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Antibiotics in Neonatal Infections
A Review

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Contents

Abstract

The bacteria most commonly responsible for early-onset (materno-fetal) infections in neonates are group B streptococci, enterococci, Enterobacteriaceae and *Listeria monocytogenes*. Coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, are the main pathogens in late-onset (nosocomial) infections, especially in high-risk patients such as those with very low birth-

weight, umbilical or central venous catheters or undergoing prolonged ventilation. The primary objective of the paediatrician is to identity all potential cases of bacterial disease quickly and begin antibacterial treatment immediately after the appropriate cultures have been obtained.

Combination therapy is recommended for initial empirical treatment in the neonate. In early-onset infections, an effective first-line empirical therapy is ampicillin plus an aminoglycoside (duration of treatment 10 days). An alternative is ampicillin plus a third-generation cephalosporin such as cefotaxime, a combination particularly useful in neonatal meningitis (mean duration of treatment 14 to 21 days), in patients at risk of nephrotoxicity and/or when therapeutic monitoring of aminoglycosides is not possible. Another potential substitute for the aminoglycoside is aztreonam. Triple combination therapy (such as amoxicillin plus cefotaxime and an aminoglycoside) could also be used for the first 2 to 3 days of life, followed by dual therapy after the microbiological results. In late-onset infections the combination oxacillin plus an aminoglycoside is widely recommended. However, vancomycin plus ceftazidime (± an aminoglycoside for the first 2 to 3 days) may be a better choice. Teicoplanin may be a substitute for vancomycin. However, the initial approach should always be modified by knowledge of the local bacterial epidemiology.

After the microbiological results, treatment should be switched to narrower spectrum agents if a specific organism has been identified, and should be discontinued if cultures are negative and the neonate is in good clinical condition.

Penicillins and third-generation cephalosporins are generally well tolerated in neonates. There is controversy regarding whether therapeutic drug monitoring of aminoglycosides will decrease toxicity (particularly renal damage) in neonates, and on the efficacy and safety of a single daily dose versus multiple daily doses of these drugs. Toxic effects caused by vancomycin are uncommon, but debate still exists over the need for therapeutic drug monitoring of this agent.

When antibacterials are used in neonates, accurate determination of dosage is required, particularly for compounds with a low therapeutic index and in patients with renal failure. Very low birthweight infants are also particularly prone to antibacterial-induced toxicity.

The incidence of neonatal sepsis ranges from 1 to 10 cases per 1000 live births worldwide.[1-3] Its mortality remains high, ranging from 20 to 30%, despite antibacterial treatment.[4] Very low birth weight (VLBW) infants are high-risk patients.[5] Bacterial infections in neonates are heterogeneous, because of their different chronology, epidemiology and pathophysiology. Early-onset infections are materno-fetal (congenital) and occur in the first 5 days of life from contaminated amniotic fluid or blood. In term neonates the predominant pathogens include group B streptococci, *Escherichia coli*, enterococci and *Listeria monocytogenes*. In preterm neonates, group B streptococci, *E. coli*, *Haemophilus influenzae* and Gram-negative bacilli account for 2 out of 3 of early onset infections.[6] Late-onset infections (nosocomial) occur in the first month of life, especially from contaminated hands.[2] Coagulase-negative staphylococci are the main pathogens, particularly *Staphylococcus epidermidis* in patients with umbilical or central venous catheters.[7-9] Gram-negative organisms such as *Pseudomonas* spp., *Klebsiella* spp. and *Serratia* spp. are also common pathogens. In VLBW infants the incidence of nosocomial bacterial septicemia is 17%, about 3 times the incidence of congenital septicaemia.[5] Group B streptococci, *E. coli* and *L. monocytogenes* were responsible for 94.5% of early-onset, and 89% of late-onset, cases of neonatal meningitis, respectively.[2]

Over the past decades, there have been several shifts in the predominant organisms responsible for neonatal septicaemia and meningitis.[10-12] Moreover, regional differences in the pathogens may be present.[13-14] Finally, several uncommon pathogens have also been described in neonates.[7,15]

Presently, combination therapy is recommended for initial empirical treatment of bacterial infections in neonates.[16] In some neonates, early discontinuation of antibacterial treatment just 24 hours after initiation is possible.[17] The aim of this article is to review the literature on antibacterials used to treat neonatal infections.

1. Penicillins

Penicillins are widely used in neonatal intensive care units (NICUs). These drugs are characterised by a common penamic nucleus linked with various side chains.

1.1 Penicillin

Penicillin is active against most pneumococci, streptococci and *L. monocytogenes*. *S. pneumoniae* and staphylococci are generally resistant.[18,19] The penetration of penicillin into the cerebrospinal fluid (CSF) is poor even when the meninges are inflamed.[20-22]

The half-life of aqueous benzylpenicillin (penicillin G) is about 2.5 hours, with the exception of VLBW infants during the first week of life, where the half-life is 5 hours.[23,24] The dosage of benzylpenicillin is presented in table I. Penicillin has been used in neonatal infections for many years and it is still used in association with an aminoglycoside against group B streptococci.[26] However, ampicillin is now preferred because it provides broader antimicrobial activity without sacrificing tolerability.

Retard penicillins (benzathine benzylpenicillin or procaine benzylpenicillin) are used for gonococcal infections or asymptomatic congenital syphilis.[27] In the latter, the dosage of procaine benzylpenicillin is 50 000 units once daily intramuscularly for 14 days. The use of benzathine benzylpenicillin is controversial for infants with congenital neurosyphilis.[25,28-30]

Table I. Regimens for benzylpenicillin (penicillin G) in neonatal infections[4,23,25]

Indication	Route	Dosage (IU/kg/day)
Bacteraemia	IV, IM	25 000-50 000 (200 000 for GBHS)
Meningitis	IV, IM	75 000-100 000 (400 000 for GBHS)
Congenital syphilis	IV, IM	50 000[a]
Age	**Bodyweight (g)**	**Administration interval (h)**
<1 week	<2000	12
	>2000	8
>1 week	<2000	8
	>2000	6

a Aqueous benzylpenicillin.

