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Antibacterial-Induced Nephrotoxicity in the Newborn

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Abstract

Antibacterials are the primary cause of drug-induced kidney disease in all age groups and these agents bring about renal damage by 2 main mechanisms, namely, direct and immunologically mediated.

For some antibacterials (aminoglycosides and vancomycin) nephrotoxicity is very frequent but generally reversible upon discontinuation of the drug. However, the development of acute renal failure with these agents is possible and its incidence in the newborn seems to be increasing.

Antibacterials are very often used in the neonatal period especially in very low birthweight neonates. The role of neonatal age in developing nephrotoxicity has still to be defined.

Since the traditional laboratory parameters of nephrotoxicity are abnormal only in the presence of substantial renal damage, the identification of early non-invasive markers of the renal damage (urinary microglobulins, enzymes and growth factors) is of importance.

Aminoglycosides and glycopeptides are still frequently used, either alone or in combination, despite their low therapeutic index. Numerous factors intervene in bringing about the kidney damage induced by these 2 classes of antibacterials, such as factors related to the antibacterial itself and others related to the associated pathology as well as pharmacological factors. Nephrotoxicity can be caused by the ß-lactams and related compounds. Their potential to cause nephrotoxicity decreases in the order: carbapenems > cephalosporins > penicillins > monobactams. Third generation cephalosporins are frequently used in neonates. However, they are well tolerated compounds at the renal level.

The nephrotoxicity of other classes of antibacterials is not discussed either because they are only used in neonates in exceptional circumstances, for example, chloramphenicol and cotrimoxazole (trimethoprim-sulfamethoxazole) or are not associated with significant nephrotoxicity, for example macrolides, clindamicin, quinolones, rifampicin (rifampin) and metronidazole.

Antibacterial-induced nephrotoxicity is an important parameter to be considered when treating the newborn and this is particularly true when use of a combination of different antibacterials and/or drugs with a nephrotoxic potential is being considered. However, other parameters, such as antibacterial spectrum, pharmacokinetics, post-antibacterial effect, clinical efficacy, general adverse effect profile and cost, must also be considered in the choice of antibacterial therapy in the neonate.

Knowledge of the renal safety of antibacterials and the correct approach to therapeutic drug monitoring may be useful elements for preventing iatrogenic renal disorders.

Drug-induced kidney disease are frequent in all age groups[1] and antibacterials are the leading cause of this disorder.[2,3] The main reasons for this are the intrinsic nephrotoxicity of some antibacterials, the predominantly renal excretion of most antibacterials, the high renal blood flow and the high degree of specialisation of the tubular cells.[2]

Antibacterials may give rise to kidney damage essentially via two mechanisms, namely, direct and immunologically mediated.[3,4] The direct type of damage (which is the more frequent) is dose-dependent, is generally of surreptitious onset (with symptoms often undetected in the early stages) and is characterised by necrosis of a proportion of the cells of renal proximal tubule. The pathological changes, in severe instances, correspond to a picture of acute tubular necrosis. This is typical of renal damage related to aminoglycosides and glycopeptides. When considering nephrotoxicity, the nephrotoxicity that occurs in the neonate is generally this type of damage.[5]

The immunologically-mediated damage, on the other hand, is independent of dose and usually presents acutely, accompanied by allergic manifestations. Histologically, it is characterised by the presence of infiltrates of mononuclear cells, plasma cells and immunoglobulin (Ig) E.[3,6] The hypersensitivity reaction can mostly be due to a cellular mechanism (more common), resulting in acute tubule-interstitial nephritis, or to a humoral mechanism (less common), resulting in focal glomerulonephritis.[6] This damage is typical of penicillins and is very rare in the newborn.[2,3,5] Cephalosporins can give rise to both direct and immunologically-mediated damage.[6,7]

It should be noted that the evolution of drug-induced nephropathies differs completely from idiopathic nephropathies. Indeed, renal lesions usu-

ally regress when drug administration is stopped.[1] For example, aminoglycoside nephrotoxicity, and particularly tubulotoxicity, is frequent but generally reversible upon discontinuation of the drug.[1] However, the renal damage may alter the pharmacokinetics of the antibacterials, reducing renal excretion and creating a dangerous vicious cycle. The possible consequences may involve other organs, such as the inner ear, where toxicity is rare but the consequences can be irreversible.[8] Furthermore, the development of acute renal failure is possible.[8]

One-third of adult cases of drug-induced acute renal failure are brought about by antibacterials.[9] Systematic epidemiological data on the incidence of drug-induced acute renal failure in the newborn are not available. However, an increase, up to 8-fold in the last 10 years, in the involvement of drugs in neonatal acute renal failure has been observed, both in infants and the newborn.[10-12] The actual importance of antibacterials in determining nephrotoxicity as sole agents is difficult to define: in fact the antibacterials are administered to newborns who are sick and often seriously ill, who have haemodynamic abnormalities and/or electrolyte derangements. All these situations may be important co-factors in bringing about the renal damage.

Antibacterials are frequently used in the neonatal period. In the very low birthweight neonates exposure to antibacterials may be extremely widespread (98.8%)[13] and this patient group may be exceptionally prone to kidney damage.[14] Thus, neonatal age may itself be a risk factor for antibacterial-induced nephrotoxicity and is likely to be all the more important, the greater the degree of prematurity.[15] However, this subject is controversial. In fact a number of investigators claim that antibacterial-induced kidney damage (especially that caused by aminoglycosides or glycopeptides) is less frequent and severe in newborns than it is in adults.

Three hypotheses have been suggested that are not mutually exclusive: (i) the 'renal volume to body volume' ratio is greater in newborns; (ii) newborns achieve less uptake of the antibacterial by the proximal tubule because of incomplete maturation of the tubule; and (iii) there is less sensitivity of the immature kidney to the toxic agent.[4,15] However, a particular constitutional susceptibility to antibacterial-induced nephrotoxicity may be present. In some newborns, the renal damage occurs even at minimal antibacterial dosages and after very brief periods of treatment compared with other newborns.[8,16] The role of individual factors, however, has still to be better defined. It is important to underline that dosage adjustment should always be made in patients with renal impairment since antibacterial accumulation can lead to increased non-renal and renal adverse effects.[17]

1. Definition and Evaluation of Nephrotoxicity

The definition of nephrotoxicity has been well established for the aminoglycosides and this definition can be used also for the other antibacterials. Aminoglycoside-induced nephrotoxicity was initially defined clinically in terms of an increase in serum creatinine levels of >20% in relation to baseline values.[18] Later on, it was defined in greater detail: increases in serum creatinine level of ≥44.2 μmol/L (0.5 mg/dl) in patients with a basal serum creatinine level of ≤265 μmol/L (3 mg/dl), and increases in serum creatinine level of ≥ 88 μmol/L in patients with a basal serum creatinine level of >265 μmol/L (3 mg/dl), were regarded as indicative of a nephrotoxic action of the drug administered.[19]

However, traditional laboratory parameters of nephrotoxicity such as serum creatinine level, blood urea nitrogen (BUN) level and urinalysis are abnormal only in the presence of substantial renal damage.[20] Recently, cystatin C, a marker of glomerular function in the 'creatinine blind' period, was evaluated in the newborn, establishing normal values.[21,22] Urinary biomarkers of nephrotoxicity (microglobulins, enzymes and growth factors) have been used in neonatology for the early non-invasive identification of the renal tubular damage occurring in the course of antibacterial therapy.

