Antibiotics and lactation: An overview of relative infant doses and a systematic assessment of clinical studies

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Abstract

Breastfeeding is important for the development of the child. Many antibiotics are considered safe during breastfeeding. The aim of the study was to assess the quality of lactation studies with antibiotics using the FDA and International Lactation Consultant Association (ILCA) quality guidelines for lactation studies. The secondary goal was to determine the exposure of the breastfed infant to antibiotics in relation to bacterial resistance and the developing microbiome.

A literature search was performed and the included studies were scored on methodology, parameters concerning maternal exposure to antibiotics, maternal plasma and milk sampling. The infant exposure has been calculated and expressed as a percentage of a normal infant therapeutic dose.

Sixty-six studies were included in 5 antibiotic groups (broad-spectrum penicillin, cephalosporins, macrolides and lincosamides, quinolones and sulfonamides). Cephalosporins were the most studied group of antibiotics (n=21). Fifteen studies met all...
the criteria of ‘mother exposure to antibiotic’. Six studies met every criterion related to ‘plasma sampling’. Only one case-report met all listed criteria for lactation studies. The correct calculation of infant exposure to antibiotics via the milk:plasma ratio (AUC) varies between 13% for macrolides and 38% for broad-spectrum penicillin. The highest assessed exposure as a percentage of infant therapeutic dose was for metronidazole (11%).

The studies meet to a limited extent with the quality standards for lactation research. The breastfed infants are exposed to a sub-therapeutic concentration of antibiotics.

**Keywords:** Infancy • Antibiotics • Breastfeeding • Microbiome

**Introduction**

Breastfeeding has numerous advantages over infant formula milk for the development of the neonate and decreases health risks of the nursing mother. Breastfeeding protects the neonate against child infections and malocclusions, increased intelligence at later age and protects against overweight and diabetes. For the mother, breastfeeding protects against breast cancer, ovarian cancer and type II diabetes (1).

The World Health Organization recommends breastfeeding exclusively during the first six months and as a supplement up to 2 years. This is due to the earlier mentioned benefits and the low costs for the developing world. In the United States, 75% of mothers breastfeed their infants in the early post-partum period and 36% are exclusively breastfeeding at 3 months (2). One of the concerns in the lactation period is the safety of drugs being used by mothers, because transfer of the drug over the mammary gland may lead to side effects in the suckling infant.

Antibiotics are probably among the most prescribed drugs during lactation. The prevalence of mastitis treated with antibiotics in lactating women is estimated between 16 and 49% (3,4). Most antibiotics are considered to be safe during breastfeeding, except quinolones, chloramphenicol, aminoglycosides during early postnatal period and possibly metronidazole (5,6).

Nowadays, resistance to antibiotic drugs forms a great problem. Studies in both humans and animals show that low-dose exposure or inadequate exposure time to antibiotics correlates to the development of resistant microbes (7-9). Therefore, (long-term) sub-therapeutic transmission of antibiotics via breast milk to the infant could possibly contribute to antibiotic resistance in the infant. However, no data establishing this relation could be found. Furthermore, recent research shows that the neonatal microbiome is affected by intrapartum...
antibiotics (10-13) and maternal use of antibiotics in the lactation period (14). In turn, the microbiome may affect brain development, behaviour and obesity (15-17).

To assess the safety of antibiotics in the light of the developing microbiome, it is of paramount importance to know the amount of antibiotics transferred into breast milk which reaches the neonatal gastrointestinal tract. The most important parameter for the exposure of an infant to maternal use of antibiotics is the Absolut Infant Dose (AID) of which the formula is described in fig. 1. By calculating the AID, the infant dose per kilogram per day is known. Furthermore, the AID can be compared with the therapeutic infant dose.

**Objective and rationale**

In this study we aimed, using guidelines of the FDA (18) and ILCA (19), to determine the quality of lactation studies that investigated antibiotics in breast milk and examined the data regarding absolute infant dose.