GBHS = group B haemolytic streptococci; **IM** = intramuscular; **IV** = intravenous.

Allergy, diarrhoea, *Candida* superinfection, haemolytic anaemia, haematuria and interstitial nephritis are possible adverse effects of penicillin.[4,30] Seizures may occur with rapid bolus administration, particularly with the high doses used in meningitis; therefore, the drug should be administered intravenously over 15 to 30 minutes.[30]

During treatment it is important to monitor serum sodium and potassium concentrations (content 1.7 mEq/million units of aqueous penicillin) in patients with renal failure.[31]

1.2 Aminopenicillins

This group includes ampicillin (which may be given with sulbactam, a potent synergist)[32] and amoxicillin (which may be given with clavulanic acid).[33]

Ampicillin plus an aminoglycoside is frequently used for the initial empirical treatment of early-onset neonatal sepsis (duration of treatment 10 days).[2,4,31,32,34-37] However, epidemics caused by organisms resistant to ampicillin, kanamycin, gentamicin or amikacin have been described.[38] Ampicillin is the drug of choice for *L. monocytogenes* and most strains of enterococci. In the latter case, mezlocillin (section 1.5) may be an alternative.[39] Almost all *Proteus mirabilis* strains

and 50% of *E. coli* strains are inhibited by ampicillin. *Klebsiella* spp., *Enterobacter* spp. and *Pseudomonas* spp. are resistant.[40] The half-life of ampicillin is 5 to 6.5 hours in infants 0 to 7 days old and 2 hours in older infants.[41,42] The drug is excreted mainly (90%) unchanged in urine. The low CSF penetration of ampicillin increases in meningitis.[37,43] The dosage of ampicillin is presented in table II. A continuous infusion of ampicillin and gentamicin during parenteral nutrition has also been used in the neonate.[44] In meningitis, the recommended duration of treatment with ampicillin is 15 and 21 days for group B streptococci and Gram-negative bacteria, respectively.[2,4]

Amoxicillin achieves higher serum and CSF concentrations than ampicillin.[23] A triple combination therapy (amoxicillin plus cefotaxime and an aminoglycoside) could also be used for the first 2 to 3 days of empirical treatment of early-onset disease, followed by dual therapy after the microbiological results.[45] The dosage of amoxicillin is 50 mg/kg every 12 hours in the first week of life, and 50 mg/kg every 8 hours afterwards.

Adverse effects of aminopenicillins are rare, but include rashes, urticaria, diarrhoea, eosinophilia, elevation of liver and muscle enzymes, and seizures after intravenous doses >100 mg/kg.[4,30,43]

1.3 Antistaphylococcal Penicillins

1.3.1 Methicillin

In VLBW infants the serum half-life of methicillin is 3 hours, and in term infants about 1 to 2 hours.[46,47] The drug is excreted in urine. The sodium content is 2.9 mEq/g.[23] Very rarely described adverse effects include interstitial nephritis, sterile abscess at the site of intramuscular injection, phlebitis and suppression of bone marrow.[30,48,49] Recently, methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* (MRSE) have been, respectively, the causes of infection outbreaks in some nurseries and of catheter-associated diseases.[50-52] Consequently, methicillin is rarely used today.

Table II. Regimens for ampicillin, methicillin and nafcillin in neonates[4,23,25]

Age	Bodyweight (g)	Total daily dosage[a,b] (mg/kg)	Administration interval (h)
0-7 days	<2000	50	12
	>2000	75	8
>7 days	<2000	75	8
	>2000	100	6

a If meningitis is proven or strongly suspected, the dosage must be doubled.

b Give intramuscularly, or intravenously over 20 min.

1.3.2 Nafcillin

The half-life of nafcillin in neonates is about 4 hours.[23,53] This drug has better penetration into the CSF than methicillin. Since nafcillin is at least 80% excreted by the liver, it should not be used in preterm neonates and in infants with hepatic dysfunction.[54] However, it is less nephrotoxic than methicillin.[53,55]

1.3.3 Oxacillin

The pharmacokinetics and dosage of oxacillin are similar to those of methicillin in the first week of life. Afterwards a higher dosage is required (100 mg/kg/day and 150 mg/kg/day for neonates with birthweight <2000g and >2000g, respectively).[4,23,25] Oxacillin has been associated with cholestatic jaundice, elevation of liver enzymes and mild leucopenia.[30,54]

Because of its high protein binding (90%), oxacillin should not be used in neonates with hyperbilirubinaemia. The combination oxacillin (or nafcillin) plus an aminoglycoside is widely recommended for empirical treatment of late-onset infections in the neonate.[2,4] However, in NICUs with high rates of methicillin resistance and increasing rates of aminoglycoside resistance,[51] a combination of vancomycin plus ceftazidime is frequently recommended (some authors add an aminoglycoside for 2 to 3 days).[2]

1.4 Carboxipenicillins

This group comprises carbenicillin and ticarcillin, both excreted by the kidney.[56] Compared with ampicillin, they are less active against *L. monocytogenes*. However, they present a higher ac-

tivity against Gram-negative bacteria, but have no activity on *Klebsiella* spp. and often on enterococci. Carboxipenicillins inactivate the aminoglycosides when mixed in the same intravenous infusion. Inhibition of platelet aggregation, hypernatraemia, hypokalaemia, thrombocytopenia, allergic reactions and elevation of liver enzymes are the reported adverse effects.[30,56] Carboxipenicillins should be carefully used in neonates with heart failure, renal disorders, hypernatraemia and fluid overload.[30,56] In these situations, ureidopenicillins such as piperacillin, which also have an expanded spectrum but with a lower salt load, may be used.[57]

The dosage of carbenicillin is 100 mg/kg (intramuscularly or intravenously) administered every 12 hours to infants younger than 1 week of age, and 75 mg/kg every 8 or 6 hours to older infants weighing <2000g and >2000g at birth, respectively.[4,25,56] When used alone this drug can lead to rapid development of resistant forms.[58,59] The dosage of ticarcillin is 75 mg/kg every 12 hours in the first week of life; afterwards it is similar to that of carbenicillin.[52,60-62] Ticarcillin is preferred over carbenicillin for its superior activity against *Pseudomonas* spp.[61,62] The coadministration of clavulanic acid significantly enhances antibacterial activity.[62-66] This combination has been used in the neonate.[66]

