breastfeeding is on the rise. The Centers for Disease Control and Prevention report an increase of breastfeeding initiation from 74.6% in 2008 to 76.9% in 2009, which is the largest annual increase in the past 10 years. As the incidence rises, there are more situations in which lactating women are exposed to various medications and more questions regarding the safety of these medications to the infant. Almost all medications enter the breast milk, but the amount in breast milk, and more importantly the amount absorbed by the infant, is rarely well defined. Despite this lack of information, most drugs are considered safe while breastfeeding. In the absence of specific details for a particular drug’s passage into breast milk, the clinician can evaluate the physicochemical characteristics of the drug as well as the patient characteristics to determine the appropriateness of breastfeeding while the mother is taking the medication.

### Passage of Exogenous Compounds from Maternal Blood to Milk

In general, drugs enter breast milk by passive diffusion. The presence and concentration of compounds in breast milk depend on a number of important factors, including the drug’s molecular weight, degree of ionization, protein binding in blood, lipid solubility, and specific uptake by mammary tissue, as well as the amount and composition of the milk. The constituents of breast milk vary relative to the postpartum period and could influence drug distribution and accumulation within breast milk, depending on the drug’s physiochemical characteristics.

Small compounds with molecular weights of less than about 200 daltons appear freely in breast milk and are presumed to have passed through pores in the mammary alveolar cell. Large compounds such as insulin or heparin, or those that are protein bound, do not enter the milk. Intermediate-sized compounds must penetrate the lipoprotein cell membrane by diffusion or active transport. Drugs or other chemicals that are very lipid soluble readily cross the alveolar cell, and because breast milk contains a considerable amount of lipid, these compounds are trapped in the milk. In general, drugs that are not ionized at blood pH traverse the alveolar cell membrane with greater ease than highly ionized compounds. Therefore, weak acids, which are more likely to be ionized at the plasma pH of 7.4, are less likely to enter breast milk, whereas weak bases pass into breast milk more readily. Because breast milk pH is 7 or slightly less, once a weak base crosses into breast milk, it may become more ionized and trapped.

A number of important variables specific for the type of drug, age, and time after delivery or disease influence a drug’s ability to penetrate into breast milk. The interrelationships between these and other variables yet to be identified are complex, making it very difficult to predict the actual amount of drug distribution into the milk. Although many investigators and clinicians have attempted to collapse the many important characteristics into one simple surrogate marker of drug penetration into breast milk—the ratio of milk to plasma protein (M/P ratio)—this parameter is overly simplistic and often misrepresents the true nature of drug distribution into breast milk. The M/P ratio is defined as the ratio of the drug concentration in breast milk to the drug concentration in maternal plasma at a simultaneous point in time after maternal drug administration. A low M/P ratio (<1) is supposed to indicate no accumulation of drug in the mother’s milk. However, the M/P ratio is based on the assumption that the drug concentrations in maternal blood and milk are constant and in equilibrium at the time of sampling, which is most often not true. Based on its limitations, the M/P ratio should be used with caution, if at all, as a means of quantitating drug distribution in breast milk and infant exposure.

Alternatively, the relative infant dose (RID) can be used as more accurate tool to estimate infant exposure to a drug if there are data available on the concentration of drug in the breast milk and volume of milk ingested by the infant (often estimated at 150 mL/kg/day). The RID can then be calculated by dividing the infant dose measured in the breast milk (mg/kg per day) by the maternal dose (mg/kg per day) and expressing it as a percentage. It has been suggested that a RID greater than 10% may be of concern; however, every drug is different and depending on the specific patient and drug characteristics, a RID greater than 10% may be acceptable.
Delivery of Compounds to and Disposition by the Infant

After ingestion of a drug via breast milk, the drug must either act locally in the infant’s gut or be absorbed by the infant into systemic circulation to produce an effect. Generally, if a drug is not orally bioavailable (e.g., vancomycin), the infant will not absorb the medication, even if it is present in breast milk. However, it is possible that the bowel of a very young infant may permit the absorption of large molecules that are normally excluded. Another potential barrier to absorption is found in milk proteins that bind certain drugs and impede absorption. Unfortunately, for most drugs, the extent of oral absorption by the breastfed infant is unknown. If absorption does occur, the infant’s handling of the medication is often unclear and changes with postnatal age. Ultimately, close monitoring of the infant for adverse effects associated with the maternal drug therapy is required.

COMPUNDS IN BREAST MILK

Antibiotics

Fortunately, most antimicrobial agents in breast milk appear to be safe for nursing infants. Some antibiotics, particularly those with broad antimicrobial spectra, may change the infant’s intestinal flora and cause diarrhea or thrush, but this quickly resolves upon discontinuation of the antibiotic, and is not considered a contraindication to breastfeeding. Two antibiotic classes that are sometimes considered contraindicated in breastfeeding include sulfonamides and tetracyclines.