**Search methods**

**Antibiotics**

A literature search was performed using the PubMed database using the following search strings: (Milk, Human[MeSH Terms] OR Breast Milk[Title/Abstract] OR Human Milk[Title/Abstract]) or Lactation AND (a specific antibiotic drug (table 2)). See appendix 1 for detailed search strings. Cross references were searched for additional studies. An additional search was performed using the LactMed® database. Antibiotics were categorized in 17 groups based on their chemical and physical properties (table 2).

**Inclusion and exclusion criteria**

Only articles containing primary data in humans published from 1970 until March 2017 were included in this study. We excluded studies of languages other than English, German and Dutch. Studies without reported drug concentrations in the mother’s plasma or mother’s milk were also excluded.

**Guidelines**

The FDA (18) and ILCA (19) draft guidelines were used to review the quality of the included articles. These guidelines provide recommendations on how to conduct clinical lactation studies. In more detail, information is given about the recommended study design and the data analysis that is favoured. In this MiniReview, the recommendations of the FDA and ILCA were combined to create a checklist (table 1). Due to the limited amount of studies available per antibiotic, solely the results of antibiotic groups containing a minimum of 5 papers are presented in this study (fig. 3).
**Absolute infant dose**

We determined the AIDs that are known for each group of antibiotics, by using the reported values or by calculating using the formula provided in fig. 1, using 150ml/kg/day as a standard for daily milk intake (20). We used a mean value for the AID for two published reports and a median value for three or more reports. The AID as a percentage of the Therapeutic Infant Dose (mg/kg/day) was calculated using the pediatric drug formulary of the Netherlands (21).

**Outcomes**

Using the search strings, we found 229 articles in the LactMed database and 808 articles in PubMed. In total, 174 articles and 797 articles were excluded in LactMed and PubMed, respectively. Reasons for exclusion were different language (n=127), no concentrations (n=254), review (n=169), animal study (n=258), paper published before 1970 (n=38), already in LactMed database (n=76) and duplicates (n=49) (fig. 2). We found no studies that met the inclusion criteria for the antibiotics of the groups ‘Trimethoprim and similar compounds’ and ‘Polymixins’ (table 2). In total, 66 studies were assessed using the checklist based on FDA (18) and ILCA (19,22) guidelines (table 1). For five antibiotic groups, only 1 study (23-27) was included and for three antibiotic groups, 2 studies (28-31) were included. The results of the quality determination of the different parameters (table 1) of 6 antibiotic groups with at least 5 studies are shown in fig. 3A-D.

The parameters (table 1) that most frequently met the quality criteria set by combining the FDA and ILCA guidelines are the reported daily dose and dose regimen, see fig. 3A. Shortcomings of most studies were the absence of whole milk portions, see fig. 3B.

Fifteen studies (23,27,29,32-43) met all the criteria of ‘mother exposure to drug’; this includes the presence of the administered daily dose and dose regimen, the analysis of concentrations during steady state and the use of longitudinal data (table 1). In only one case-report study with cephalexin (32), the breast milk sampling met all listed criteria. In six of the 66 assessed studies (37,38,42,44-46), every criterion related to ‘plasma sampling’ (table 1) was present. Only one study with cephalexin (32) met all the criteria of ‘method / data analysis’, including M:P, RID and AID are correctly measured and a validated method of analysis is used. Infant’s plasma concentrations or the occurrence of adverse reactions in the breastfeeding infant were only addressed in 10 of the 66 assessed studies (23,31,32,42,45,47-51).

Next to the quality determination, we also assessed the potential infant risk based on the Absolute Infant Dose (AID) for different antibiotic drugs (fig. 4A). The highest AID corresponded to sulfapyridin (median AID: 2.68 mg/kg/day (N=4)) (37,45,52,53). The infant risk as a percentage of the daily therapeutic infant dose (fig. 4B) was the highest for metronidazole (11% based on a median AID: 1.59 mg/kg/day (N=4)) (42,43,54,55).
Wider implications

Of all assessed antibiotic groups, cephalosporins was the most documented group, with 21 different studies, including 226 patients (table 2). The data on the quality determination (fig. 3) also reveal a prominent place for cephalosporins in relation to the validation criteria (table 1). This could be related to the fact that cephalosporins are frequently used antibiotics in hospitals and especially in gynaecological care departments (56-58), with attendance of nursing mothers. Most other antibiotics are poorly studied like broad-spectrum penicillins (8 studies, 78 patients), sulfonamides (5 studies, 27 patients) macrolides and lincosamides (8 studies, 67 patients) and quinolones (7 studies, 59 patients).