1.5 Ureidopenicillins

Ureidopenicillins (mezlocillin, piperacillin and azlocillin) are more active than ampicillin against *P. aeruginosa*, *Citrobacter diversus* and the *Klebsiella*/*Enterobacter*/*Serratia* group.[67] They are excreted primarily by the kidney[68,69] with a half-life of about 3 to 4 hours in the neonate. CSF penetration is not well established. The sodium content of both piperacillin and azlocillin is 1.9 mEq/g.[70-73]

Mezlocillin is administered in a 75 mg/kg unit dose at 6, 8 or 12 hour intervals, depending on birthweight and gestational age. For piperacillin, 75 mg/kg intravenously every 12 hours during the first week of life and every 8 hours afterwards are suggested in preterm infants. In term neonates, 3 administrations in the first week and 4 thereafter are required.[73-75] The dosage for azlocillin is not well established.[4] Impaired homeostasis occurs less frequently with ureidopenicillins than with carboxipenicillins.[3,4,25,76] At present, the use of piperacillin-tazobactam in neonates is not recommended.[25]

2. Cephalosporins

Cephalosporins are semisynthetic derivatives of a 7-aminocephalosporanic acid nucleus. It is usual to divide the cephalosporins into 4 generations.[77]

2.1 First-, Second- and Fourth-Generation Cephalosporins

The first-generation cephalosporins (including cefazolin, cephalotin and cephalexin) exert their action primarily against Gram-positive cocci, and should never be used in suspected neonatal infections, notably in suspected meningitis.[4]

The second generation cephalosporins (including cefaclor, cefamandole, cefuroxime and cefoxitine) are active against many Gram-negative bacteria, but are not recommended for routine use in neonatology since third genertion cephalosporins are preferred.[4] Cefuroxime was efficacious in neonates even as monotherapy[78] but, despite its adequate penetration into the CSF, it should not be used in neonatal meningitis.[79] In fact, a delayed sterilisation of CSF (>24 hours) was reported in 10% of cases of meningitis treated with cefuroxime.[80] Among the oral compounds, cefaclor is suggested for prevention or treatment of recurrent urinary tract infections in neonates[81-84] or adults,[85-87] since it has good clinical efficacy with a low rate of adverse effects.[88,89]

The fourth-generation cephalosporins, such as cefepime and cefpirome, are still undergoing clinical evaluation in the newborn.

2.2 Third-Generation Cephalosporins

The third-generation cephalosporins, which include cefoperazone, cefotaxime, ceftizoxime, ceftriaxone, cefsulodin and ceftazidime, are active

against the major pathogens of neonates, are highly effective against aminoglycoside-resistant strains, achieve excellent activity in neonatal meningitis and do not require therapeutic drug monitoring (TDM).[90-96] On this basis, third-generation cephalosporins, notably cefotaxime and ceftriaxone, are widely recommended and used for treatment of neonatal meningitis (mean duration of treatment 2 to 3 weeks).[97-99] However, they are not active against *L. monocytogenes* and should not be used in staphylococcal infections, especially caused by MRSA and MRSE.

Cefotaxime is converted to an active metabolite, desacetylcefotaxime, which possesses antimicrobial activity and which has been shown to be additive with the parent compound *in vitro*[100] and *in vivo*.[101] Ceftazidime and cefsulodin are the only compounds among the cephalosporins that are highly active on *Pseudomonas* spp.[102] Ceftriaxone has a high protein binding (90%), a significant elimination via the biliary system and a long elimination half-life (ranging between 9.2 and 19 hours in the first week of life[103]).[57] The dosage of cefotaxime and ceftazidime is 50 mg/kg every 12 hours in the first week of life and every 8 to 12 hours thereafter. The dosage of ceftriaxone is 50 mg/kg every 24 hours in the first week and 50 to 75 mg/kg every 24 hours thereafter.

In adults, third-generation cephalosporins can cause mild adverse effects[104] (local pain on administration, phlebitis,[105] fever, pruritus, rashes, vomiting, nonspecific diarrhoea and abnormal liver tests[106]). In children, the overall incidence of adverse reactions in a large series of cefotaxime-treated patients was very low (2.5%).[107]

Third-generation cephalosporins only occasionally produce serious reactions.[108,109] Latamoxef (moxalactam), normally discussed with the cephalosporins, is no longer used in children[110] because of its high potential for bleeding, resulting from interference in prothrombin synthesis and platelet function.[111,112] Immune haemolytic anaemias, leucopenia and thrombocytopenia are rare but severe and, with ceftriaxone treatment, occasionally fatal.[113,114] Diarrhoea is usually self-limiting. However, pseudomembranous colitis caused by *Clostridium difficile* may occasionally be seen.[115] Ceftriaxone may cause cholecystitis associated with precipitated material collecting in the gall bladder (pseudolithiasis or biliary sludge, detectable with ultrasonography) in up to 25% of paediatric patients. This condition usually resolves with discontinuation of ceftriaxone ('reversible cholelithiasis').[116] Third-generation cephalosporins (particularly ceftazidime) very rarely cause seizures.[114]

All cephalosporins are potentially nephrotoxic.[117-121] In adults, third-generation cephalosporins, particularly, give rise to an increase in serum creatinine in less than 2% of treated patients and an increase of enzymuria in less than 10% of patients;[122] elevated renal function values were observed more often with cefoperazone.[106] The determinant for the development of nephrotoxicity is the equilibrium created at the tubule cell level between active transport, secretion and reabsorption of the cephalosporin.[123] Cefotaxime appears to be well tolerated in patients at high risk for nephrotoxicity,[124-129] in children (only 0.27% of 2243 treated had increased azotaemia)[107] and in neonates.[128,130] Because of its low sodium content, cefotaxime could be useful in neonates with hypernatraemia and/or fluid overload.[129] Ceftazidime, despite its significant intrinsic 'reactivity', presents a very limited active transport in the tubule proximal cell. Consequently, it is regarded experimentally as the least nephrotoxic compound.[123,130,131]