Moreover, they are helpful in establishing its extent and monitoring its time course.[23-28] A classification of some of these parameters, based on the type of renal damage and/or its repair is presented in table I.[8]

1.1 Functional Tubular Damage

Urinary microglobulins, ß$_2$-microglobulin,[17,18] α_1-microglobulin[29-32] and retinol binding protein,[33] are low molecular weight proteins (<33 000D) filtered by the glomerulus and almost entirely reabsorbed and catabolised at the proximal tubule cell level.[20,28] Therefore, in basal conditions only a small amount of microglobulin is detectable in the urine. In the course of tubular functional damage, however, the amount reabsorbed is reduced and the urinary level of microglobulins is increased.[20] They have also been measured in amniotic fluid and fetal urine for determining fetal renal tubular function.[34-38] Measurement of α_1-microglobulin is preferable to measurement of β_2-microglobulin, inasmuch as measurement of the former is not affected by the presence of extra-renal factors and/or an acid urinary pH.[20,38]

Table I. Urinary biomarkers: type of kidney damage and damage repair (reproduced from Fanos & Cataldi,[8] with permission)

Functional damage
Microglobulins:
α_1-Microglobulin
β_2-Microglobulin
Retinol binding protein
Structural damage
Enzymes:
Alanine aminopeptidase
N-acetyl-β-D-glucosaminidase
Antigens:
Proximal tubule
Distal tubule
Phospholipids:
Total
Phosphatidylinositol
Damage repair
Growth factors:
Epidermal growth factor
Transforming growth factor-α (hyperplasia)
Insulin-like growth factor I (hyperplasia)
Hepatocyte growth factor (hyperplasia)
Transforming growth factor-β (hypertrophy)[a]
Tamm-Horsfall protein (?)

a Mediates cellular hypertrophic processes, all the other growth factors reported mediate cellular hyperplastic processes.

? = Role uncertain.

1.2 Structural Tubular Damage

Structural damage is diagnosed by measurement of the levels of urinary enzymes, proximal (such as adenosine deaminase binding protein)[39] and distal tubule antigens, and phospholipids (total and phosphatidylinositol).[40-44]

The most important enzymes are *N*-acetyl-ß-D-glucosaminidase (EC: 3.2.1.30) present in lysosomes, and alanine aminopeptidase (EC: 3.4.11.2) present in the brush border of convoluted tubule cells. Because of their high molecular weight (136 000 and 240 000D, respectively) they are not filtered by the glomerulus.[40,41] In urine, there is usually low enzymatic activity derived from metabolic activity (exocytosis, pinocytosis) and from the turnover of the renal tubule cells. Consequently, in the presence of intact glomerular function, high levels of alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase activity in the urine are derived exclusively from damage to the renal parenchyma.[40,41] *N*-acetyl-β-D-glucosaminidase is the reference enzyme by virtue of its relative stability in urine, even at acid pH, and by the fact that it is easy to store.[42] Moreover, assessment of the *N*-acetyl-β-D-glucosaminidase isoenzymes could enable the physician to identify the antibacterial responsible for the nephrotoxicity;[45] however, this has not been proven in the neonate.[46]

1.3 Renal Damage Repair

The kidney damage repair is promoted by growth factors. They are polypeptides or proteins that regulate crucial events in cell proliferation and differentiation via an autocrine and/or paracrine mechanism.[47,48] Particularly important is the epidermal growth factor (molecular weight of 6045D), produced to a large extent by the cells of Henle's loop and of the distal tubule.[47,48] Urinary

epidermal growth factor values are reduced in the course of acute and chronic renal failure[47] and their increase after renal impairment is a predictive indicator of the rate and extent of renal functional recovery.[48] Other important factors are insulin-like growth factor (IGF)-I and IGF-II, transforming growth factor (TGF)-α and TGF-ß and Tamm-Horsfall protein.[8]

2. Aminoglycosides

Aminoglycosides continue to be used in spite of their low therapeutic index. In the US alone, 3.2 million patients each year receive a course of aminoglycoside therapy.[49] In neonatology, a combination of ampicillin plus an aminoglycoside is currently suggested as the first-line choice of therapy for the empirical treatment of early-onset bacterial infections[50] and a high percentage of newborns are treated with aminoglycosides.[8,13,51] For example, roughly 85% of all neonates treated with antibacterials had received netilmicin.[52]

Approximately 50% of cases of drug-induced hospital-acquired acute renal failure in patients of all ages are related to the use of aminoglycosides[53] and 6 to 26% of patients treated with gentamicin develop acute renal failure.[53] Among antibacterial-induced acute renal failure, 80% were related to the aminoglycosides (60% in single-drug therapy and 20% in combination with cephalosporins).[9]

Glomerular damage is present during aminoglycoside therapy in about 3 to 10%[54] of adult patients (and up to 70% in high risk patients)[55] and in 0 to 10% of newborns.[1] Tubular damage is observed in 50 to 100% of both adults and neonates treated with aminoglycosides, despite individualised therapeutic drug monitoring of the antibacterial. However, urinary *N*-acetyl-β-D-glucosaminidase levels increase 20-fold over basal values in adults and 10-fold in neonates.[28] Papers presenting data on documented aminoglycoside-induced tubular toxicity in neonates are shown in table II.

Aminoglycosides are almost entirely excreted by glomerular filtration. Within the proximal tubule, aminoglycoside-brush border binding occurs, causing an alteration of normal tubular protein reabsorption. Specifically, aminoglycosides bind to glycoprotein 330, a receptor on proximal tubule cells that mediates cell uptake and toxicity of aminoglycosides.[60] The clinical pattern of most aminoglycoside-induced nephrotoxicity is often characterised by an asymptomatic modest rise in serum creatinine level that occurs after 5 to 10 days of therapy and returns to normal within a few days after cessation of therapy.[61] The patient is usually non-oliguric, although rarely a more severe renal impairment may be seen, especially when concomitant renal insults are present.[61] The appearance of low molecular weight proteins and enzymes in urine is a finding that may antedate a rise in serum creatinine level.[61] In particular, increased levels of urinary proteins appear to be the first detectable event in the time course of aminoglycoside-induced kidney damage.[8,25,62]

The urinary excretion of β_2-microglobulin was found to be higher in neonates treated with gentamicin compared with control neonates.[46,56] The urinary excretion of α_1-microglobulin was found to be increased in preterm neonates treated with amikacin (despite therapeutic drug monitoring of the aminoglycoside)[57] or tobramycin compared with control neonates.[39] Neonates receiving

Table II. Changes in urinary biomarkers documenting aminoglycoside-induced tubular toxicity in neonates (reproduced from Fanos & Cataldi,[8] with permission)

Marker	Changes *vs* mean values of controls (no. times)	Reference
β_2m	↑7	Elinder & Aperia[56]
α_1m	↑5	Fanos et al.[57]
ABP	↑24	Gordjani et al.[39]
NAG	↑8-10 (TDM)	Padovani et al.[16]
AAP	↑2 (TDM)	Tessin et al.[58]
EGF	↓2	Watanabe et al.[47]
THP	↓6	Leititis et al.[59]

α_1m = α_1-microglobulins; **β_2m** = $\beta_2$microglobulins; **AAP** = alanine aminopeptidase; **ABP** = adenosine deaminase binding protein; **EGF** = epidermal growth factor; **NAG** = *N*-acetyl-β-D-glucosaminidase; **TDM** = therapeutic drug monitoring; **THP** = Tamm-Horsfall protein.

netilmicin treatment were found to have much higher urinary retinol binding protein levels than control neonates.[63]

