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Review Article

Antibiotics In Lactating Mother And Breast Feeding

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ABSTRACT

Breast feeding is the best form of infant feeding. Percentage of taking antibiotics in lactating mother is not much high in developed nation but it is quite high in developing nation specially in case of hospital delivery. Generally breast milk does not adversely affect the infant of lactating mother taking majority of antibiotics. But sometimes unrestricted use of antibiotics may invite deleterious effects to the newborn infants. So it is necessary to use antibiotics judiciously in lactating mother. Issues regarding antibiotic use in breast feeding mother are to be considered. These are (i) amount of ingested antibiotic that reaches to newborn infant through breast milk and (ii) whether this causes unwanted effects or not. Again, factors relating to antibiotic molecule, lactating mother and infant are responsible for transfer of antibiotics to infant. Antibiotics causing potential problems in breastfeeding infants are (i) modification of gut flora with alteration of defense mechanism. (ii) direct adverse effects to infants and (iii) alteration of microbial culture. On the basis of drug safety, antibiotics can be categorized into some groups. Drugs of same group are expected to behave almost similarly. But side effects of one drug may not similar to other agent of same group. Unwanted effects of antibiotics in breast feeding infant can be minimized through its judicious use of drugs on mother, decreasing its transfer to breast milk and monitoring the infant properly. Development of an antibiotic policy on lactating mother along with time to time evaluation and its circulation may play a pivotal role in this respect.

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INTRODUCTION:

Breast feeding is the best form of nutrition in neonates and young infants. The benefits of breast feeding specially on human offspring are immense. Breast feeding is one of the few interventions where the survival benefits newborn, infancy, early childhood directly and whole life even indirectly. Both the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend early initiation of breast feeding, exclusive breastfeeding for first 6 months of life and continuation of breastfeeding until 24 months of age.[1] Neonates are mostly benefited from breast feeding and beneficial effect of breastfeeding on specific infections like pneumonia and diarrhea are immense.[2] The optimal breast feeding is a key intervention that could prevent up to 13% of under-5 child deaths.[3] Considering the benefit and cost effectiveness of breast milk, breastfeeding is not absolutely contraindicated even in HIV infected mothers in this region.[1]

Percentages of mothers taking antibiotics after delivery in developed nation is not much high[4] but it is quite high even 90% especially in case of hospital delivery in this region.[5] Besides immediate side effects, some drugs may have long term adverse effects on growth and development of newborn infant. Preterm infant suppose to face more adverse effects when lactating mother takes these kinds of drugs.[6] But generally breast milk does not adversely affect the infants of lactating mothers taking majority of antibiotics. There is hardly contraindication of breastfeeding from mothers who necessitates medications.[7] Sometimes in one hand, risk of breast feeding is over highlighted when mother takes an antibiotic even which is quite safe to neonate. This may leads to unnecessary avoidance of essential drugs by the mother or avoidance of breast feeding even by the newborn infants. On the other hand sometimes unrestricted use of a harmful medicine even antibiotic may invite deleterious effects to the newborn infants. So, the issue on antibiotic in lactating mother is sometimes confusing even in health professionals. It is necessary to update information relating to antibiotic use in lactating mother, so that such medicines are used judiciously. The review is written to orient health personals particularly Obstetricians, Neonatologists and Pediatricians regarding related fundamental aspects of antibiotics so that antibiotics can be used judiciously on lactating mothers.

Transfer of antibiotics through breast milk:

There are two problematic issues regarding antibiotic use in breast feeding mother. The first one is ●how much ingested antibiotic really reaches to the newborn infant through breast milk? This is relatively easier to answer; often predictable and to an extent can be calculated mathematically. The second one is if antibiotic is transferred ●whether this is responsible for unwanted effects or not? This is difficult to predict due to paucity of data in human beings (8).