Clinically, nephrotoxicity has been observed rarely in children[132,133] and only in 3 of 271 neonates (1.1%).[92] *N*-Acetylglucosaminidase (NAG) enzymuria values were normal in preterm neonates treated with ceftazidime as monotherapy,[134,135] but not in combination with ampicillin.[92] Renal tolerability of ceftriaxone was good both in children (alterations of serum creatinine were observed in only 3 of 4743 patients)[136] and neonates,[137] even when combined with gentamicin.[138,139] This low potential for nephrotoxicity is a major argument for the use of third-generation cephalosporins

rather than aminoglycosides in many children with serious infections.[108,140]

A combination of ampicillin plus cefotaxime can replace ampicillin plus an aminoglycoside for empirical treatment of neonatal sepsis and meningitis, especially where TDM of the aminoglycoside is not possible.[2] However, the adoption of third-generation cephalosporins by some clinics during the 1980s has led to outbreaks of organisms resistant to these antibacterials.[38] Rapid emergence of cefotaxime-resistant Gram-negative bacteria[141-143] can be prevented by an appropriate use of antibacterials in the NICU.[79,80] Ceftazidime (plus gentamicin/tobramycin)[39] is more suitable when Gram- negative bacteria, such as *P. aeruginosa*, are strongly suspected.[144] Ceftazidime has been widely used in neonatology.[144,145] However, empirical monotherapy with ceftazidime,[130,146,147] because of its lack of activity against *L. monocytogenes*, is not recommended.[148,149]

Ceftriaxone presents the advantages of a single daily administration and an excellent activity in CSF against susceptible bacteria.[136,137] However, ceftriaxone should not be used in the first week of life and/or in VLBW infants[139] for the following reasons: (i) displacement of bilirubin from albumin,[150-152] due to its high protein binding; and (ii) diarrhoea, observed in up to 41% of treated children.[153]

3. Monobactams

Aztreonam, the first monobactam antibacterial used,[154] acts by binding to the penicillin-binding protein of aerobic Gram-negative bacteria; its activity against Gram-positive or anaerobic bacteria is poor.[155] Aztreonam has good penetration into the CSF of neonates with meningitis.[156] The drug is primarily excreted unchanged in urine. In neonates, its half-life ranges between 3 and 10 hours.[155,157-159] The incidence of adverse reactions, such as cutaneous or gastrointestinal effects, is very low (<4%).[155,160] The arginine content of aztreonam (780 mg/g) gave rise to questions regarding a potential arginine-induced hypoglycaemia.[161] However, aztreonam is well tolerated with concomitant infusion of glucose solution (>5 mg/kg/min). Absence of nephrotoxicity was documented in a large series both in adults and children.[154-156] In 283 neonates treated in 5 international trials,[154,162-165] only 0.7% had increased creatinine. Enzymuria during aztreonam treatment in VLBW infants was not observed.[164] A 30 mg/kg dose is appropriate, every 12 hours in the first week of life and every 8 hours afterwards.

The use of aztreonam combined with ampicillin could be suggested as initial empirical therapy of neonatal sepsis in the following situations: (i) TDM of aminoglycosides is impracticable; (ii) patient at risk for nephrotoxicity and ototoxicity; or (iii) site of infection with aerobic milieu, which inhibits aminoglycoside activity.[155] The clinical efficacy of aztreonam in neonates has been proven.[163,165]

4. Carbapenems

Both carbapenems (imipenem and meropenem) have an extremely broad spectrum of activity against Gram-positive and Gram-negative bacteria, including anaerobes.[166,167] They should be used against organisms resistant to the usual antibacterials,[168-170] such as *K. pneumoniae* and Enterobacteriaceae producing extended-spectrum β-lactamase.[2] Data on use in neonates are limited.[169,171]

4.1 Imipenem

Typically, imipenem is administered together with cilastatin (in a 1 : 1 ratio), which prevents nephrotoxicity. The half-life in neonates is about 2 hours. The dosage is 20 mg/kg intravenously every 12 hours.[168,169] Adverse effects are nausea, vomiting, diarrhoea, skin rashes, phlebitis, eosinophilia, transient elevation of liver function tests and seizures (in patients with pre-existing CNS dysfunction and renal failure).[172,173] The sodium content of the drug is 3.2 mEq/g.

4.2 Meropenem

The dosage of meropenem is 10 to 20 mg/kg every 8 hours.[174-176] The half-life in premature

and full-term neonates is 3 and 2 hours, respectively.[176] The adverse effects are similar to those of imipenem. However, a lower potential for the induction of epileptogenic activity and nephrotoxicity was observed with meropenem.[176]

5. Aminoglycosides

The aminoglycosides are widely used throughout the world.[177,178] They have proved to be reliable for the treatment of serious neonatal infections because of their rapid bactericidal activity against a wide range of Gram-negative bacteria and their 'postantibiotic' effect.[179] They act on microbial ribosomes to irreversibly inhibit protein synthesis.

5.1 Pharmacokinetic Considerations

Aminoglycosides have poor absorption after oral administration, poor penetration into the CSF, modest diffusion into cells and secretions, negligible binding with plasma albumin and rapid urinary excretion.[180,181] They are rapidly absorbed intramuscularly. However, a 20- to 30-min intravenous infusion is preferred.

Streptomycin and kanamycin are no longer used because of toxicity and the development of Gram-negative resistant strains of bacilli, respectively.[4] Gentamicin (the most widely studied aminoglycoside),[182] tobramycin, amikacin and netilmicin are commonly used. Aminoglycoside pharmacokinetics present a strong interindividual[183-190] and intraindividual variability in the neonate.[191] Furthermore, associated conditions, such as hypoxia, respiratory distress syndrome, fever, renal failure,[182] patent ductus arteriosus,[180,192,193] indomethacin administration and extracorporeal membrane oxygenation, are known to modify the pharmacokinetics of aminoglycosides.[182] Nomograms and algorithms based on gestational age, birthweight, body surface and glomerular function do not allow adequate predictability of aminoglycoside serum concentrations.