Once inside the proximal tubule cell the aminoglycosides are sequestered in the lysosomes, where they bind to phospholipids. Lysosomal phospholipidosis occurs with lysosomal rupture, impairment of mitochondrial respiration, alteration of protein synthesis by endoplasmatic reticulum and depression of sodium/potassium pump (fig. 1). The consequent structural damage may result in cell necrosis, and is associated with a corresponding microscopy finding in light (formation of multilaminated membrane structures: myeloid bodies) or electron microscopy.[64,65] The main studies dealing with enzymuria and aminoglycosides treatment in neonates have been previously reviewed.[4,5,8,25]

Finally, aminoglycosides inhibit cell damage repair processes.[47] Levels of epidermal growth factor were found to be reduced in term newborns receiving tobramycin therapy without therapeutic drug monitoring.[47]

It has been hypothesised that the neonatal kidney has a low susceptibility to aminoglycoside-induced nephrotoxicity.[14] However, the trans-

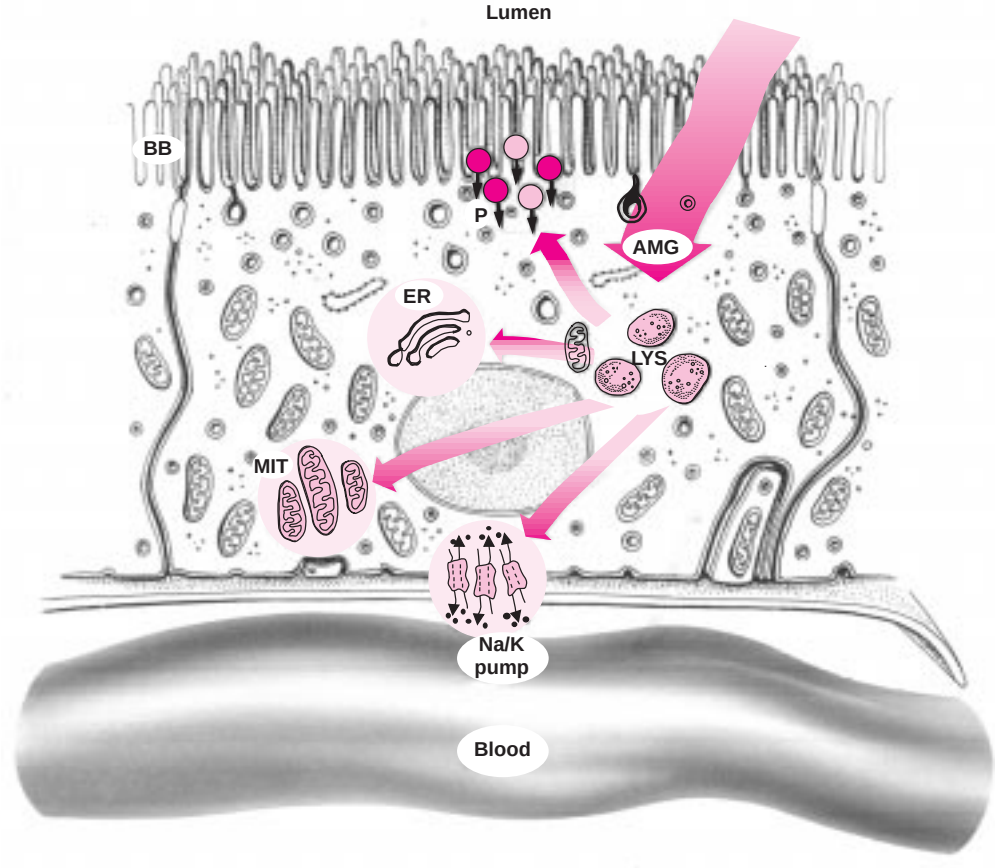

Fig. 1. Basal mechanism of aminoglycoside (AMG) nephrotoxicity. Within the proximal tubule, binding of aminoglycoside to the brush border (BB) occurs. Once inside the proximal tubule cell the aminoglycosides are sequestered in the lysosomes (LYS), where they bind to phospholipids. Lysosomal phospholipidosis occurs with lysosomal rupture, impairment of mitochondrial (MIT) respiration, alteration of normal protein (P) tubular reabsorption, alteration of protein synthesis by endoplasmic reticulum (ER) and depression of the sodium/potassium (Na/K) pump. The consequent structural damage may result in cell necrosis.

placental effects of gentamicin in renal proximal tubular cells of rats exposed *in utero* to gentamicin (a 20% reduction of final number of nephrons, a delay in the maturity of the glomerular filtration barrier and proteinuria)[66-68] suggest that caution is required when exposing immature kidneys to aminoglycosides, especially in the first days of life.

2.1 Risk Factors Related to the Aminoglycosides

Numerous risk factors intervene in bringing about aminoglycoside-induced kidney damage. They are presented in table III.

Table III. Risk factors for aminoglycoside-induced nephrotoxicity in the neonate[4,8]

Risk factors related to the drug
Intrinsic toxicity
Administration regimen
Monitoring modality (high trough and peak levels)
Prolonged therapy
Risk factors related to the associated pathology
Neonatal anoxia
Respiratory distress/mechanical ventilation
Hyperbilirubinaemia/phototherapy
Sepsis
Electrolyte disorders
Hypovolaemia
Renal hypoperfusion
Abnormal renal function
Pharmacological risk factors
Antibacterials (glycopeptides, cephalosporins)
Indomethacin
Furosemide (frusemide)
Amphotericin
Radiocontrast agents

2.1.1 Intrinsic Toxicity

The aminoglycosides can be listed in decreasing order of propensity to cause glomerular toxicity as follows: gentamicin > tobramycin > amikacin > netilmicin.[69] The superior renal tubular tolerability of netilmicin in adults has also been seen in newborns when structural kidney damage is measured by urinary enzyme levels[5,25,70] but not when urinary phospholipids are used as the indicator.[70] However, in the opinion of some authors, based on currently available data, no aminoglycoside has conclusively been found less nephrotoxic than any other.[61]

2.1.2 Administration Modalities

Although aminoglycosides are usually administered daily in 2 or 3 divided doses, a series of findings support the concept that once daily, high dosage aminoglycoside administration offers advantages in terms of efficacy, general and renal safety.[71] Experimentally, the modalities of aminoglycoside administration (continuous or intermittent infusion) affect the renal accumulation kinetics of aminoglycosides and thus their nephrotoxicity.[72]

Gentamicin and netilmicin have saturable renal accumulation kinetics. The accumulation of gentamicin and netilmicin in the renal cortex is significantly reduced if doses are given at widely spaced intervals, preferably in single daily doses.[73] Prins et al.[74] reported a 5-fold difference in nephrotoxicity due to gentamicin in a population study of 1250 patients between once daily and thrice daily administration (5% in patients receiving the single daily dose and 24% in patients receiving the multiple daily doses). In other 12 studies involving a total of 1250 patients treated with various aminoglycosides a statistical difference was not observed, although a trend toward a decrease in nephrotoxicity appeared to exist with single daily administration.[61]

In contrast, tobramycin has nonsaturable renal accumulation kinetics. The renal accumulation kinetics of amikacin are mixed, being saturable at low serum concentrations and nonsaturable at high concentrations.[72] These data are confirmed in clinical studies both in adult and paediatric patients.[75,76] In contrast, in the newborn no significant differences in enzymuria (alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase) was found in the first 3 months of life in 105 term and preterm newborns treated with gentamicin by continuous or intermittent infusion, given the same total daily dose.[77] Moreover, no significant differences in urinary alanine aminopeptidase excretion were found in 20 term neonates (in the first 3 months of life) treated with the same dose of

aminoglycoside, administered in twice daily or once daily doses.[78]

In adults, a series of recent meta-analyses comparing once daily administration with multiple daily administration have shown that the former is as efficacious as and is potentially less toxic than the latter administration regimens.[79-81] In contrast, a recent review on aminoglycoside administration as single daily doses in adults suggests that this scheme appears no more efficacious and no less toxic.[54] In the opinion of the authors of the review, the importance of once daily aminoglycoside administration in reducing toxic effects of these drugs in the neonatal period requires further evaluation.