Majority of antibiotics in maternal plasma are similar to breast milk component. Theoretically, all maternal drugs have the potential crossing over from maternal plasma into breast milk. Antibiotics transfer from maternal plasma to breast milk occurs mainly by (i) passive diffusion across a concentration gradient and (ii) active transport against a concentration gradient. Drug transfer is negligible by (iii) transcellular diffusion. The factors responsible for antibiotics transfer to breast milk are: antibiotic molecules factors, maternal factors, infant factors.[8]

A. *Antibiotic factors*: antibiotics can cross biological membrane only in ionized state and follow the law of Henderson-Hasselbach equation: pH= pKa + log (base/ acid). As pH of breast milk is lower than plasma (7.2 vs.7.4), the weakly basic medication like erythromycin and metronidazole tend to concentrate in milk whereas weakly acidic drugs like suphonamides and penicillins accumulate higher in plasma.[8] Antibiotic with low molecular weight reaches breast milk more readily than with high molecular weight.[9] Protein binding of antibiotic molecules is one of the important factors determining drug transfer to milk. Transfer of drug is greater which binds less loosely to maternal plasma proteins.[8] Fat soluble antibiotics can cross cell membranes more easily. For this reason lipid soluble sulfonamides and chloramphenicol are more commonly found in mature milk with higher fat. Antibiotics with longer half life or with active metabolites provide longer infant exposure to the drugs.[10] B. *Maternal factors:* there is an individual variation in breast milk in relation to its

contents and pH. Again, milk tends to become more acidic with maturity; colostrums may have a pH of ~7.4 and transitional milk about 7.05. Similarly, milk from mother of preterm baby has higher protein content.[11] Again, hind milk has a higher pH and fat content than foremilk. Increase in mammary blood flow result in increase in drug supply to breast milk but its significance is uncertain.[8] Factors that minimize antibiotic excretion or metabolism by mother may increase drug concentration in breast milk.[12] Therefore, precaution is needed during prescription of antibiotics in breast feeding mother with liver or kidney disease.[10] Antibiotics use topically or as in inhalation forms do not reach significantly in blood or breast milk.[13] C. *Infant factors:* Infants varies in relation to drug absorption, distribution, metabolism and elimination. Premature infants differ from their counterpart in respect of renal elimination, enzymatic function, hepatic maturation and in some mechanical functions leading variation in antibiotic transfer and function in neonate.[8]

Box-1: **Factors modifying effects in infant by maternal antibiotics**	
A. Antibiotic factors:	(i) State of ionization: • pKa of antibiotic molecule. • pH of maternal plasma. • pH of breast milk. (ii) Affinity for proteins: • Plasma proteins. • Milk proteins. (iii) Half life. (iv) Molecular weight. (v) Lipid solubility.
B. Maternal factors:	(i) Interindividual variations. (ii) Intraindividual variations: • Variation in composition of breast milk with time. • Variation in pH of breast milk with time. (iii) Mammary blood flow. (iv) Drug metabolism in breast tissue.
C. Infant factors:	(i) Gestational age. (ii) Gastrointestinal emptying time. (iii) Gastro-oesophageal reflux. (iv) Intestinal surface area. (v) Idiosyncratic reactions.

Lastly, it is necessary to remember that adverse reaction to drug is not only dose depended rather idiosyncratic and two babies may behave differently receiving same antibiotics.

Significance of antibiotic transfer to infants:

Antibiotics can cause three potential problems in breastfeeding infants. These are (i) modification of gut flora and alteration of gut defense mechanism. (ii) direct effects to infants which may or may not be dose depended and (iii) alteration of microbial culture results in infants investigating for infection. On the basis of drug safety in breastfeeding infants, antibiotics can be categorized into three groups (Box-2).[8] Drugs of same class are expected to behave almost similarly in infants. But side effects of one drug may not similar to other agent of same group. As side effects of drug taking by lactating mother on infant are not reported always it does not indicate the drug is safe always. On the other hand, occurrence of side effects

in isolated case does not imply restriction of prescription of that drug in other case.