Many studies lack information about the sample size, method of collection (electric pump or ‘normal’) and whether foremilk or hindmilk was sampled. Without a standardized method of collection, it is hard to compare studies examining transfer of drugs into breast milk. A differentiation between foremilk and hindmilk collection is necessary, which was only performed in 6 studies (30,32,41,59-61). Hindmilk is more lipophilic than foremilk; therefore, lipophilic antibiotics like quinolones, macrolides and tetracyclines will probably penetrate more easily into hindmilk (62-64). This might result in an under- or over-estimation of antibiotic concentrations in breast milk.

Calculated parameters related to drug transfer into breast milk (M:P ratio, AID, RID) are poorly studied in the assessed lactation studies. The correct measurement of the M:P ratio varies between 13% of the studies for macrolides and lincosamides and 38% of the studies for broad-spectrum penicillin. The M:P ratio is often calculated as single point milk:plasma concentrations, where whole “area under the curve” of the milk/plasma curve is by far more accurate. However, the clinical implication of the M:P ratio is over-estimated because a low absolute dose with a high M:P ratio means that still a small amount of a particular drug can be found in the milk. The poor establishment of drug transport over the mammary gland may be related to the absence of measurements in steady-state conditions and concurrent sampling of plasma and milk in many studies.

In order to assess the infant risk to different antibiotics, when transferred into breast milk, we presented, or when necessary, calculated the Absolut Infant Dose (AID). The highest exposure in breast milk was found for sulfapyridin (2.68 mg/kg/day) based on an average milk intake of 150ml/kg/day. This sulfonamide seems compatible with breastfeeding, when the infant shows no signs of illness, stress or jaundices (5,65,66). However, based on primarily the AID, it is hard to review the risk for the infant. Therefore, we calculated the AID as a percentage of the daily therapeutic dose. The AID in perspective of the therapeutic infant dose for metronidazole (11% of therapeutic dose), ofloxacin (2% of therapeutic dose) and gentamycin (2% of therapeutic dose) (fig. 4B), would relate to the highest risk for the breastfeeding infant. For metronidazole, which is indicated for anaerobic infections, especially for prophylaxis following caesarian section and post-partum infection control (67-69), no breastfeeding is advised upon 12-24 hr after the last metronidazole dose (66). However, only one case-report describes infant diarrhoea after breast milk consumption of a mother exposed to metronidazole (70). Based on these percentages alone, it is hard to predict any infant side effects. Therefore, we would like to emphasize that like for most
drugs, minimalizing infant exposure also applies for maternal use of antibiotics and monitoring for possible adverse reactions is needed. However, only in 6 studies adverse reactions were documented using standardized methods (23,31,32,42,47,49). General concerns of maternal use of antibiotics for the infant are in potential for allergic reaction, changes in bowel flora, and confounding of culture results by the ingested antibiotic if a fever work-up is performed for the infant.

Specific for ampicillin, diarrhoea and candidiasis have been reported in nursing infants. Moxalactam, a third-generation cephalosporin, may lead to colonization of infant’s bowel with gram-positive organisms is possible, resulting in a risk for enterocolitis. (71)

Diarrhoea, irritability and pyloric stenosis have been reported for erythromycin in nursing infants. Perforated pseudomembranous colitis was reported in a breastfed infant whose mother used ciprofloxacin. For sulfasalazine, there is a risk of bilirubin displacing, and bloody diarrhoea has been reported in the nursing infant of a mother who was a slow acetylator. For chloramphenicol, refusal of the breast, somnolence during feeding, gas and post-feeding emesis have been reported in nursing infants. For metronidazole loose stools, feeding problems, and candidiasis have been reported in nursing infants. (65)