Various methods have been proposed for individualising aminoglycoside therapy. Neonates may require TDM and an individually adjusted therapeutic regimen.[194] TDM has 2 major objectives: (i) to ensure therapeutic concentrations; and (ii) to avoid toxicity. In adults, therapeutic efficacy and toxicity correlate well with serum concentrations;[195] in fact, the mortality rate is several times higher when aminoglycoside peak concentrations are low within 24 hours of the beginning of therapy.[195] It is unclear whether such findings can be extrapolated to neonates. In fact, the therapeutic range has not been so clearly defined in neonates and the incidence of toxic effects seems lower than in adults.[196] Moreover, debate exists regarding whether TDM of aminoglycosides will decrease toxicity.[197] However, in neonates receiving aminoglycosides, urinary NAG excretion, an early sign of nephrotoxicity that may antedate a rise in serum creatinine, was found to be elevated and correlated with aminoglycoside peak concentrations.[198] Furthermore, the percentage of neonates receiving aminoglycoside treatment who showed enzymuria (100% in the first studies without TDM) was reduced after the introduction of TDM.[199] In neonates, TDM of gentamicin has contributed to improved gentamicin administration over the course of time.[200] However, optimal dosage schedules with gentamicin are still needed for premature infants.[201]

Controversial data have been reported in adult patients on the efficacy and safety of single daily doses of aminoglycosides compared with multiple daily doses.[202-207] At the moment it is not possible to make any statement about the relative efficacy and toxicity of single or multiple daily doses of aminoglycosides in neonates, although the experience with once-daily aminoglycosides is promising.[208,209] However, in terms of nephrotoxicity, no significant differences were found between neonates treated with the same dosage of gentamicin given by continuous or intermittent infusion or administered as twice-daily or once-daily doses.[210,211]

The empirical initial dosage is 2.5 mg/kg for gentamicin, tobramycin and netilmicin, every 12 hours in the first week of life and every 8 hours thereafter (every 18 hours in VLBW infants for the whole first month of life); for amikacin, the dosage is 7.5 mg/kg every 12 hours in the first week of life

(or in VLBW infants), and 7.5 to 10 mg/kg every 8 to 12 hours thereafter.[4,182,212] Peak concentrations (obtained 30 min after intravenous administration or 60 min after intramuscular administration) of gentamicin, tobramycin and netilmicin should be maintained at 5 to 8 mg/L (15 to 25 mg/L for amikacin). Trough concentrations (measured immediately before the next administration) should be kept below 2 mg/L for gentamicin, tobramycin and netilmicin and below 10 mg/L for amikacin. Monitoring peak and trough concentrations ('trial and error method') allows modification of both the dosage and the administration interval. However, with this method neither the exact dose (in mg) nor the exact time (in hours) are calculated. Complex pharmacokinetic methods are needed to give quantitative information for modification of therapy. The method of Sawchuck and Zaske[213] guaranteed successful monitoring in neonates.[194,214] Good results were also achieved with the Simkin[215,216] and the PKRD[191,217] programs.

5.2 Toxicity

The major limitations and concerns surrounding the use of aminoglycosides are related to their ability to produce structural and functional renal injury.[218] In fact, approximately 50% of cases of drug-induced hospital-acquired renal failure are related to the use of aminoglycosides.[219] In the adult, the cost of nephrotoxicity[220] and the impact of a clinical pharmacokinetic approach on this field[221] have been documented.

Aminoglycoside-induced kidney damage is of direct type.[222-224] After glomerular filtration, aminoglycoside uptake occurs within the renal proximal tubule, mediated by receptor glycoprotein 330, interfering with protein reabsorption[225] and giving rise to functional tubular damage (increase of microglobulins and brush-border antigens).[226-230] The aminoglycoside subsequently concentrates mainly in the lysosomes, where it binds to phospholipids, forming multilaminated membrane structures (myeloid bodies), and causing structural tubular damage (increase of cellular enzymes and phospholipids in the urine).[199,210,231,232] Tubular damage can occur in more than 50% of neonates and glomerular damage in fewer than 10%,[222] despite adequate TDM.[222] Additionally, aminoglycosides inhibit renal damage repair processes mediated by renal growth factors, such as epidermal growth factor.[233-235]

Numerous factors intervene in the process of aminoglycoside nephrotoxicity; such factors are related to the patient, the antibacterial itself, the associated pathology and the relevant pharmacology. They are presented in table III.

In adults the general rank order for aminoglycoside-induced glomerular nephrotoxicity is gentamicin > tobramycin > amikacin > netilmicin, as reported in a very large review.[240] Some of these data were also demonstrated in prospective studies.[252] It is difficult to assess actual toxicities in neonates since absence of large comparative studies, variable use of TDM and variability of methods to detect renal injury do not permit the assignment of a definite rank order for nephrotoxicity. The traditional parameters of nephrotoxicity were elevated in neonates treated with aminoglycosides in some studies,[253-255] although in other studies they remained within the normal range.[256,257] Urinary excretion of enzymes and microglobulins was elevated in neonates treated with gentamicin[198,199,249,258,259] and amikacin,[229] but not with netilmicin.[184] Aminoglycoside-induced tubular toxicity is frequent, but is generally reversible on discontinuing the drug. The patient is usually not oliguric, although rarely a more severe renal impairment may be observed, especially if concomitant renal insults are present.[201] However, it should be taken into account that renal damage may alter the pharmacokinetics of a drug, reducing renal excretion and inducing further toxicity, with possible consequences also at the auditory level.

Ototoxicity is rare and may take considerable time to become apparent[260] and is consequently difficult to demonstrate in neonates; however, it is irreversible. In a review of 1321 neonates and infants included in 7 studies, it was concluded that ototoxicity is very unusual.[261] Amikacin presents the highest ototoxicity.