Cephalosporins are safe drugs in lactating mothers irrespective of generation and route of administration. But third generation cephalosporins has more chance of altering bowel flora. Macrolides are safe though they may change gut bacterial flora. Aminoglycosides are safe because though they are transferred to breast milk they are not absorbed through gastrointestinal tract (GIT) of infants.[8] Sulphonamides are excreted into breast milk but are not risk factor for term neonates. But this should be avoided in sick, preterm or jaundiced infants or in infants with glucose-6-phosphate deficiency. American Academy of Pediatrics recommends this drug in lactating mothers.[14] Trimethoprim along with sulphonamide is also recommended in lactating mothers.[8] Ciprofluxacin is excreated in breast milk but the amount of exposure in infant is low. Although manufacturer and some authorities advise against ciprofloxacin use in lactating mother, clinical data shows no remarkable evidence of arthopathy in neonate and children with systemic use of this drug in them. Therefore, interruption of breastfeeding during treatment of mother with ciprofloxacin is unnecessary.[15] Transfer of Tetracyclines into breast milk is low but they are usually avoided due to the possibility of adverse bone growth or dental staining[16].Penicillin is considered compatible with breastfeeding although there is a theoretical risk of alteration to gut flora and allergic sensitization.[16] Metronidazole is excreated in milk at concentrations which causes no serious reactions in the infants. The drug may be safely administered to mothers at oral conventional dose of 400 mg thrice daily.[16] It is better to avoid Metronidazole in single high dose in lactating mother.[8] Clindamycin given to lactating mothers does not show any side effects to their infants. But as this drug passes to the breast milk in a concentration of 0.7 to 3.8 µg/ml and which may cause toxic effects it is may be advisable to use alternative drug to lactating mother.[17] Though study on Meropenem in this respect is not sufficient, the drug appears acceptable to use during breast- feeding.[18] Americam Academy of Pediatrics categorizes antitubercular drugs as compatible with breast feeding. However, Isoniazid (INH) interferers nucleic acid metabolism and can be hepatotoxic.[8] Evidence of INH side effects in infants might be remembered during its treatment. Streptomycin is not ototoxicity in this case as the drug is poorly absorbed through gut mucosa. Few data is available on other first line antitubercular drugs but are compatible with breast feeding.[8] A standard short course regimen with first line drugs is recommended therapy in lactating mother.[19]

Transfer of acyclovir through breast milk is significant but absorption through infant gut wall is poor.[8] No harmful effects is seen in breast fed neonate whose mother takes even large dose of acyclovir.[20] Highly active antiretroviral therapy (HAART) during breast feeding is a strategy to reduce breast milk HIV transmission. This reduces plasma and breast milk HIV concentration and provides prophylaxis to the infant through ingestion of antiretrovirals in breast milk.[21] There is paucity of data on use of Ganciclovir on lactating mother. But the manufacturer recommends not using this drug on lactating mother due to risk of toxicity in neonate.[22]

Griseofulvin is tumorigenic and should be avoided. Fluconazole is safe for neonate. Ketoconazole and itraconazole are absorbed poorly in milk but better to avoid during lactation. There is no long term effect of terbinafine administration in mother on infants. The dosage in lactating mother is similar to nonpregnant women.[23] Limited information is available on antimalarias on lactating mother, but most of the first-line drugs are safe to breastfed infant. Primaquine can't be given to lactating mother if G6PD status of infant is not known.[24,25] There is scarcity of data on effects of anhelminthics on breastfed infant. Transfer of Mebendazole and Pyrantal pamoate to breast milk is not clear (Box-3); but the drugs may be safe because of poor absorption from gastrointestinal tract.[26] However, Mebendazole may decrease milk flow in some lactating mother.[8]

Box-2: **Antibacterial antibiotics and breast feeding**	
A. Safe for administration:	Aminoglycosides, Amoxycillin, Amoxycillin-clavulanate, Antituberculer drugs, Cephalosporins, Macrolides, Trimethoprim-sulphamethoxazole.
B:Effects not known/to be used with caution	Chloramphenicol, Clindamycin, Dapsone, Mandelic acid, Metronidazole (Low dose), Nalidixic acid, Nitrofurantoin, Penicillins, Tetracyclines.
C.Not recommended:	Metronidazole (Single high dose), Quinolones (as first-line).