The use of maternal antibiotics could also play a role in bacterial resistance and modification of the infant microbiome. As mentioned earlier, sub-therapeutic dosing of antibiotics is associated with the development of resistant microorganisms (7-9). Based on our results, all assessed antibiotics (fig. 4B) are transferred into breast milk in sub-therapeutic levels ranging from 0.05% for cefotaxime to 10.61% for metronidazole of the therapeutic infant dose. This low-dose exposure might induce antibiotic resistance in the infant and might lead to a reduced diversity of intestinal microbiota during infancy and the occurrence of allergies later in life (72-74), and contribute to the development of infant diseases, even later in life, like disturbances in brain development, immunity, behaviour and obesity (15-17,75,76). Also, the infant colonization rate of microorganisms is affected by maternal use of antibiotics in the lactation period (77), which is one of the first signs of altered gut microbiota composition. The safety of maternal use of antibiotics in relation to the infant’s microbiome and its effects later in life should be further studied.

Conclusion

This MiniReview assessed the quality of lactation studies according to FDA and ILCA guidelines, and most studies did not comply with these guidelines. Especially, the study methodology was poorly described. We found that antibiotics like metronidazole with a relatively high AID of 11% of the therapeutic infant dose, is suspected of antibiotic resistance and microbiome alterations in the suckling infant. However, further research on these effects in breastfeeding infants is needed. In the meantime, the benefits of maternal antibiotic therapy should be weighed against the potential (long-term) risk for the breastfeeding infant.

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References


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Figure 1. Formulas for the calculation of M:P, AID and RID, according to the ILCA guidelines. In this study, the AID calculation is based on a C\textsubscript{milk} of 150ml/kg/day (20).
Figure 2. Flowchart of included and excluded studies using PubMed and LactMed as database.
Figure 3. Quality determination of the lactation studies of different antibiotic groups.

For different parameters based on FDA (18) and ILCA (19) guidelines, the percentage of correctly performed studies is presented. Studies are scored based on parameters related to drug exposure of the mother (A), plasma sampling parameters (B), milk sampling parameters (C) and method/analytic parameters (D) (see table 1)
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Figure 4. Absolute Infant Dose for different antibiotic drugs.

Presented is the Absolute Infant Dose (mg/kg/day) for 57 different antibiotic drugs, when a daily infant milk intake of 150ml/kg/day is used (20). (A) and Absolute Infant Dose as a percentage of the Therapeutic Infant Dose (mg/kg/day) for 20 different antibiotic drugs (B). A mean AID based on data from 2 different studies was calculated for Tetracycline, Chloramphenicol, Ceftriaxone, Ciprofloxacin and Tinidazole. A median AID based on data from 3 different studies was calculated for Cefotaxime, Cephalexin, Clindamycin, Azithromycin, Metronidazole, and Nitrofurantoin. A median AID based on data from 4 different studies was calculated for Sulfapyridine, Cefoxitin and Ampicillin.
**Table 1.** Checklist for the quality of lactation studies involving antibiotic use, based on the ILCA (19) and FDA (18) guidelines.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>No FDA and ILCA recommendations</td>
</tr>
<tr>
<td>Full article</td>
<td>No FDA and ILCA recommendations</td>
</tr>
<tr>
<td><strong>Mother exposure to drug</strong></td>
<td></td>
</tr>
<tr>
<td>Daily dose given</td>
<td>Daily dose exposure to the mother is known</td>
</tr>
<tr>
<td>Dose regimen given</td>
<td>Dose regimen is known</td>
</tr>
<tr>
<td>Steady state</td>
<td>Rate of drug absorption is equal to rate of drug elimination</td>
</tr>
<tr>
<td>Longitudinal data</td>
<td>Samples are obtained between two postpartum periods in individual woman for drugs that are administered chronically in several treatment cycles</td>
</tr>
<tr>
<td><strong>Breast milk sampling</strong></td>
<td></td>
</tr>
<tr>
<td>Time compared to drug intake known</td>
<td>Time between administration of the drug and sampling is known</td>
</tr>
<tr>
<td>Multiple measures in dose interval</td>
<td>Minimum 5 samples are taken more than one hour from each other</td>
</tr>
<tr>
<td>Full method of collection given</td>
<td>Method including; how milk is withdrawn (manual or electric), sample volume, milk type (pre- or postfeeding)</td>
</tr>
<tr>
<td>Representative for for and hind milk</td>
<td>Samples are taken from for and hindmilk</td>
</tr>
<tr>
<td>Both breast</td>
<td>Both breast are sampled</td>
</tr>
<tr>
<td><strong>Plasma sampling</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma levels measured</td>
<td>Mothers plasma level of the drug is known</td>
</tr>
<tr>
<td>Sampled concomitted with milk</td>
<td>Plasma is simultaneously sampled with breast milk</td>
</tr>
<tr>
<td>Multiple measures in dose interval</td>
<td>Minimum 5 samples are taken more than one hour from each other</td>
</tr>
</tbody>
</table>
Metabolites taken into account: Drug metabolites are analysed