Table III. Risk factors for aminoglycoside-induced nephrotoxicity which may be present in the neonate (modified from Khoory et al.,[223] with permission). An extended explanation of these findings can be found in Fanos & Cataldi[222] and Khoory et al.[223]

Risk factor	Comment	References
Patient		
Neonatal age	Controversial (neonate at lower risk than adult?)	236-239
Constitutional factors	Possible; about one-third of neonates are not involved	199
Aminoglycoside		
Intrinsic toxicity	Gentamicin > tobramycin > amikacin > netilmicin	222,240
Mode of administration (continuous or intermittent)	Demonstrated experimentally, but not clinically relevant	210, 211
Drug monitoring	Therapeutic drug monitoring can halve tubular toxicity	199,222, 240
Length of therapy	High risk of renal failure after 2 weeks of therapy	240
Clinical conditions (all increase risk)		
Anoxia	Increases the intensity of damage	241, 242
Respiratory distress syndrome/mechanical ventilation	Increases tubular toxicity	243, 244
Hyperbilirubinaemia/phototherapy	Prolongs the duration of tubular toxicity	245, 246
Gram-negative sepsis	Endotoxaemia plus fever = high risk	247
Pre-existing renal or hepatic failure	Increase glomerular damage	224
Pre-existing renal ischaemia	Increases glomerular damage in 30% of patients	248
Concomitant drugs	Furosemide (frusemide), indomethacin and vancomycin increase toxicity (the last by 8-fold)	249-251
Electrolyte disorders	Hypercalcaemia, K^+, Na^+ and Mg^{2+} depletion	224, 232

Aminoglycoside-associated neuromuscular blockade, related to an inhibition of acetylcholine release at the neuromuscular junction, is rarely described.[262] Kanamycin presents the highest toxicity.[218]

6. Glycopeptides

Glycopeptides are selectively active against Gram-positive bacteria, including multidrug-resistant strains such as MRSA and MRSE, enterococci and *Clostridium* spp.[206,263] They exert a prompt bactericidal effect, inhibiting cell wall synthesis. The emergency of coagulase-negative staphylococcal strains with decreased susceptibility to both vancomycin and teicoplanin has been described.[264,265] Protein binding is 10 to 30% for vancomycin and 90% for teicoplanin. The elimination half-life is 6 to 11 hours for vancomycin, and about 30 to 40 hours for teicoplanin. CSF penetration is poor for both agents. Excretion is by glomerular filtration.[266-270] Some characteristics of glycopeptide administration are summarised in table IV.

The exposure of neonates to glycopeptides, particularly to vancomycin, is now extremely widespread. Potential reasons for this increased exposure include the longer survival of preterm and term neonates, expanded intensive care periods, prolonged ventilatory support,[271] the use of intravenous catheters and intravenous lipid emulsions[272] and an increased incidence of bloodstream infections caused by staphylococcal and enterococcal species that are resistant to conventional antibacterials.[273]

6.1 Vancomycin

Initially, empirical dosage guidelines for vancomycin in neonates were based on postnatal age,[274] gestational age and birthweight.[275] Currently, the dosage suggested in the first week of life is a function of postconceptional age (15 mg/kg every 24 hours if <30 weeks, or 10 mg/kg every 12 hours if >30 weeks). After the first week of life, the dosage is related to renal function (15 mg/kg every 24 hours if serum creatinine is >106 μmol/L, 10 mg/kg every 12 hours if serum creatinine is between 62 and 106 μmol/L, and 10 mg/kg every 8 hours

with serum creatinine <62 μmol/L).[276] Among patients treated with these guidelines, 78% had both optimal peak and trough concentrations of vancomycin.[276] A new dosage schedule has been recently proposed in the literature.[277] However, since the pharmacokinetics of vancomycin in neonates reveal a high degree of variability,[152] TDM of the drug is generally suggested, especially in neonates weighing less than 1200g.[278] Much of the discussion regarding the aminoglycosides is also applicable to vancomycin.[269,280] In fact, controversy exists regarding the need for TDM of vancomycin and, similarly, there is no consensus on time of first sampling and frequency of determinations.[281] Trough and peak concentrations should be obtained 30 min before and after infusion, respectively.[273] In preterm neonates with impaired renal function or a recent history of treatment with indomethacin, the use of an individualised pharmacokinetic profile should offer advantages.[282] In fact, concomitant treatment with indomethacin increases the half-life of vancomycin by 2 to 3 times as a result of reduced glycopeptide clearance.[283] A continuous infusion of vancomycin (10 to 40 mg/kg/day according to renal function) has also been employed.[284]

Table IV. Some differences between vancomycin and teicoplanin administration in the neonate (modified from Fanos et al.,[268] with permission)

Factor	Vancomycin	Teicoplanin
Stability of the solution (4°C)	4 days	7 days
Administration	Intravenous	Intravenous or intramuscular
Infusion	Slow (1 hour)[a]	Rapid
Daily doses	1-3	1
Volume of diluent	++	+
Therapeutic drug monitoring[b]	Required[c]	Not required[d]

a Slow infusion may prevent anaphylactoid reactions.

b Peak concentrations should be obtained 15-30 min after a 1-hour infusion after the third dose of vancomycin.

c Maintain peak concentration <40 mg/L and trough concentration <10 mg/L.

d May be suggested in patients with pre-existing renal failure.

+ indicates lower volume (may be important in very low birth weight infants with fluid overload).

With elimination of the impurities contained in early preparations of vancomycin, the 3 main adverse effects (nephrotoxicity, ototoxicity and 'red man' syndrome) became much less common.

