Drug Saf (2013) 36:217–230
DOI 10.1007/s40264-013-0031-0

REVIEW ARTICLE

Aminoglycosides in Septic Shock

An Overview, with Specific Consideration Given to their Nephrotoxic Risk

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Published online: 19 March 2013

Abstract Aminoglycoside nephrotoxicity has been reported in patients with sepsis, and several risk factors have been described. Once-daily dosing and shorter treatment have reduced nephrotoxicity risk, and simplified aminoglycoside monitoring. This review focuses on nephrotoxicity associated with aminoglycosides in the subset of patients with septic shock or severe sepsis. These patients are radically different from those with less severe sepsis. They may have, for instance, renal impairment due to the shock *per se*, sepsis-related acute kidney injury, frequent association with pre-existing risk factors for renal failure such as diabetes, dehydration and other nephrotoxic treatments. In this category of patients, these risk factors might modify substantially the benefit-risk ratio of aminoglycosides. In addition, aminoglycoside administration in critically ill patients with sepsis is complicated by an extreme inter- and intra-individual variability in drug pharmacokinetic/pharmacodynamic characteristics: the volume of distribution (Vd) is frequently increased while the elimination constant can be either increased or decreased. Consequently, and although its effect on nephrotoxicity has not been explored, a different administration schedule, i.e. a high-dose once daily (HDOD), and several therapeutic drug monitoring (TDM) options have been proposed in these patients. This review describes the historical perspective of these different options, including those applying to subsets of patients in which aminoglycoside administration is even more complex (obese intensive care unit [ICU] patients, patients needing continuous or discontinuous renal replacement therapy [CRRT/DRRT]). A simple linear dose adjustment according to aminoglycoside serum concentration can be classified as low-intensity TDM. Nomograms have also been proposed, based on the maximum (peak) plasma concentration (C_{max}) objectives, weight and creatinine clearance. The Sawchuk and Zaske method (based on the determination of C_{max} and an intermediate aminoglycoside assay before minimum plasma concentration) and the Bayesian method were both classified as high-intensity TDM programmes. Given the mean cost of aminoglycoside nephrotoxicity, these programmes may be cost-effective if its prevalence is above 10 %. However, none of these high-intensity TDM programmes have demonstrated a reduction of aminoglycoside-associated nephrotoxicity in patients with septic shock. Therefore, the questions remain as to, first, whether a TDM programme is relevant and, second, what intensity of TDM is achievable in the ICU, i.e. how it can be practically applied in the ICU setting where urgent care and high workload are substantial obstacles to a sophisticated, optimized aminoglycoside administration.

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1 Introduction

The characteristics of aminoglycosides play a crucial role in the empiric antibacterial treatment of sepsis. First, their

broad-spectrum activity includes both Gram-negative bacilli (GNB) and Gram-positive cocci (GPC). Moreover, *in vitro* synergism with β-lactams has been proven against many GNB or GPC, and they have demonstrated a post-antibiotic effect. Finally, while infections occurring in intensive care units (ICUs) are increasingly caused by highly resistant bacteria, bacterial resistance to aminoglycosides at the individual [1] or global scale [2] remains stable despite years of use. For other considerations, such as, for instance, the rise in *Clostridium difficile* infections, restrictions in broad spectrum antibiotics has been accompanied by an increase in the use of aminoglycosides [3]. Most common aminoglycoside indications have been extensively reviewed in recent publications [4–6]. Adding an aminoglycoside to a standard antibacterial treatment did not translate into a reduction of mortality either in GPC endocarditis or GNB sepsis, at least in subgroups of patients with degrees of severity or a resistance to β-lactams of less than 10 % [7, 8]. This was consistent with the increase in mortality recently reported in a meta-analysis comparing a bitherapy with a β-lactam alone in patients presenting with severe sepsis [9]. Conversely, one may notice that a bitherapy improved the prognosis of patients with septic shock compared with β-lactams alone [9]. In addition, aminoglycosides enlarge the spectrum of the antibacterial treatment, which should be advantageous in populations with an increased risk of resistant bacteria (such as healthcare-associated vs. community-acquired infections) [10]. ICUs frequently admit such patients [4, 5]. Empiric antibacterial treatments including aminoglycosides could be more appropriate in up to 15–20 % of cases compared with a β-lactam alone [11, 12]. Furthermore, particularly in the ICU setting, modifications of the empiric antibacterial treatment or the addition of a new antibacterial occur less frequently with bitherapy than with monotherapy [13].