Sulfonamide derivatives are sometimes avoided during lactation because they have the potential to displace bilirubin from albumin. The amounts present in breast milk, combined with the actual bioavailable dose to the infant, suggest that maternal sulfonamide administration is acceptable during breastfeeding except in neonates at high risk for hyperbilirubinemia, including extremely premature neonates or those with very low birth weight.

Tetracyclines in breast milk purportedly have the potential to cause dental staining, and many sources have suggested that women taking tetracyclines avoid breastfeeding. Closer examination of these suggestions against breastfeeding during tetracycline therapy appear to be based on theoretical grounds rather than any supporting evidence. Moreover, the bioavailability of tetracyclines under the conditions of breastfeeding suggests that the maternal administration of tetracycline and its analogues is safe and without complications in infants.

Overall, maternally administered antibiotics are considered safe for the breastfed infant, and only in rare instances should mothers requiring antibiotic therapy be recommended to discontinue breastfeeding their infant.

Anticoagulants

The use of anticoagulants may be critical to health of a mother with a history of pulmonary embolism, venous thrombosis, or other clotting disorder. Both parenteral and oral anticoagulant options are available that are compatible with breastfeeding. Heparin has a molecular weight of about 20,000 daltons and does not enter breast milk. Newer synthetic heparin has a much lower molecular weight (3000 daltons), but is still too large for passage into breast milk. Additionally, heparins are unstable in gastric contents, so any small amount that might pass into breast milk would be quickly degraded. Oral anticoagulants of the indanedione group, as well as bisphosphonates and ethyl biscoumacetate, are found in milk and have been associated with infant coagulopathies; therefore warfarin is considered the drug of choice. Warfarin is a weak acid with a high degree of protein binding and it is undetectable in breast milk.

Anticonvulsants

Anticonvulsants are a common concern for breastfeeding mothers, whether being used for treatment of a seizure disorder or as a mood stabilizer. Valproic acid, lamotrigine, and topiramate are a few of the commonly used anticonvulsants. Valproic acid is known to have teratogenic potential when taken during pregnancy, but is thought to be compatible with breastfeeding because of the low levels of drug transferred to milk (RID = 1.4% - 1.7%). Lamotrigine and topiramate, on the other hand, are more readily transferred into breast milk, with a RID of 9.2% to 18.3% and 3% to 23%, respectively. Despite the fact that these drugs can be detected at significant levels in the plasma of breastfeeding infants, there are minimal reports of adverse effects in the infants. Breastfeeding while taking any of the above anticonvulsants should be encouraged, with appropriate monitoring of the infant for any signs of toxicity (e.g., apnea, sedation).

Other anticonvulsants that are less commonly used include phenytoin, phenobarbital, and lithium. Phenytoin is found in small amounts in breast milk and is considered compatible with breastfeeding. Barbirate, including phenobarbital, appear to be safe. However, phenobarbital is metabolized much more slowly in neonates than adults; it is possible that the drug may accumulate in the breastfed infants of phenobarbital-treated mothers. These infants should be monitored for lethargy and poor weight gain.

Lithium has been contraindicated during lactation because of a few case reports that described significant cardiovascular and central nervous system signs in two infants. It would appear from a closer evaluation of these cases that transplacental exposure cannot be ruled out, and maternal drug interaction may have predisposed these infants to a level of lithium toxicity beyond what would have occurred from breastfeeding alone. As a result, breastfeeding mothers who require lithium therapy should be permitted to continue to breastfeed, with close infant monitoring that could include the measurement of blood lithium concentrations in the infant 1 to 2 weeks after initiating breastfeeding, renal function tests, and thyroid function tests. Consideration should be given to an alternative anticonvulsant if an adjustment in the mother’s therapy is not likely to compromise her health.

Antidepressants and Antipsychotics

Postpartum depression affects up to 20% of women and left untreated can be detrimental to both mother and
baby. Unfortunately, breastfeeding mothers often discontinue therapy to avoid perceived harm to the infant, despite the fact that there are many antidepressants that are considered safe while breastfeeding. Selective serotonin reuptake inhibitors (SSRIs) and selective nor-epinephrine reuptake inhibitors (SNRIs) are the most common antidepressants used in breastfeeding mothers. Sertraline is the most well-studied SSRI; it produces very low or undetectable milk and infant plasma levels. Fluoxetine, which has a long half-life and active metabo-lite, is also well-studied. There are reports of significant fluoxetine plasma levels in infants, but no adverse effects have been identified. In general, SSRIs and SNRIs are considered compatible with breastfeeding, and few if any adverse effects in the infant have been reported. Ser-traline is often the drug of choice for nursing mothers; however, if another SSRI/SNRI is more effective or better tolerated by both mother and baby, it is an acceptable alternative.