In children and neonates, the glomerular toxicity of vancomycin seems generally lower than in adults.[285-287] The most important risk factors for the development of nephrotoxicity are: (i) trough concentrations >10 mg/L; (ii) concomitant treatment with aminoglycosides;[286,288] and (iii) prolonged therapy (>21 days).[288,289] In situations (i) and (ii) the risk of nephrotoxicity increases in some cases up to 8-fold.[286] Other risk factors include high peak concentrations, high total dose, preexisting renal failure, and concurrent treatment with amphotericin and/or furosemide (frusemide).[286] However, the role of these factors is not so well established in the neonatal population.[266]

There is no confirmed evidence that transient high peak concentrations are associated with toxicity.[251] Consequently, it may be necessary to monitor only trough concentrations of vancomycin. In fact, the maintenance of adequate trough concentrations is the principal determinant of bactericidal activity, and elevated trough concentrations are predictive of accumulation and subsequent renal deterioration.[290] Proper TDM of vancomycin minimised both glomerular and tubular nephrotoxicity in 2 studies involving children (including 30 neonates).[291,292] In most cases vancomycin nephrotoxicity is reversible, even after high doses.[251]

Vancomycin-induced ototoxicity seems to be very rare in humans, with only 28 cases published over a 30-year period,[293] but may be underestimated; however, deafness is permanent. Ototoxicity is generally associated with serum concentrations >80 mg/L.[293] In neonates treated for 21 days with vancomycin, audiometric studies failed to demonstrate otoxicity.[294]

'Red man' syndrome is an anaphylactoid reaction characterised by tachycardia, an erythematous macular rash involving the face, neck and upper trunk, and arterial hypotension. It can persist for several hours and tends to improve with antihista-

mine medications.[295,296] In paediatric patients its frequency ranges from 1.6%[296] to 35%.[297] In neonates, rashes, shock[298] and even cardiac arrest[299] have been reported during treatment with vancomycin. A slow infusion rate (60 min) seems to be an effective measure of prevention.[295,296]

For late-onset sepsis acquired in the NICU, a glycopeptide should be used in association with an aminoglycoside (in place of ampicillin).[2,4] Vancomycin is currently the antibacterial of choice in severe staphylococcal infections. Prophylaxis with vancomycin 2.5 to 5 mg/kg twice daily has been proposed for preventing infections in VLBW infants.[300-303] Immediate removal of potentially infected catheters has also been recommended in case of suspected infection.[304,305]

6.2 Teicoplanin

The tolerability of teicoplanin seems superior to that of vancomycin. In a meta-analysis of 11 comparative studies in adults, the overall incidence of adverse effects was significantly lower in patients who received teicoplanin rather than vancomycin (14 *vs* 22%).[306] Moreover, teicoplanin nephrotoxicity was lower (4.8 *vs* 10.7%),[306] even in association with the aminoglycosides.[286] The rate of teicoplanin nephrotoxicity is low in adults (0.6% of 3377 patients)[307] and neonates (none of the 187 cases published to date).[267,268,308-312]

Moreover, teicoplanin presents interesting pharmacokinetic properties[313,314] and therapeutic efficacy in adults[315] and children.[316,317]

Teicoplanin 8 to 10 mg/kg administered intravenously or intramuscularly once daily after a loading dose of 15 to 20 mg/kg appears to be an effective and well tolerated treatment for Gram-positive infections in neonates.[267] Teicoplanin may also be an alternative to vancomycin in the empirical treatment of late-onset infections in the neonate (or for prophylaxis in VLBW infants),[318,319] and is particularly indicated in patients at risk for nephrotoxicity and when TDM of vancomycin is impractical.[320]

7. Chloramphenicol

Chloramphenicol has broad antimicrobial activity.[321-324] A large variability of half-life, particularly among VLBW infants, has been documented.[325-327] Concentrations in CSF are 35 to 90% of those in serum, regardless of the extent of meningeal inflammation.[323,327-329] The dosage is 25 mg/kg every 24 hours, but should be adjusted to maintain peak serum concentrations ranging from 10 to 25 mg/L to avoid toxicities.

Chloramphenicol commonly causes the following adverse effects: skin rash and gastrointestinal effects; retinal and peripheral neuropathy; red cell maturation arrest; and, less frequently, thrombocytopenia and leucopenia. The 'grey syndrome', a peculiar syndrome characterised by cardiovascular collapse, has also been described.[30,330] The toxicity of chloramphenicol is the major limiting factor for its routine use and, presently, because of the availability of safer antibacterials, there are no indications for its use in the neonatal period. In developing countries where third-generation cephalosporins are not readily available, chloramphenicol is still used in combination with aminoglycosides for the treatment of Gram-negative meningitis.[322,331]

8. Cotrimoxazole (Trimethoprim-Sulfamethoxazole)

Cotrimoxazole is a potentially useful agent against neonatal infections caused by multidrug-resistant Gram-negative organisms, *Toxoplasma* spp. and *Pneumocystis carinii*.[332-335] The initial dosage of the components should be trimethoprim 2 mg/kg (maintenance dose 1 mg/kg) and sulfamethoxazole 10 mg/kg, administered twice daily.[336-337] Serum bilirubin binding capacity is not affected.[338] However because of the paucity of information on this drug in the newborn,[4] cotrimoxazole should be used with caution in neonates and only in exceptional circumstances. The drug may also give rise to hyperkaliemia, reducing the urinary excretion of potassium by blocking the sodium-potassium pump in the distal nephron.[339]

9. Macrolides

Erythromycin is active against most Gram-positive bacteria, including many penicillin-resistant strains of staphylococci. Most strains of *H. influenzae*, *Neisseria* spp. and *Bordetella pertussis* are susceptible. The drug may also be useful against *Chlamydia* spp. and *Ureaplasma* spp.[340-342] It is concentrated in the liver and excreted in active form in the bile. CSF penetration is poor.[4,25] Erythromycin is available as several different salts for oral and intravenous administration only.