2.1.3 High trough and peak concentrations

Debate exists as to whether therapeutic drug monitoring of aminoglycosides will decrease nephrotoxicity. The occurrence of elevated serum trough concentrations over a prolonged period of time (such as those achieved by administration of multiple daily doses) is more likely to cause nephrotoxicity (and ototoxicity) than the occurrence of transient, high peak concentrations such as those achieved after once daily administration. Although high peak and trough concentrations appear to correlate with toxicity, they are relatively insensitive and can be poor predictors of nephrotoxicity in many patients.[82] Most investigators relate nephrotoxicity to high trough concentrations (as measured immediately before the next dose of aminoglycoside is administered).[8]

Trough concentrations should be kept below 10 mg/L for amikacin and below 2 mg/L for the other aminoglycosides.[50] Peak concentrations (obtained 30 minutes after an intravenous administration and 60 minutes after an intramuscular administration) of gentamicin, tobramycin and netilmicin should be maintained at 5 to 8 mg/L and at 15 to 25 mg/L for amikacin.[50] *N*-acetyl-β-D-glucosaminidase enzymuria was found to be correlated with aminoglycoside peak concentrations only in a single study in neonatology.[83] In the early neonatal studies the percentage of newborns receiving aminoglycoside treatment who developed enzymuria was 100%.[84] This was probably due the fact that these studies included no therapeutic drug monitoring of aminoglycosides using the 'peak and trough' method or complex pharmacokinetic methods (such as the methods of Sawchuck and Zaske,[85] Simkin[86] and the PKRD program[87]). The latter methods calculate the exact dose of aminoglycoside (in mg) and the exact interval (in hours) of administration. By employing these methods the percentage of newborns receiving aminoglycoside treatment and presenting with enzymuria is reduced to 50 to 60%.[8,16,28]

2.1.4 Prolonged Therapy

In adult studies, the incidence of aminoglycoside-related nephrotoxicity may vary from as little as 2 to 4% to as much as approximately 55% of patients according to the duration of the treatment; there is a high risk of nephrotoxicity when treatment lasts >10 days).[88]

2.2 Risk Factors Related to the Associated Pathology

Clinical conditions commonly observed in the newborn may amplify aminoglycoside nephrotoxicity.

Neonatal anoxia causes renal distress in 50% of newborns.[89-93] In newborns with asphyxia, the level of urinary retinol binding protein was a predictive indicator of acute renal failure development.[94] Studies with β_2-microglobulin[91] show that neonatal anoxia and aminoglycoside administration have an additive or potentiating effect.[93]

Respiratory distress syndrome and mechanical ventilation produce well known negative effects on the kidney.[95,96] These effects are potentiated by the administration of aminoglycosides.[8]

In neonates with hyperbilirubinaemia, bilirubin (and its photoderivates) and the use of aminoglycosides bring about a summation of the renal damaging effects (as assessed by enzymuria) expected as a result of each of the factors alone, probably by acting upon the cell target itself (oxidative phosphorylation).[97,98]

Sepsis due to Gram-negative bacteria is associated with aminoglycoside-induced kidney damage

especially in presence of renal hypoperfusion, fever and endotoxinaemia.[99]

Electrolyte disorders (hypercalcaemia or potassium and magnesium depletion) in newborns may constitute an additional risk for aminoglycoside-induced nephrotoxicity.[8,100] On the other hand, aminoglycoside therapy in preterm newborns may trigger a vicious circle,[101] by causing an increase in fractionated sodium and magnesium excretion.

It is unclear whether underlying renal insufficiency either predisposes to aminoglycoside nephrotoxicity or simply makes it easier to detect. The former hypothesis has not been confirmed.[61]

2.3 Pharmacological Risk Factors

The interaction of aminoglycosides with glycopeptide antibacterials is briefly considered in section 3. The nephrotoxicity of the combined use of an aminoglycoside plus cephalosporins has been extensively reviewed; however, no definite conclusion has been reached.[61,102]

The use of indomethacin might increase aminoglycoside-induced nephrotoxicity by two mechanisms: (i) by increasing in both peak and trough concentrations of the aminoglycoside;[103] and (ii) by blocking the synthesis of urinary prostaglandin E_2, a vasodilating substance usually produced when aminoglycoside-induced nephrotoxicity is developing.[104] In rats treated with aminoglycosides, levels of urinary *N*-acetyl-β-D-glucosaminidase proved to be inversely proportional to urinary prostaglandin E_2 levels.[105]

Furosemide (frusemide), the most commonly used diuretic in the neonatal period, potentiates aminoglycoside-induced nephrotoxicity,[106,107] especially if volume depletion occurs.[61]

Other nephrotoxins include amphotericin and radiocontrast agents. Both should be avoided during aminoglycoside treatment.[61]

2.4 Guidelines for Preventing Aminoglycoside-Induced Nephrotoxicity

In discussing this topic, the rationale for using an aminoglycoside at all must first be considered.[108,109] For example, the low nephrotoxic potential of the third generation cephalosporins and aztreonam is a major argument for the use of these agents rather than aminoglycosides in many children with serious infections.[108,109] In particular, aminoglycosides should be avoided in patients with potential risk factors such as hypovolaemia, renal hypoperfusion and abnormal renal function.[8] From a practical viewpoint, the presence before treatment of high urinary *N*-acetyl-β-D-glucosaminidase excretion (>99° percentile: > 2 U/day in the first 2 weeks of life) may suggest the need for an alternative antibacterial for the empirical treatment of the infection. Similarly, a conspicuous increment of *N*-acetyl-β-D-glucosaminidase during treatment suggests that aminoglycoside therapy should only be continued with caution.[4,8,28,108,110]

Once aminoglycoside therapy has been decided on, the less nephrotoxic compounds should be used (netilmicin, amikacin).[8,61]

In every case, the empirical initial dosage should be as follows: 2.5 mg/kg every 12 hours for gentamicin, tobramycin and netilmicin in the first week of life, then every 8 hours or every 18 hours in very low birthweight for the whole first month of life, and 7.5 mg/kg every 12 hours for amikacin in the first week of life (or in very low birthweight) followed by 7.5 to 10 mg/kg every 8 to 12 hours thereafter.[50]

Therapeutic drug monitoring should be performed: peak and trough concentrations should be measured after administration of the fifth dose of aminoglycoside, if the drug is being administered twice daily.[8,61]

Every other day of treatment serum creatinine level and electrolyte level measurement is mandatory and electrolyte disorders should be corrected.[61] If the serum creatinine level increases to >44.2 μmol/L (0.5 mg/dl), aminoglycoside therapy should be discontinued if trough concentrations are subtoxic and no other source of renal impairment is found. If toxic trough concentrations occur, correction of the dosage and/or interval for dose administration should be performed.[61]

3. Glycopeptides

The exposure of neonates to glycopeptides, and particularly to vancomycin, is actually extremely widespread. In fact, vancomycin is currently the antibacterial of choice for the treatment of severe staphylococcal infections.[111-113] Moreover, vancomycin plus ceftazidime could be the recommended combination for the empirical treatment of neonatal late-onset sepsis, especially in neonatal intensive care units where a significant resistance of coagulase negative staphylococci to methicillin is present.[111-113] In some neonatal intensive care units resistance to methicillin may be as high as 70%.[114] However, vancomycin is associated with a significative incidence of anaphylactoid reactions and with oto- and renal toxicity. Teicoplanin offers some administration advantages over vancomycin and is associated with fewer adverse effects.[115] A comparison between vancomycin and teicoplanin is presented in table IV.