The exacerbation of psychotic disorders is also very common in the postpartum period, and is often treated with a newer class of drugs, the atypical antipsychotics. Quetiapine, risperidone, and olanzapine are three drugs within this class that have some data available from breastfeeding mothers/infants. For each of these medications, there are few reported adverse effects in the breast-feeding infant, and the RID is low for olanzapine (1.2%) and quetiapine (0.07%-0.1%).8 For risperidone, the RID is widely variable (2.8%-9.1%) and dependent on maternal dose, so it is recommended that the lowest effective dose be used and that the infant be monitored closely for signs of toxicity such as somnolence or lethargy.8

**Antihypertensives**

There are multiple drug classes available to treat hyper-tension in breastfeeding women. Within each class, some drugs have more information about compatibility with breastfeeding than others, but there are multiple safe options for the treatment of hypertension in a breastfeeding mother. β-Blockers are often one of the first drug classes used in treating hypertension, and most are compat-ible with breastfeeding. Metoprolol, propranolol, and labetalol have been used in breastfeeding mothers with no adverse effects experienced in the exposed infants. Other β-blockers (atenolol, acebutolol) have been associ-ated with cyanosis, hypotension, and bradycardia and should not be used in breastfeeding mothers.11

Angiotensin-converting enzyme inhibitors (ACEIs) are also a mainstay in the treatment of hypertension. Two drugs in this class have data to support their use while breastfeeding. Captopril and enalapril have a RID of 0.002% and 0.175%, respectively, and neither has been associated with adverse effects in exposed infants. A related class of drugs, angiotensin receptor blockers (ARBs), is often substituted for ACEIs if a patient experiences side effects from the ACEI. In the case of the breast-feeding mother, there are far more data and experience with ACEIs, so ARBs should be avoided if possible.

Calcium channel blockers may also be used to treat hypertension, typically as adjunct therapy, and have been used successfully in breastfeeding mothers without causing harm to the infant. There are studies evaluating the use of nifedipine, verapamil, and diltiazem, and all are considered compatible with breastfeeding.

Finally, diuretics are often part of a multidrug regimen to treat hypertension, and these are also likely to be compati-ble with breastfeeding. Theoretically, if a nursing woman became dehydrated because of diuretic use, milk production could be impacted, but this is controversial, and there is no contraindication to diuretic use and breastfeeding.

**Oral Contraceptives**

A common problem confronting health care providers is the maternal concern over the use of oral contraceptives during lactation. Contraceptives with a high concentra-tion of estrogen and progestin may depress lactation, especially if they are begun soon after parturition. It is best to start treatment about 4 weeks after delivery, ensuring that lactation is already well established, and to use the lowest dosage possible. Previously, it was believed that progesterone-only contraception would decrease the risk of lactation suppression, but more recent data suggest no difference between progesterone-only or combined oral contraceptives with regard to successful breastfeeding and milk production. Thus, any of the contemporary oral contraceptives, which contain low maternal hormone doses, are considered compatible with breastfeeding.

**Pain Medications**

Pain medications are frequently needed while breastfeed-ing, especially after cesarean section. Depending on the severity of pain, the medications used range from acet-a-minophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are acidic drugs with low lipid solubility and high protein binding; thus, transfer into breast milk is not favored. In a case report of ibuprofen use while breastfeeding, the RID was 0.0008%, reflective of the physicochemical properties of the drug.13 For acet-a-minophen, the RID is higher (8.81%), but still likely to be safe, considering it is commonly used in infants for the treatment of pain and fever.

Opioids are reserved for more severe pain, but are often necessary after surgery (e.g., cesarean section) or injury. The concern for the breastfed infant with any maternal opioid use is most often sedation or lethargy. The choice of opioid, use of the lowest effective dose, and a limited duration of therapy can decrease this risk. Morphine and hydrocodone are preferred agents over codeine and oxycodone. Morphine has poor oral bioavailability in infants, along with a RID of 9.1%. Hydrocodone effi-cacy is largely a result of its active metabolite, hydromorphone, which also has a relatively low RID (0.2%-9%).11 Codeine and oxycodone are not as predictable as mor-phine or hydrocodone and are associated with higher rates of infant sedation (16.7% and 20.1%, respectively).11 Both agents are metabolized by CYP2D6 in an unpredictable manner to active metabolites. This is thought to be the underlying cause of the death of a breastfed infant associated with maternal codeine use. An increased rate of maternal metabolism of codeine to morphine likely played an important role in this scenario.9
Methadone, although not often used to treat pain, is another opioid that is frequently used in breastfeeding mothers. Its use is most common as part of an addiction program, and the infant has most likely been exposed to the drug in utero as well. Methadone does transfer into breast milk, and the RID is about 2% to 3%. Its use while breastfeeding may actually alleviate some of the withdrawal symptoms that these infants often exhibit, and breastfeeding while on methadone as part of a treatment program should be encouraged.