**Method / Data analysis**

M:P correctly measured: The antibiotic concentration in breast milk divided by the antibiotic concentration in mother’s plasma (fig. 1)

RID and AID correctly measured:
- AID: the absolute amount of antibiotic consumed by the infant per kilogram per day (fig. 1)
- RID: infant drug exposure as a percentage of the maternal dose normalized by the maternal and infant weight (fig. 1)

Method analysis given, validated: Method of sample analysis is given and a validated method is used.

**Child observation**

Plasma level known in child: Drug plasma levels of the infant are known

Behaviour monitored in child: Behaviour of the infant is assessed by a validated method
### Registered and unregistered antibiotics categorized by group (antibiotic group name in bold)

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>Betalactamase Susceptible</th>
<th>Betalactamase Resistant</th>
<th>Macrolides and Lincosamides</th>
<th>Aminoglycosides</th>
<th>Glycopeptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclins</td>
<td>Sulfaflazine</td>
<td>Telithromycin</td>
<td>Cefpodoxime</td>
<td>Norfloxacin</td>
<td>Muriplacin</td>
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<tr>
<td>Demeclocycline</td>
<td>Penicillins</td>
<td>Clindamycin (28,59,78)</td>
<td>Cefacetrile</td>
<td>Lomefloxacin</td>
<td>Tedizolid</td>
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<tr>
<td>Doxycycline (30)</td>
<td>BENZYL Penicillin (28)</td>
<td>Lincomycin</td>
<td>Ceftazidime (28)</td>
<td>Fleroxacin (46)</td>
<td>Nifurtimol</td>
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<td>Phenoxy methyl penicillin (31)</td>
<td>Sulfamoxole</td>
<td>Cephalexins</td>
<td>Ceftazoline</td>
<td>Sparfloxacin</td>
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<td>Propicillin</td>
<td>Cefalotin (79)</td>
<td>Cepiprome</td>
<td>Rufloxacin</td>
<td>Xibornol</td>
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<td>Metacycline</td>
<td>Penemecillin</td>
<td>Cefadroxil (28,79)</td>
<td>Cefapirine (79)</td>
<td>Gatifloxacin</td>
<td>Daptomycin (85)</td>
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<tr>
<td>Oxytetracycline</td>
<td>Clometocillin</td>
<td>Cefotaxime (28,79,86,87)</td>
<td>Cefradine (88)</td>
<td>Prulifloxacin</td>
<td>Fidaxomycin</td>
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<td>Tetracycline (28,30)</td>
<td>BENZYL Penicillin benzathin</td>
<td>Sulfamethox Diazine</td>
<td>Cefuroxime</td>
<td>Trofloxacin</td>
<td>Methenamine (61)</td>
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<td>Sulfamethoxy Pyridazine</td>
<td>Cefamandol</td>
<td>Moxifloxacin</td>
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<td>Ceftibuten (89)</td>
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<td>Amphenicolos</td>
<td>Cloxacillin</td>
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<td>Ceﬁdinir</td>
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<td>Rosoxacin</td>
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**Table 2.** List of included antibiotics in this MiniReview. References of the included antibiotics are presented in brackets. No studies were included for the antibiotics without references.