3.1 Vancomycin

The mechanism of vancomycin nephrotoxicity is not well understood. However, a number of experimental and clinical studies have elucidated some aspects.

- The accumulation of vancomycin in the lysosomes of proximal tubular cells is not similar to the behaviour of aminoglycosides.[126]
- Aminoglycosides are associated with a higher incidence of nephrotoxicity than glycopeptides. Tobramycin was significantly more nephrotoxic than vancomycin and the combination of the 2 drugs was significantly more nephrotoxic than either alone.[127] The same results were found with vancomycin and gentamicin.[127]
- There is a chronotoxicity with vancomycin, evaluated by brush border and lysosomal enzymes, with morning doses being associated with less adverse effects than evening doses.[128]
- From a pharmacodynamic point of view, vancomycin nephrotoxicity relates to the combined effect of a large area under the concentration-time curve and duration of therapy.[129]
- In most cases nephrotoxicity associated with vancomycin is reversible, even after the administration of high dosages.[129]

The basal mechanism of vancomycin nephrotoxicity seems related to 2 distinct processes which are illustrated in figure 2. These two process are:

Table IV. A comparison between vancomycin and teicoplanin in the newborn

Parameter	Vancomycin	Teicoplanin	References
Pharmacokinetics			
Protein binding (%)[a]	10-30	90	50, 116-117
Elimination half-life (h)	6-11	30	116-118
Administration modalities			
Administration	IV[b]	IV or IM	115
Infusion	Slow (1h)	Rapid	115
Daily doses	1-3	1	7, 113, 115
Therapeutic drug monitoring	Required	Not required[c]	7, 115
Tolerability			
Incidence of red man syndrome (%)[a]	1.6-35%	0.1-1.4	119-121
Ototoxicity[a]	Very rare	Very rare	7, 118, 122
Nephrotoxicity	++	+	108, 115, 122, 123
Cardiac arrest	Extremely rare	Not described	124-125

a Data referred to paediatric and adult patients.

b Slow infusion may prevent anaphylactoid reactions.

c May be warranted in patients with pre-existing renal failure.

+ = Less frequent; **++** = more frequent.

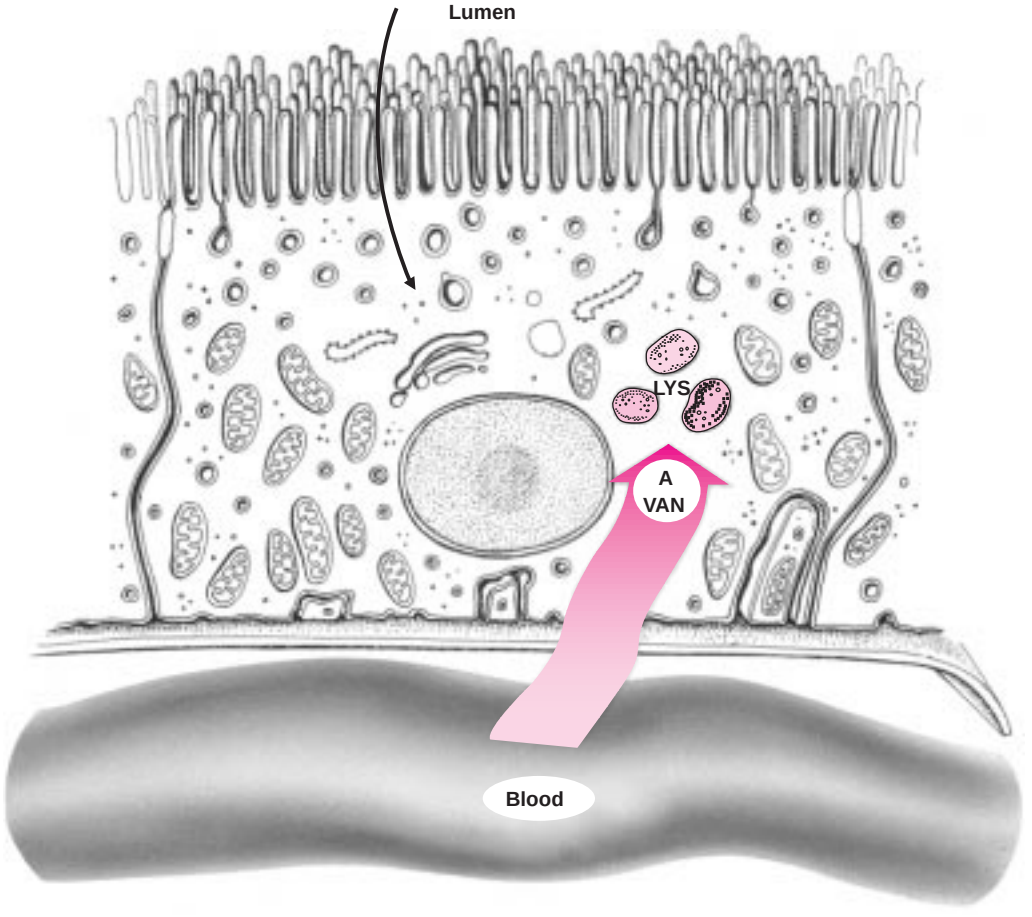

Fig. 2. Basal mechanism of vancomycin nephrotoxicity. Vancomycin nephrotoxicity seems to be related to 2 distinct processes: (i) the energy-dependent tubular transport of the glycopeptide from the blood to the tubular cell across the basolateral membrane (**A**); and (ii) tubular reabsorption; however, although this mechanism is probably involved, it does not seem so relevant to nephrotoxicity. The accumulation of vancomycin in the lysosomes of proximal tubular cells is not similar to the behaviour of aminoglycosides. However, the actual mechanism of vancomycin nephrotoxicity is not well understood. **LYS** = lysosome; **VAN** = vancomycin.

(i) the energy-dependent tubular transport of the glycopeptide from the blood to the tubular cell across the basolateral membrane; as occurs with some aminoglycosides saturation of this tubular transport occurs at a particular concentration;[130] and, (ii) tubular reabsorption; however, although this mechanism is probably involved, it does not seem so relevant to nephrotoxicity.[130]

The results of clinical studies published to date on vancomycin nephrotoxicity are controversial. In fact the results of these studies differ considerably depending on the following factors: the period considered, the populations treated, the dosage regimen used, the duration of therapy, the definition of nephrotoxicity, the sensitivity of the methods used to indicate renal damage, the type of infection being treated and the presence of concurrent diseases and/or drugs.