The prescription of aminoglycosides is simple in most hospitalized patients and it has been suggested to simplify or even abandon their monitoring. Indeed, many authors recommend no trough plasma concentration monitoring if creatinine clearance (CR_{CL}) exceeds 60 mL/min and/or the treatment duration is less than 5 days [14, 15]. Also, maximum (peak) plasma concentration (C_{max}) monitoring would be futile in case of bacteria with low aminoglycoside minimum inhibitory concentration (MIC) [16]. In their institution, Zahar et al. reserved drug level monitoring to patients with renal failure or those treated for more than 5 days, and showed, however, a reduction in aminoglycoside nephrotoxicity [17]. In patients admitted to the ICUs, the context is fundamentally different. Twenty-five percent of the most commonly used drugs are potentially nephrotoxic [18] and nephrotoxic-associated acute renal failure (ARF) occurs in 10–20 % of patients [19]. Unfortunately, aminoglycosides have an important limitation, namely their nephrotoxicity, which has been one of the oldest studied drug complications [20]. Therefore, nephrotoxicity of aminoglycosides is as feared, as their efficacy is needed [5, 6, 9, 10]. In critically ill patients, aminoglycoside monitoring is probably crucial and subsequent optimization critical. Our main goal was to give an overview of aminoglycoside use in the septic shock population with specific considerations to nephrotoxicity risk.

The present review is based on an evaluation of the literature, selected using a computerized MEDLINE search limited to adults, without limit in the past publication dates, and updated on 1 June 2012. Search terms were 'aminoglycoside', 'nephrotoxicity', 'acute renal failure', 'acute kidney injury', 'intensive care', 'critical care', 'septic shock', 'severe sepsis' and 'drug monitoring', as well as a combination of these terms. Review articles, consensus statements and the references cited herein were also considered in order to update our current knowledge on this topic. To the best of our knowledge, no previous review has focused on this subset of patients. This review could also give some perspective on the opportunity to optimize aminoglycoside administration and to determine what future studies should be planned.

2 Aminoglycoside Nephrotoxicity

2.1 Mechanisms

Following intravenous infusion, aminoglycosides are minimally bound to plasma proteins and their elimination occurs primarily via glomerular filtration. After that, aminoglycosides bind to the brush-border membrane of the proximal tubule epithelial cells [21]. This uptake depends on the aminoglycoside cationic charge, which attaches to the negatively charged acid phospholipids of the brush-border. This phenomenon is saturable and only a small amount of circulating aminoglycoside is concerned. The megalin-cubilin system allows their internalization mostly into the endosome then the lysosome via the physiological endosome-lysosome fusion [21]. Once in the lysosome, aminoglycoside accumulation will result in several cellular alterations. First, (mostly proximal) tubular cell apoptosis and necrosis occur through both a mitochondrial effect impairing adenosine triphosphate production and producing oxidative stress, and an effect on endoplasmic reticulum inhibiting protein synthesis [21]. Aminoglycosides also impair tubular reabsorption through the inhibition of membrane transporters [21]. The tubular-induced decreased reabsorption of water and electrolytes results in osmotic diuresis and renin-angiotensin system activation, which further decreases the glomerular filtration rate

(GFR) in parallel with the leaking of tissue and cellular residues to the tubular lumen. Moreover, an aminoglycoside-associated mesangial contraction has also been suggested [21]. Morphologic alterations of glomerular endothelial fenestrae also participate in reducing GFR. Finally, a decrease in vasodilator prostaglandins strengthens both the vasoconstrictor effect of the renin-angiotensin activation and the impairment of vascular smooth muscle-relaxing capacity, and results in a subsequent and sometimes final reduction in GFR [22].

2.2 Clinical and Biological Manifestations

Aminoglycoside nephrotoxicity can be accompanied by an increase in plasma creatinine and a polyuric renal excretion with a progression to oligo-anuric renal failure, which remains uncommon. This generally occurs during the treatment or a few days after aminoglycosides have been stopped. A mean delay of 9 days between the first aminoglycoside administration and the subsequent nephrotoxicity has been described by Rybak et al. [23]. Conversely, Cosgrove et al. recently reported later plasma creatinine increase (up to day 21) in patients receiving prolonged aminoglycoside treatment for endocarditis in association with vancomycin [24]. Recovery upon discontinuation is usual and the need for renal replacement therapy (RRT) remains occasional [21].

2.3 Biological Surrogates for Aminoglycoside Nephrotoxicity

Several biological surrogates have been studied. It has been shown that β_2-microglobulin, urinary casts [25–27] and urinary gentamicin concentrations [28] increased a few days before CR_{CL} decreased. Urine N-acetyl-β-D-glucosaminidase (NAD) and alanine aminopeptidase (AAP) have also been proposed owing to their specificity, sensitivity and early detection properties [29–33]. A randomized study comparing two aminoglycoside regimens (once-daily dose [ODD] vs. multiple daily doses [MDD]) in selected critically ill patients revealed that NAD and AAP decreased in the ODD arm [34]. To date, no study evaluating the impact of a prevention strategy, including the level of these markers on nephrotoxicity, has been performed.