<table>
<thead>
<tr>
<th>Antibiotics</th>
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<td>HETACILLIN</td>
<td>SULFAMETHIZOL</td>
<td>FLURITHROMYCIN</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CEPHALORDINE (28)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>TEMAFLOXACIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TINIDAZOLE (60,105)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Appendix 1 – detailed search parameters


TETRACYCLINES
(DEMECLOCYCLIN* OR DOXYCYCLIN* OR CHLORTETRACYCLIN* OR LYMECYCLIN* OR METACYCLIN* OR OXYTETRACYCLIN* TETRACYCLIN* OR MINOCYCLIN* OR ROLITETRACYCLIN* OR PENIMECYCLIN* OR CLOMOCYCLIN* TIGECYCLIN*)

AMPHENICOLEs
(CHLORAMPHENICOL* OR THIAMPHENICOL*)

BROAD SPECTRUM PENICILLIN
(AMPICILLIN* OR PIVAMPICILLIN* OR CARBENICILLIN* OR AMOXICILLIN* OR CARINDACILLIN* OR BACAMPICILLIN* OR EPICILLIN* OR PIVMECILLINAM* OR AZLOCCILLIN* OR MEZLOCILLIN* OR MECILLINAM* OR PIPERACILLIN* OR TICARCCILLIN* OR METAMPICILLIN* OR TALAMPICILLIN* OR SULBENICILLIN* OR TEMOCILLIN* OR HETACILLIN*)

BETA-LACTAMASE-SENSITIVE PENICILLIN
(BENZYLPCILLIN* OR FENOXYMETHYLPENICILLIN* OR PHENOXYMETHYLPCILLIN* OR PROPICILLIN* OR AZIDOCILLIN* OR FENETICILLIN* OR PENEMECILLIN* OR CLOMETOCILLIN* OR BENZYLPCILLINEBENZATHIN* OR (PENICILLIN* V) OR (PENICILLIN* G))

BETA-LACTAMASE-RESENT PENICILLIN
(DICLOXACILLIN* OR CLOXACILLIN* OR METICILLIN* OR OXACILLIN* OR FLUCLOXACILLIN* OR FLOXACILLIN*)

BETA-LACTAMASE-INHIBITORS
(SULBACTAM OR TAZOBACTAM)

CEFALOSPORINS
(CEFALEXIN* OR CEFALORIDIN* OR CEFALOTIN* OR CEFAZOLIN* OR CEFOXITIN* OR CEFUROXIM* OR CEFAMANDOL* OR CEFACLOR* OR CEFADROXIL* OR CEFOTAXIM* OR
CEFTAZIDIM* OR CEFSULODIN* OR CEFTRIAXON* OR CEFOFETAN* OR CEFAZEDON* OR CEFMENOXIM* OR CEFONICID* OR LATAMOXEF* OR MOXALACTAM OR CEFOTIAM* OR CEFATRIZIN* OR CEFIXIM* OR CEFEPIM* OR CEFETAMET* OR CEFPIRAMID* OR CEFAPIRIN* OR CEFRADIN* OR CEFOPERAZON* OR CEFPODOXIM* OR CEFACETRIL* OR CEFROXADIN* OR CEFTEZOL* OR CEFPIROM* OR LORACARBEF* OR CEFTIBUTEN OR CEFDINIR* OR CEFMETAZOL* OR CEFPROZIL* OR CEFORANID* OR CEFTIZOXIM* OR CEFDITOREN* OR CEFTAROLIN* OR CEFTOLOZAN*)

MONOBACTAM-ANTIBIOTICS
(AZTREONAM)

CARBAPENES
(MEROPENEM OR ERTAPENEM OR DORIPENEM OR IMIPENEM)

TRIMETHOPRIM AND DERIVATIVES
(TRIMETHOPRIM OR BRODIMOPRIM)