Nephrotoxicity with vancomycin is generally mild and develops in less than 5% of patients of all age groups; however, some studies report a higher incidence if the patients are also receiving aminoglycosides.[131,132] Vancomycin-nephrotoxicity occurring before 1980 has been attributed to impur-

ities present in the preparations the available.[131,132] Generally speaking, with the more highly purified preparations, adverse effects are uncommon.[132] After 1980, the incidence of glomerular toxicity in 460 adult patients treated with vancomycin as single-drug therapy was 8.2%.[130] In contrast, mean urinary biomarkers values remained stable in healthy volunteers treated for 3 days with vancomycin.[44]

Though the topic is controversial, the neonatal kidney seems as a rule less susceptible to vancomycin toxicity than the adult kidney,[118,122,133] thus confirming a number of experimental observations.[129] Immaturity of proximal tubular cells could determine a lower uptake of vancomycin when compared with other paediatric ages. The incidence of nephrotoxicity was 11% in children receiving vancomycin alone.[123] In newborns and young infants treated in another study, vancomycin was found to be well tolerated without alteration of renal function tests.[134] However, blood urea nitrogen and serum creatinine levels should be measured 2 or 3 times weekly in newborn babies receiving vancomycin treatment.[135]

3.1.1 Risk Factors Related to Vancomycin

Controversy still exist over the need for therapeutic drug monitoring with vancomycin.[136,137] Since the pharmacokinetics of vancomycin in newborns show a high degree of variability,[113] therapeutic drug monitoring is strongly suggested in order to maintain adequate concentrations and to avoid adverse effects. The situation is confused because in different studies the time of sampling after infusion has varied from 15 minutes to 3 or more hours.[113] Plasma concentrations should be measured 30 minutes before and 30 minutes after infusion,[113,133] especially after the third dose of vancomycin.[132] Similarly there is no consensus as to how frequently such determinations should be repeated: it depends by the presence of different risk factors.[132]

High Trough Values

Trough vancomycin concentrations of >10 mg/L have been associated with a 7.9-fold increase in the risk of nephrotoxicity, compared with lower predose values.[138] Moreover, high trough values of the drug may indicate an alteration in the pharmacokinetic profile with increased risk of both nephro- and ototoxicity. If therapeutic drug monitoring is impracticable, the suggested dosage should be calculated based on postconceptional age in the first week of life[139,140] and is related to renal function after the first week of life.[7,139] Guidelines for the dosage of vancomycin are presented in table V. For patients treated using these guidelines, 78% had both optimal peak and trough concentrations of vancomycin.[139] Administration by continuous infusion has also been associated with good renal tolerability.[141]

High Peak Concentrations

There is no confirmed evidence that transient high peak concentrations (>40 mg/L) are associated with toxicity.[129] Consequently some authors believe that trough-only monitoring can provide all the necessary information.[133,142]

Prolonged therapy

Patients being treated for periods of >3 weeks, and consequently receiving a high total dose, appear to be at increased risk for developing nephrotoxicity.[129] In the neonatal period it is rare to prolong therapy for more than 2 weeks.

3.1.2 Risk Factors Related to the Associated Pathology

High baseline serum creatinine levels and the presence of liver disease, neutropenia and peritonitis are considered significant risk factors for the development of nephrotoxicity.[129,130]

Table V. Vancomycin dosage guidelines for neonates[7,113,139]

Postnatal age ≤7 days	
Post-conceptional age (wk)	Dosage
≤30	15 mg/kg q24h
>30	10 mg/kg q12h
Postnatal age >7 days	
Serum creatinine level (μmol/L)	Dosage
>106	15 mg/kg q24h
62-106	10 mg/kg q12h
<62	10 mg/kg q8h

q8h = every 8 hours; **q12h** = every 12 hours; **q24h** = every 24 hours.

3.1.3 Pharmacological Risk Factors

When vancomycin is combined with other nephrotoxic drugs, such as an aminoglycoside, amphotericin or furosemide, the incidence of nephrotoxicity may be very high, with an incidence of up to 43%.[129] The combination of and aminoglycoside plus vancomycin is believed to increase the nephrotoxic risk 7-fold.[130] In paediatric patients who had received this combination, the incidence of nephrotoxicity was 22%.[123] In contrast, proper therapeutic drug monitoring of both the glycopeptide and the aminoglycoside minimised the nephrotoxicity in 60 children and 30 neonates.[143] Furthermore vancomycin was not found to potentiate amikacin-induced tubular nephrotoxicity in leukaemic, feverish and neutropenic children.[144] However, the combination of aminoglycoside plus vancomycin should be used with caution when an alternative combination is possible, when therapeutic drug monitoring of both drugs is impracticable, and in very low birthweight neonates.[108]

The use of indomethacin in combination with vancomycin was associated with a 2-fold increase in the elimination half-life of the glycopeptide.[145,146] Similar results were reported in patients treated with vancomycin and extra-corporeal membrane oxygenation.[113]

3.2 Teicoplanin

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%).[147] Moreover, the incidence of teicoplanin nephrotoxicity was lower (4.8%) when the agent was given in combination with an aminoglycoside than the incidence observed with the combination of vancomycin plus an aminoglycoside (10.7%).[114]

In a large study population consisting of 3377 hospitalised adults treated with teicoplanin, the incidence of nephrotoxicity (in this instance indicated by a transient increase in serum creatinine levels), was found to be 0.6%.[148] In paediatric patients the rate of nephrotoxicity is similar or lower.[149,150]

In neonates, 7 studies have been published to date and reviewed[115] and none of the 187 study participants treated with teicoplanin experienced an increase in serum creatinine levels. The participants of the studies received a dosage of 8 to 10 mg/kg after receiving a loading-dose regimen of 15 to 20 mg/kg/day. In the same patient group, 2 studies have compared the incidence of nephrotoxicity with vancomycin and teicoplanin.[151,152] In the first study, involving 63 neutropenic children, an increase serum creatinine levels was observed in 11.4% of vancomycin-treated and in 3.6% of teicoplanin-treated patients, respectively.[151] However, this difference was not significant. In the second study, involving 36 very low birthweight neonates (21 treated with teicoplanin and 15 with vancomycin) a significant difference was reported between mean serum creatinine values in the teicoplanin and vancomycin groups (60.5 μmol/L and 84.4 μmol/L, respectively); however, both values were within the normal range.[152]

Good general and renal safety has been demonstrated for teicoplanin in preterm neonates with staphylococcal late-onset sepsis[153] and when the agent is used for prophylaxis in very low birthweight neonates.[154] Finally, teicoplanin has been found to be well tolerated renally even following an overdose in a neonate; serum creatinine, cystatin C and BUN levels and urinary biomarkers remained constantly within the normal range.[155]

4. Cephalosporins

Cephalosporins and particularly third-generation compounds are very frequently used in the neonatal intensive care unit. Their low nephrotoxic potential is a major argument for their use rather than aminoglycosides in many children with serious infections.[156] A combination of ampicillin plus cefotaxime can be used as a substitute for ampicillin plus gentamicin for the empirical treatment of neonatal sepsis and meningitis, especially where therapeutic drug monitoring of the aminoglycoside is not possible.[50,11,112] The nephrotoxicity of cephalosporins, which has been extensively studied[50,111,112,133,157-160] depends mainly on 2 factors:

(i) the intra-cortical concentration of the drug; and (ii) the intrinsic reactivity of the drug.

4.1 Intra-Cortical Concentration

Many cephalosporins pass from the bloodstream into the tubule cells via an energy-dependent antiluminal active organic acid transport and are subsequently secreted by the proximal tubule cells into the lumen.[158-160] For cefaloridine, cefaloglycin and cefalexin tubular reabsorption is also postulated.[159] So the equilibrium created at the level of the tubule cell between active transport, secretion and reabsorption of the cephalosporin is determines the development of nephrotoxicity (fig. 3).[158-160]

The extreme importance of organic acid transport has been confirmed.[161] In fact, nephrotoxicity caused by cephalosporins (and more generally by ß-lactams) is limited to the compounds transported within this system. Moreover, prevention of nephrotoxicity is possible by inhibiting this transport. Finally, procedures that increase the intracellular uptake of cephalosporin increase toxicity.[161]