Box-3: **Other antibiotics and breast feeding**	
A.Antiviral:	• Compatible with breast feeding: Acyclovir, Amantadine, Valacyclovir. • Effects during breast feeding are not known: Antiretrovirals, Famciclovir, Foscarnet, Ganciclovir.
B:Antifungal:	• Compatible with breast feeding: Ketoconazole. • Effects during breast feeding are not known: Amphotericin, Fluconazole, Flucytosine, Itraconazole.
C:Antimalarial:	• Compatible with breast feeding: Chloroquine, Hydroxychloroquine, Quinine. Artemether, Lumefantrine, Artesunate. • Effects during breast feeding are not known: Mefloquine, Pentamidine, Proguanil, Primaquine, Pyrimethamine.
D:Antihelminthic:	• Effects during breast feeding are not known: Mebendazole, Pyrantel Pamoate, Praziquantel, Quinacrine Antihelminth, Thiabendazole, Piperazine.

Minimization risk of antibiotics:

Risk of maternal antibiotics in breastfeed infant can be minimized through proper knowledge on antibiotics and its judicious application. This can be achieved through (i) awareness of unwanted effects of maternal antibiotics (ii) judicious use of antibiotics to lactating mother (iii) limiting absorption of antibiotics into neonate and (iv) monitoring of nursing baby (Box- 4).

Box-4: **Minimizing exposure of infants to undesirable maternal antibiotic effects**	
A. Strategy 1:	• Judicious prescription of antibiotics to lactating mothers: I. Is antibiotic necessary? II. If yes, does it have to be administered systematically? III. Weigh likely benefits and risks. IV. Discuss benefits and risks with mother/ parents.
B. Strategy 2:	• Decreasing transfer of antibiotics to breast milk: I. Prescription of antibiotics that have poor oral bioavailability. II. Use of topical/ local antibiotics where feasible. III. Preferential prescription of antibiotics with rapid clearance from plasma. IV. Feeding the baby immediately before antibiotic dose.

	V. Dose modification of maternal antibiotic. VI. Spoon feeding at time of peak plasma concentration of antibiotic. VII. Omission of breast feeding is a last theoretical resort.
C. Strategy 3:	• Monitoring the infant: I. Watching untoward/ unexpected/unexplained effects. II. Finding association of such effects to maternal antibiotics. III. Monitoring of serum levels.

CONCLUSION:

There are enormous benefits of breast feeding on neonate. Pediatricians and Neonatologists do not prescribe drugs to mother; but their opinion might be sought by Obstetricians and others. Emphasis on safety of breast feed infant is to be given during prescribing a drug on lactating mother. Generally, everyone including lactating mother has to avoid antibiotics. Prescription of antibiotics if unavoidable should reasonably be safer. Either the drug should not excrete through breast milk or should excrete in very minimum amounts. Absorption of prescribed antibiotics through infant GIT should be minimum or none. The drug which does not show unwanted effects to breastfed infant is better to chose. It is possible to minimize such effects of antibiotics to infant when is used to lactating mother. Selection of safe and right antibiotic in right dose schedule, alternative route through awareness is necessary. Talking of physician with mother in this vital issue before taking antibiotics is essential. Development of a policy by professional bodies involving government along with time to time circulation may play a pivotal role in antibiotic use on lactating mother.