SULFONAMIDES
(SULFISOMIDIN* OR SULFAMETHIZOL* OR SULFADIMIDIN* OR SULFAPYRIDIN* OR SULFAFURAZOL* OR SULFANILAMID* OR SULFATHIAZOL* OR SULFAMETHOXAZOL* OR SULFADIAZIN* OR SULFAMOXOL* OR SULFADIMETHOXIN* OR SULFALEEN OR SULFAMETOMIDIN* OR SULFAMETHOXYDIAZIN* OR SULFAMETHOXYPYRIDAZIN* OR SULFAPERIN* OR SULFAMERAZIN* OR SULFAPYRIDAZIN* OR SULFAMETHOSULFONATE* OR SULFAGUANIDINE* OR SULFAMETHOXAZOL* OR SULFAMETROXAZOL* OR SULFAMETHOXYPRIDAZIN*)

MACROLIDE ANTIBIOTICS AND LINCOSAMIDE
(ERYTHROMYCIN* OR SPIRAMYCIN* OR MIDECAMYCIN* OR PRISTINAMYCIN* OR OLEANDOMYCIN* OR ROXITHROMYCIN* OR JOSAMYCIN* OR TROLEANDOMYCIN* OR CLARITHROMYCIN* OR AZITHROMYCIN* OR MIOCAMYCIN* OR ROKITAMYCIN* OR DIRITHROMYCIN* OR FLURITHROMYCIN* OR TELITHROMYCIN* OR CLINDAMYCIN* OR LINCOMYCIN*)

AMINOLYCOSIDES
(STREPTOMYCIN* OR STREPTODUOCIN* OR TOBRAMYCIN* OR GENTAMICIN* OR KANAMYCIN* OR NEOMYCIN* OR AMIKACIN* OR NETILMICIN* OR SISOMICIN* OR DIBEKACIN* OR RIBOSTAMYCIN* OR ISEPAMICIN* OR FRAMYCETIN* OR PAROMOMYCIN* OR STREPTOZOCIN*)

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QUINOLONES

(OFLOXACIN* OR CIPROFLOXACIN* OR PEFLOXACIN* OR ENOXACIN* OR TEMAFLOXACIN*
OR NORFLOXACIN* OR LOMEFLOXACIN* OR FLEROXACIN* OR SPARFLOXACIN* OR
RUFLOXACIN* OR GREPAFLOXACIN* OR LEVOFLOXACIN* OR TROVAFLOXACIN* OR
MOXIFLOXACIN* OR GEMIFLOXACIN* OR GATIFLOXACIN* OR PRULIFLOXACIN* OR
PAZUFLOXACIN* OR GARENOXACIN* OR ROSOXACIN* OR NALIDIXIN* OR PIROMIDIN* OR
PIPEMIDIN* OR OXOLIN* OR CINOXACIN* OR FLUMEQUIN* OR PIPEMIDIC* OR NALIDIXIC* OR
PIROMIDIC*)

GLYCOPEPTIDES

(VANCOMYCIN* OR TEICOPLANIN* OR TELAVANCIN* OR DALBAVANCIN* OR ORITAVANCIN*)

POLYMYXINS

(COLISTIN* OR "POLYMYXIN B" OR BACTRACIN* OR GRAMICIDIN*)

ADDITIONAL ANTIBIOTICS

(METRONIDAZOL* OR TINIDAZOL* OR ORNIDAZOL* OR NITROFURANTOIN* OR NIFURTOINOL
OR FOSFOMYCIN* OR PHOSPHOMYCIN* OR XIBORNOI* OR CLOFOCTOL* OR
SPECTINOMYCIN* OR METHENAMIN* OR NITROXOLIN* OR LINEZOLID OR DAPTOMYCIN* OR
FIDAXOMICIN* OR MURIPOCIN* OR TEDIZOLID)

ANTITUBERCULOUS DRUGS

(AMINOSALICYL* OR CYCLOSERIN* OR RIFAMPICIN* OR RIFAMYCIN* OR RIFABUTIN* OR
RIFAPENTIN* OR RIFAXIMIN* OR CAPREOMYCIN* OR ISONIAZID* OR PROTIONAMID* OR
TIOCARLID* OR ETHIONAMID* OR PYRAZINAMID* OR ETHAMBUTOL OR TERIZIDON* OR
MORINAMID* OR BEDAQUILIN* OR DELAMANID)