4.2 Intrinsic 'Reactivity'

The intrinsic 'reactivity' of a cephalosporin relates to its potential negative interaction with intracellular targets at 3 levels: (i) lipid peroxidation; (ii) acylation and inactivation of tubule proteins; and (iii) competitive inhibition of mitochondrial respiration.[159,160] Lipid peroxidation appears to play a major pathogenic role in the damage caused by cefaloridine.[161,162] Competitive inhibition of mitochondrial respiration could be the common pathway for the amplification of the damage in the case of aminoglycoside therapy combined with cephalosporins.[161,162] Cefaloridine and cefaloglycine are the only cephalosporins capable of causing kidney damage that involved the mitochondria at therapeutic dosages.[102,160-164] Cefaloridine can accumulate intracortically at very high levels, but the mitochondrial toxicity is reversible. Cefaloglycine also accumulates intracortically at high levels, but mitochondrial toxicity is not reversible.[159-161]

For all the other cephalosporins, renal damage can occur only at extremely high dosages, much greater than the routine therapeutic dosage.[156] The decreasing order of nephrotoxicity for the cephalosporins *in vivo* is cefaloglycin > cefaloridine > cefaclor > cefazolin > cefalothin >>> cefalexin > ceftazidime.[158] Cefalexin and ceftazidime are associated with a very reduced nephrotoxicity when compared with the other agents. In particular, ceftazidime, despite its significant intrinsic 'reactivity', achieves very limited active transport in the tubule proximal cell. Consequently, it is regarded as the least toxic compound from a renal standpoint in absolute terms.[157-160]

4.3 Third Generation Cephalosporins

The incidence of direct renal toxicity (defined as significant increase in serum creatinine levels) with the third generation cephalosporins is less than 2% of treated cases.[157] The exception is cefoperazone for which the incidence is 5%.[157]

When measuring serum creatinine levels, it should be remembered that cephalosporins are capable of interfering with the Jaffè reaction, which is the most commonly used technique for assaying creatinine levels in the blood and urine.[165]

4.3.1 Cefotaxime

Cefotaxime is unlikely to cause significant renal injury. This cephalosporin has not been shown to increase alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase enzymuria caused by aminoglycosides and furosemide.[167,168] The same results were obtained with enzymuria in patients with severe infection[169] and patients undergoing heart or lung surgery.[170] Cefotaxime has been used extensively in paediatric patients[171,172] and is generally well tolerated by newborn infants,[173] with respect to renal functional tests, even when it is administered with netilmicin.[5]

Another interest characteristic of cefotaxime is its low sodium content (about 20% and 25% of the sodium levels of ceftazidime and ceftriaxone, respectively): this could be a useful feature in newborns with hypernatraemia and/or fluid overload.[166]

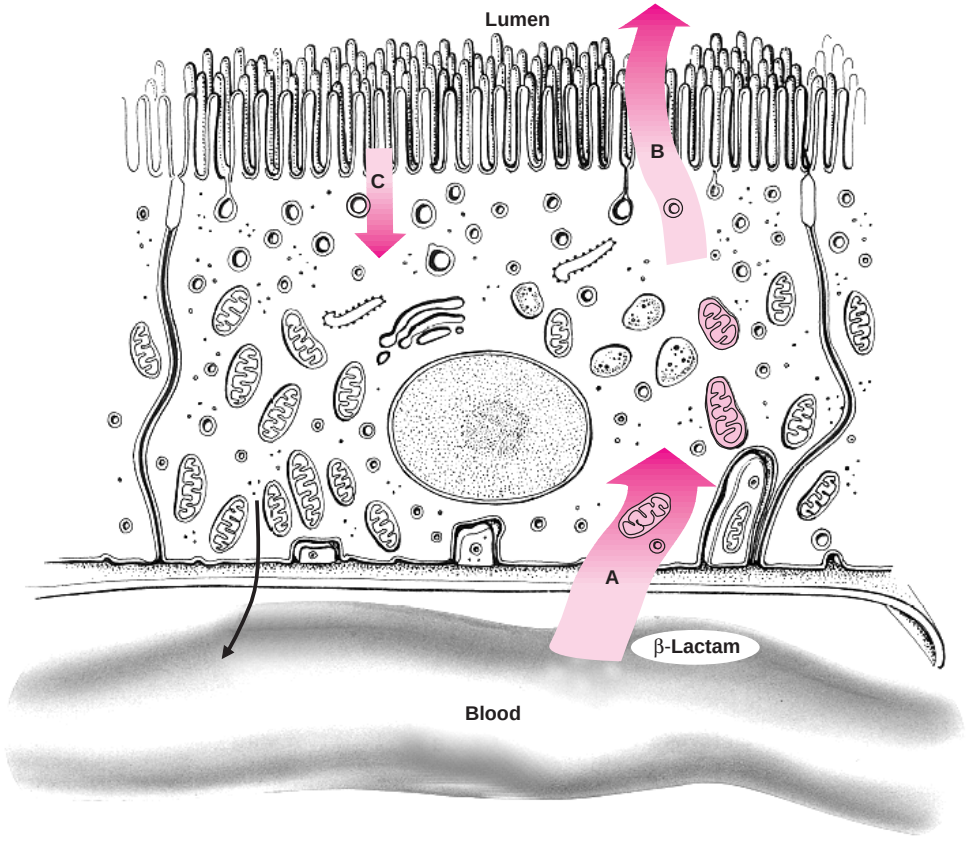

Fig. 3. Basal mechanism of ß-lactam (cephalosporin) nephrotoxicity. Three main processes are involved: (i) an energy-dependent antiluminal active organic acid transport (**A**); (ii) tubular secretion by the proximal tubule cells into the lumen (**B**); and (iii) tubular reabsorption (**C**). Other processes have little importance. The equilibrium created at the level of the tubule cell between these 3 processes determines the development of nephrotoxicity. The intrinsic 'reactivity' of the β-lactam means its potential negative interaction with the intracellular targets, namely a competitive inhibition of mitochondrial respiration. This mechanism could be the common pathway for the amplification of renal damage when aminoglycosides and cephalosporins are combined.

4.3.2 Ceftriaxone

Renal tolerability of ceftriaxone has been found to be good both in children (alterations in serum creatinine levels were seen in only 3 out of 4743 patients treated with ceftriaxone)[174] and in neonates,[175] even when given in combination with gentamicin.[176,177] Ceftriaxone has the advantage of a single daily administration. However, it should be used with caution in neonates, especially during the first week of life and/or in very low birthweight neonates[178] for the following 2 reasons: (i) the displacement of bilirubin from albumin, due to high protein binding; and (ii) diarrhoea, observed in 24 to 40% of treated children.[179]

4.3.3 Ceftazidime

An increase in serum creatinine level with ceftazidime has been observed only rarely in children[180] and neonates.[181] Only in 3 out of 271 neonates (1.1%)[173] treated with ceftazidime experienced an increase in serum creatinine level.

In both adults and children urinary microglobulins and enzyme levels remained unchanged during the course of ceftazidime treatment, com-

pared with control participants.[182,183] During ceftazidime plus tobramycin treatment enzymuria is identical to that obtained with the administration of tobramycin alone.[182] Increases in enzymuria or in urinary microglobulins were not observed in children treated with ceftazidime.[183] *N*-acetyl-β-D-glucosaminidase enzymuria values in preterm neonates treated with ceftazidime as single-drug therapy were normal.[110] In contrast, increases in alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase compared with baseline values were observed in newborns treated with a combination of ampicillin and ceftazidime, similar to those observed with ampicillin plus tobramycin.[58,184]

A comparison of the clinical use of the third generation cephalosporin in the newborn is presented in table VI.

5. Penicillins

Penicillins are widely used in neonatology. Penicillin is indicated in gonococcal infections or congenital syphilis. Ampicillin, as mentioned in section 2, in combination with an aminoglycoside is currently suggested as the first-line choice of therapy for the empirical treatment of early-onset bacterial infections. Methicillin, nafcillin and carboxypenicillins are rarely used today. Oxacillin is employed only in neonatal intensive care units that have low rates of methicillin-resistant bacteria. Ureidopenicillins are frequently used in the newborn.[50] Dosages of penicillins are calculated on the basis of birthweight and postnatal age. The recommended dosages for ampicillin, methicillin and nafcillin are presented in table VII.