Oral administration should be performed with milk formula to enhance absorption and to reduce possible gastrointestinal adverse effects. The suggested dosage of the estolate form is 10 mg/kg every 12 hours during the first week of life and every 8 hours thereafter.[343-344] Intravenous administration (5 to 10 mg/kg) must be given slowly by infusion pump over at least 60 min every 6 hours.[23,25,344] Heart rate and blood pressure must be closely monitored during intravenous administration. Cholestatic jaundice occurs rarely in neonates.[345,346] The pharmacological effects of cyclosporin, digoxin, methylprednisolone and theophylline may be increased by concurrent administration of erythromycin.[347]

Spiramycin has been used in neonatal toxoplasmosis, but doubts remain regarding its efficacy.[348] There are no data concerning the safety and efficacy of newer macrolides (such as clarithromycin, roxithromycin and azithromycin) in neonates.[4,30]

10. Clindamycin

Clindamycin is active against Gram-positive cocci and anaerobic bacteria.[349] The serum half-life is 11 hours in preterm infants and about 5 hours in full-term infants.[350] The main elimination of the drug is by hepatic inactivation (90%). Clindamycin penetration into the CSF is poor; metronidazole or chloramphenicol are preferred in the rare *Bacteroides fragilis* infections of the CNS. The dosage of clindamycin is 15 mg/kg/day (in 3 divided doses) in preterm infants at any age and in term infants in the first week of life, and 20 mg/kg/day (in 4 divided doses) in term infants after the first week of life.[25,350-352]

Diarrhoea, pseudomembranous colitis, rashes, Stevens-Johnson syndrome, elevation of liver enzymes, sterile abscesses, thrombophlebitis, granulocytopenia and thrombocytopenia have been reported in children after administration of clindamycin.[4,30]

11. Rifampicin (Rifampin)

Rifampicin may be useful in staphylococcal infections. The oral preparation contains a high osmolar load, which precludes its use in preterm infants. In term neonates, an intravenous dosage of 5 mg/kg every 12 hours is generally effective. It is important not to exceed this dosage so that high blood concentrations and consequent adverse effects (jaundice, thrombocytopenia, nausea and vomiting) are avoided.[352-354]

12. Quinolones

The quinolones have a broad spectrum of activity against Gram-positive and Gram-negative organisms.[349] However, the potential for toxicity to the cartilage of weight-bearing joints in children has restricted their use to 'life saving' therapy without alternative options.[25] No osteoarticular problems were observed in a recent study,[355] although in a previous paper a greenish discolouration of deciduous teeth was reported.[356] The literature on the use of ciprofloxacin in 28 preterm or low birth weight infants has recently been reviewed.[357] The dosage of intravenous ciprofloxacin ranges from 10 to 40 mg/kg/day, administered in 2 doses.[25]

13. Metronidazole

Metronidazole is active against anaerobic bacterial infections, amoebiasis, *Giardia lamblia* and *Trichomonas* spp. It is frequently used in necrotising enterocolitis, particularly if perforation is present, and in antibacterial-associated colitis caused by *C. difficile*.[358-360] The dosage (intravenous or oral) is 7.5 mg/kg every 12 hours. In term neonates after the first week of life the dosage can be dou-

Table V. Dosages of selected antibacterials in different degrees of renal failure in the neonate[180,361-364]

Drug	Dosage (mg/kg) and administration interval at residual glomerular filtration rate of		
	>50%	10-50%	<10%
Amikacin	10 q12-24h	10 q24-36h	5 q24-48h
Ampicillin	50-100 q12h	50 q12h	50 q24-48h
Aztreonam	30-60 q12h	15-30 q12h	15-30 q24h
Benzylpenicillin	25 000-50 000IU q12h	20 000-40 000IU q12h	10 000-50 000IU q12h
Cefotaxime	50-75 q12h	40-60 q12h	25-40 q12h
Ceftazidime	50-75 q12h	35-50 q12h	15-25 q12h
Ceftriaxone	50-75 q24h	50-75 q24h	50-75 q24h
Clindamycin	2.5-5 q12h	2.5-5 q12h	2.5-5 q12h
Gentamicin	2.5 q12h	2.5 q24-36h	2.5 q36-48h
Piperacillin	50-100 q12h	40-75 q12h	25-50 q12h
Ticarcillin	75-150 q12h	40-75 q12h	20-40 q12h
Teicoplanin	8 q24h	8 q36h	8 q48h
Tobramicin	2.5 q12h	2.5 q24-36h	2.5 q36-48h
Vancomycin	7.5-10 q24h	4-5 q36h	4-5 q48h

qxh = every x hours.

bled. In the first week of life, the interval should be 48 hours in neonates with birthweight <1200g and 24 hours in neonates with birthweight between 1200 and 2000g. The main adverse effects of metronidazole are nausea, vomiting, neutropenia and, rarely, seizures.[4,30]

14. Dosage of Antibacterials in Renal Failure

Normal renal function is important for the excretion and metabolism of many antimicrobial drugs. Renal failure alters antibacterial clearance and requires modifications in dosage to optimise therapeutic outcome and minimise the risk of toxicity. Recommendations are presented in table V.[180,361-364]

15. Conclusions

Combination therapy is recommended for the initial empirical treatment of bacterial infections in the neonate. Selection of an antibacterial bacterial regimen is based on: (i) bacterial prevalence and susceptibility; (ii) drug characteristics such as spectrum, pharmacokinetics, CSF penetration, clinical efficacy, tolerability and costs; and (iii) neonate–specific factors such as birthweight, underlying illness or concomitant therapies.

Penicillins, cephalosporins, monobactams, aminoglycosides and glycopeptides are commonly used in neonatal infection. In selected cases (infections with multiple and/or resistant organisms), carbapenems and quinolones may be useful; quinolones should only be used in 'life saving' situations. Macrolides, clindamycin, rifampicin and metronidazole are rarely indicated. The use of chloramphenicol and cotrimoxazole in neonates is exceptional.

The dosage of antibacterials should be individualised, especially in very low birthweight infants and in renal failure. TDM is generally suggested for aminoglycosides in order to reach therapeutic goals and prevent toxicity. At the moment it is not possible to make any statement regarding the relative efficacy and toxicity of single or multiple daily doses of aminoglycosides in neonates. Controversy still exists over the need for TDM of vancomycin: determination of trough concentrations may be sufficient.

Although antibacterials have greatly improved the treatment outcome of neonatal sepsis, additional interventions will be required to reduce the morbidity and mortality of neonatal infections.

Survey and prevention systems should be continuously reinforced. Preventing iatrogenic toxicity is not only possible and desirable, but essential.

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