REFERENCES:

1. Sankar MJ, Sinha B, Chowdhury R, Bhandari N, Taneja S, Martines J et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. Acta Pædiatrica 2015; 104: 3–13
2. Khan J, Vesel L, Bahl R, Martines JC. Timing of breast feeding initiation and exclusivity of breast feeding during the first month of life: effects on neonatal mortality and morbidity–a systematic review and meta-analysis. Matern Child Health J 2015; 19:468–79.
3. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, Bellagio Child Survival Study G. How many child deaths canwe prevent this year? Lancet 2003; 362: 65–71
4. Olesen C, Steffensen FH, Nielsen GL, De JDBL, Olsen J, Sorensen HT. Drug use in first pregnancy and lactation: a population based survey among Danish women. The EUROMAP group. Eur J Clin Pharmacol1999; 55: 139-44.
5. Uppal R, Karmakar S, Singh MM, Dhall GI, Gupta I, Sharma PL. Prescription drug use in lactating mothers: an experience at a referral hospital and in a community in India. Int J Clin Pharmacol Ther Toxicol 1993: 31: 93-‘5.
6. Hoppu K, Kettunen K, Remes R. maternal drug treatment and human milk banking. Int J Clin Pharmacol Ther 1994; 32: 488-90.
7. Chin KG, Mactal- HC, McPherson CE. Use of ant-infective agents during lactation: Part-1 beta lactum antibiotics, vancomycin, quinupristan- dalfopristin and linezolid. J Hum Lact 200; 16: 351-8.
8. Mathew JL. Effect of maternal antibiotics on breast feeding infants. *Postgrad Med J* 2004; 80: 196-200.
9. Auerbach KG. Breast feeding and maternal medication use. JOGNN 1999; 28:554-63.
10. Roberto GC and Joel AL. Breast feeding and maternal medications. J Pediatr (Rio J) 2004; 80(suppl):S189-S198.
11. Chung AM, Reed MD, Blumer JL. Antibiotic and breast feeding: a critical review of the literature. Pediatr Drugs 2002; 4:817-37.
12. Howard CR, Lawrence RA. Drugs and breast feeding. Clin Perinatol.1999; 26:447-78.
13. Hale TW. Drug therapy and breast feeding; pharmacokinetics, risk factors, and effects on milk production. Neoreviews 2004; 5: e164.

14. Committee on drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 1994; 93:137-50.
15. Kaplan YC and Koren G. Use of Ciprofluxacin during breastfeeding. Canadian Family Physician 2015; 61:344.
16. Gardiner S. Drug safety in lactation. Prescriber Update 2001; 21:10-23
17. Mann CF. Clindamycin and breast-feeding. Pediatrics 1980; 66:1030.
18. Suberan JB, Bradley JS, Blumer J, Stellwagen LM. Transmission of Meropenem in breast milk. Pediatr Infect Dis J 2012; 31(8):832-4.
19. Divison of child health and development. Update. Breast feeding and maternal tuberculosis. World Health Organization1998; 23
20. Taddio A, Klein J, Koren G. Acyclovir excretion in human breast milk. Ann Pharmacother 1994; 28:585-7.
21. Wilfert CM, and Fowler MG. Balancing maternal and infant benefits and the consequences of breast feeding in the developing world during the era of HIV infection. J of Infect. Dis 2007; 195:165-167.
22. Drug and lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006. Ganciclovir. [Updated 2018 Dec 3, Updated Octo 31].
23. Prabhu SS, Sankineni P. Managing dermatophytoses in pregnancy, lactation and children. Clinical dermatology review2017; 1(3):34-37
24. Saito M, Gilder ME, McGready R, Nosten F. Antimalarial drugs for treating and preventing malaria in pregnant and lactating women. Expert openion on drug saifety 2018; 17(11):1129-44.
25. Olumese P. Updating the WHO guidelines for the treatment of malaria. Malaria policy advisory committee. WHO, 2014; 1-4.
26. Gardiner S. Drug safety in lactation. Prescriber Update 2001; 21:10-23.

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