Reliable statistical data on the frequency of renal complications following the use of penicillins do not exist.[6]

5.1 Acute Interstitial Nephritis

This immunologically mediated complication is characteristic of penicillins and their derivatives. In the early 1960s, methicillin was implicated in numerous well documented, biopsy-proven cases of acute interstitial nephritis.[187] Consequently, methicillin-induced acute interstitial nephritis represents the prototype for this drug-induced disorder.[187] It is reported that up to 15% of patients who receive methicillin, either continuously for 2 weeks or intermittently (i.e. 2 or 3 times a week) develop interstitial nephritis.[187] The triad of fever, rash and arthralgias occur in only 10 to 40% of patients who develop acute interstitial nephritis, eventually accompanied by eosinophilia or eosinophiluria. Urinalysis may show proteinuria, white blood cells or haematuria.[166,188] No specific tests are available for the diagnosis.[152] Discontinuation of the drug causing the acute interstitial nephritis leads almost invariably to clinical recovery.[188] Methicillin use has decreased considerably, particularly in the newborn, so reports of acute interstitial nephritis are now seen very infrequently.[187]

Table VI. A comparison of the clinical use of the third-generation cephalosporins in the newborn

Clinical situation	Cefotaxime	Ceftazidime	Ceftriaxone	References
VLBW neonates[a]	+	+	-	177
Jaundice, diarrhoea	+	+	-	177
Bleeding disorders, haemolysis	±	+	+	156-158
Fluid overload and hypernatraemia	+	-	±	108, 166
Coadministration[b] with:				
β-Lactams	+	±	+	58,108
Aminoglycosides	+	+	+	4, 77, 176

a Especially in the first week of life.

b With respect to nephrotoxicity.

+ = Prefer; – = avoid; ± = use with caution.

5.2 Toxic Nephropathy

Direct renal damage due to penicillins is rare, is similar to that produced by cephalosporins and is linked essentially to depression of mitochondrial respiration.[161] The incidence and the severity of nephrotoxicity are potentiated by coadministration of aminoglycosides, renal ischaemia and by endotoxaemia.[161]

5.3 Salt Overload

Carboxypenicillins (carbenicillin and ticarcillin) are excreted by the kidney,[154] and should be carefully used in neonates with heart failure, renal disorders, hypernatraemia or fluid overload.[189,190] In these situations ureidopenicillins (mezlocillin, piperacillin, azlocillin) which have a lower salt load, may be used.

6. Carbapenems

Carbapenems have a significant potential for nephrotoxicity. However data on their use and safety in neonates are very limited.[191] 'Reactivity' is generally greatest in the newer ß-lactam classes: penems > cephalosporins > penicillins.[160]

Together with cefaloridin and cefaloglycin, imipenem is the most nephrotoxic ß-lactam compound. Panipenem, which is comparably nephrotoxic is currently available only in Japan.[160] Imipenem is hydrolysed at the renal level by a brush border enzyme (dehydropeptidase I) giving rise to more toxic and less active metabolites. Consequently, imipenem is administered together with cilastatin, a specific inhibitor of dehydropeptidase I in a 1 : 1 ratio, which prevents nephrotoxicity. However, inhibition of penem transport across the choroid plexus increases CNS levels and predisposes to neurotoxicity.[160] In large clinical series in adults (2516 patients), an increase in serum creatinine level was seen very rarely (0.1%).[192] It is important to remember that the drug may cause seizures especially in patients with CNS dysfunction and pre-existing renal failure.[193-196] It also should be remembered that sodium content of the drug is 3.2 mmol. The dosage of imipenem for neonates is 20 mg/kg dose every 12 hours.[191]

A lower potential for the induction of epileptogenic activity and nephrotoxicity was observed with meropenem in patients of all ages.[195] However this finding requires further confirmation.

Table VII. Recommended dosages for ampicillin, methicillin and nafcillin dosage in the newborn[50,185,186]

Age	Neonatal weight (g)	Total daily dose (mg/kg)[a]	Frequency of divided doses
0-7 days	≤2000	50	q12h
	>2000	75	q8h
>7 days	≤2000	75	q8h
	>2000	100	q6h

a Give IM, or IV over 20 minutes.

q6 = every 6 hours; **q8h** = every 8 hours; **q12** = every 12 hours.

7. Monobactams

Aztreonam is the first member of the monobactam class. No evidence of nephrotoxicity with this compound has been demonstrated in adults (2388 patients) and in children (665 patients).[197-200] In 283 newborns treated in 5 international trials, only 2 cases of increased serum creatinine levels were observed (0.7%) and enzymuria remained within a normal range even in low birthweight infants.[201-205] Thus, aztreonam is a reasonable alternative to aminoglycoside therapy in newborns with Gram-negative infections at risk of both nephrotoxicity and ototoxicity or when therapeutic drug monitoring of aminoglycosides is impractical.[108] A 30 mg/kg dose given every 12 hours is appropriate in the first week of life, followed by every 8 hours thereafter.[109]

8. Conclusions

Antibacterials are the leading cause of drug-induced kidney disease in all age groups, bringing about damage essentially via 2 mechanisms, namely toxic and immunological damage. When discussing nephrotoxicity in the neonate, what is generally being referred to is toxic damage.

Nephrotoxicity is generally reversible on discontinuing therapy. However, acute renal failure can occur, and drug involvement in the development of renal impairment seems to be increasing, especially in newborns admitted in neonatal intensive care units. Preventing this occurrence will lead to decreased mortality and length and cost of hospital stay.

In newborns, especially in very low birthweight newborns, the exposure to antibacterials may be extremely widespread. Aminoglycosides (in combination with ampicillin) and vancomycin (in combination with ceftazidime) are commonly suggested for empirical treatment of early- and late-onset infections in the newborn, respectively.

However, aminoglycosides are the most nephrotoxic antibacterials and vancomycin may be associated with significative renal toxicity. This is particularly true in high risk patients. Other antibacterials, such as penicillins, cephalosporins and monobactams are less nephrotoxic. Keys to preventing nephrotoxicity are as follows.

1. Minimisation of the use of documented nephrotoxins. A third-generation cephalosporin, such as cefotaxime, or a monobactam (such as aztreonam) can be used instead of an aminoglycoside for the empirical treatment of early-onset infections in high risk patients or when the therapeutic drug monitoring of the aminoglycoside is not possible. Similarly, in the same circumstances, teicoplanin may be an alternative to vancomycin in the treatment of late-onset infections.

2. Minimisation of nephrotoxic potential of antibacterials. This may be obtained with a correct administration of the drug: namely, performing therapeutic drug monitoring and maintaining trough concentrations within a normal range, avoiding excessive length of treatment and, if possible, administration of concurrent nephrotoxins.

3. Early detection of nephrotoxicity and in particular of acute renal failure with subsequent rapid withdrawal of the offending agent. The increased urinary excretion of low molecular weight proteins and enzymes may antedate a rise in serum creatinine levels. In particular rapid and conspicuous increases (>99° percentile) of urinary *N*-acetyl-ß-D-glucosaminidase may suggest a need for re-evaluation of, if not a cessation of, therapy.

In conclusion, in view of the extremely widespread use of antibacterials in neonatology and the multiplicity of potentially nephrotoxic factors for the newborn, a knowledge of the issues outlined in this review are particularly important for the prevention of iatrogenic effects.

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