Reflex Medications
Medications for gastroesophageal reflux are readily available as over-the-counter products and, therefore, are likely to be commonly used during lactation. There are two drug classes, histamine-2 (H2) blockers and proton pump inhibitors (PPIs), that should be evaluated for safety while breastfeeding. The H2 blockers include famotidine, ranitidine, and cimetidine. Famotidine and ranitidine have relatively low RIDs (1.9% and 1.3%-4.6%, respectively) and are considered compatible with breastfeeding. Cimetidine may be actively transported into breast milk, resulting in a much higher RID (up to 32.6%). Therefore, cimetidine should be avoided during lactation given the safer alternatives. Proton pump inhibitors (e.g., omeprazole, lansoprazole) are also a safer alternative to cimetidine, as there is minimal drug transfer into breast milk and any drug that is present is not well absorbed by the infant.

Nontherapeutic Agents in Breast Milk

Caffeine. One hour after the ingestion of an average cup of coffee, a peak breast milk caffeine level of about 1.5 mg/mL is reached. Caffeine levels in breast milk are about half the corresponding maternal blood level. Although the daily amount of caffeine consumed by a nursing infant might be small, the long half-life of caffeine could cause symptoms such as wakefulness or jitteriness and might be considered in the evaluation of infants whose mothers consistently consume large quantities of caffeine-containing products (e.g., cola, diet aids, coffee, tea).

Nicotine. Nicotine from smoking or replacement therapy (e.g., patch) is transferred into breast milk along with its active metabolites. If the mother is smoking, the toxic additives that are part of the cigarette and the secondhand smoke are also transferred to the infant. In a study of smoking cessation using nicotine patches in breastfeeding women, the dose of nicotine transferred to the infant steadily decreased as the nicotine patch dose was reduced. Breastfeeding women should be encouraged to use nicotine replacement therapy to limit infant exposure to nicotine as well as other toxins in cigarettes.

Ethanol. Ethanol, a small molecule, is freely diffused into breast milk and achieves levels equivalent to those in blood. Infrequent and moderate amounts of alcohol ingestion are not a contraindication to breastfeeding, but care should be taken to avoid breastfeeding at times when the concentration of alcohol in the breast milk will likely be high. For every drink consumed, the mother should avoid breastfeeding for at least 2 hours.

Narcotics. Breastfeeding while abusing narcotics such as heroin, oxycodone, or codeine, should not be promoted. Heroin readily transfers into breast milk; however, the extent of exposure to the infant can vary widely depending on the frequency and amount the mother uses. Drug purity can also impact infant exposure, not only to heroin, but to other compounds that may be mixed with the heroin. Similar rationale is applied to the abuse of prescription narcotics (e.g., oxycodone, codeine); the varying dose and frequency of maternal use put the infant at risk for side effects from these drugs (see Pain Medications). In the setting of illicit drug use, the risks of unpredictable drug exposure outweigh the benefits of breastfeeding.

Conversely, methadone is a narcotic that is frequently used in pregnant and breastfeeding mothers as part of an addiction program. As previously mentioned, methadone does transfer into breast milk, and the RID is about 2% to 3%. Its use while breastfeeding may alleviate some withdrawal symptoms, and breastfeeding while on methadone as part of a treatment program should be encouraged.

Conclusions Concerning Breastfeeding and Maternal Drug Therapy

As with the fetus in utero, the nursing infant is exposed to nearly everything entering the body of its mother. Clinicians are often faced with difficult decisions when counseling a mother regarding the safety of a medication. In those gray situations, the following simple guidelines may be helpful:

1. Therapy should be with single agents if possible. In the case of long-term therapy, consideration should be given to monitoring the infant’s activity and growth.
2. The physiochemical characteristics of multiple drugs within a given therapeutic class should be evaluated. Based on these properties, the drug least likely to pass into breast milk or be absorbed by the infant should be prescribed.
3. Attempt to minimize the dosage to the infant. Use the lowest effective dose, and counsel mothers to avoid nursing at maternal peak plasma levels.
4. Signs and symptoms in a nursing child should be correlated with maternal drug ingestion.

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