2.4 Precipitating Factors for Aminoglycoside-Associated Nephrotoxicity in Non-Severe Patients

Studies identifying risk factors for nephrotoxicity included mainly patients with non-severe sepsis and did not necessarily focus on critically ill patients. With the exception of patients with cystic fibrosis, the risk factors for aminoglycoside-associated nephrotoxicity are summarized in Table 1. Since the GFR fluctuates according to a circadian rhythm, whether aminoglycosides are administered at 1:30 pm or 1:30 am could influence their subsequent accumulation and nephrotoxicity [35], at least in patients treated for more than 10 days [36]. Authors have proposed scores to predict the risk of nephrotoxicity [37, 38]: beyond the fact that they were developed for nephrotoxicity associated with longer aminoglycoside duration (10 days), their performance has not always proven to be consistent [39].

2.5 Protective Factors for Aminoglycoside-Associated Nephrotoxicity in Non-Severe Patients

In patients with sepsis who receive aminoglycosides, several points must be highlighted:

- 'ODD' administration, consisting of one higher dose once a day, applies perfectly to aminoglycosides, the efficiency of which is related to the C_{max}/MIC ratio [40]. The aminoglycoside post-antibiotic effect also favours the ODD regimen. Moreover, it decreases aminoglycoside accumulation in renal tissue since the aminoglycoside attachment to the brush-border is saturable [36, 41, 42]. The lower accumulation should in turn decrease nephrotoxicity, as suggested in several studies [2, 23, 36, 43–45] and confirmed by a meta-analysis [46]. However, in three other meta-analyses, the ODD regimen did not reduce aminoglycoside nephrotoxicity [47–49] and subgroups should be considered. In particular, the ODD regimen does not influence nephrotoxicity in endocarditis patients [24, 50], patients with febrile neutropenia [49] or patients with previous altered renal function [51].
- The duration of aminoglycoside treatment has been frequently associated with nephrotoxicity [2, 14, 15, 24, 43, 52–55]. An ODD-associated nephrotoxicity reduction was observed in shorter duration aminoglycoside treatment (<7 days) [53]. Beyond 7 days, the aminoglycoside duration can even be more nephrotoxic than accounted for by the administration schedule (ODD vs. MDD) [53].
- The aminoglycoside dose indirectly influences nephrotoxicity risk. As anticipated, the dose impacts minimum plasma concentration (C_{min}) and the area under the concentration-time curve (AUC) of aminoglycosides. Both have been associated with aminoglycoside nephrotoxicity [23, 54, 56, 57].
- Therapeutic drug monitoring (TDM) of aminoglycosides: The question as to whether TDM could reduce

Table 1 Risk factors for nephrotoxicity with aminoglycosides in patients with sepsis

Patient	Metabolic disturbances	Aminoglycoside treatment	Other nephrotoxic drugs [14, 54, 90]
Older age [38, 55]	*Hypercalcaemia* [93]	**Duration of therapy** [2, 14, 15, 24, 36, 37, 43, 44, 52, 54, 55, 168]	Furosemide[a] [14, 55, 169, 170]
Female sex[a] [37, 38, 168, 171]	*Metabolic acidosis* [22, 93]	**High daily AUC** [2, 23, 54, 56, 57]	Angiotensin inhibitor [172]
Diabetes [90, 172]	*Magnesium depletion* [93]	**High trough concentrations** [2, 23, 54, 56–58]	*NSAIDs* [22, 93]
Cirrhosis [55, 173]	*Potassium depletion* [93]	MDD[a] [2, 36, 44–47, 53, 125, 126]	*Cisplatin* [22, 93]
Ascitis [54, 174]	*Sodium depletion* [93]	**Circadian rhythm**[b] [35, 36]	*Ciclosporin (cyclosporine)* [22, 93]
Low albumin concentration [54, 175]		One class of aminoglycosides[a] in comparison with other classes [125, 168, 171]	Iodide contrast media [22, 90, 93]
Reduced renal function [22, 37, 38, 44, 73, 93, 173]			**Other antibacterials**
Reduced renal mass [22]			**Vancomycin** [22, 23, 54, 168]
Leukaemia [54]			Cephalosporins [22, 54]
			Piperacillin [168]
			Clindamycin [168]
			Amphotericin B [22, 54, 93]

Bold text indicates risk factors described by at least two authors with multivariate analysis

Normal text indicates risk factors described by only one author with multivariate analysis

Italicised text indicates risk factors cited by review articles without references

AUC area under the plasma concentration-time curve; *MDD* multiple daily dosing

[a] Although classified as a risk factor by at least two studies, other studies report contrasting results

[b] Night vs. diurnal administration

aminoglycoside nephrotoxicity of patients with non-severe sepsis remains debatable. While initial studies, focusing on different subgroup of patients (renal transplantation [58], febrile neutropenia [59]) or not [60], showed no nephrotoxicity reduction with TDM programmes, more recent studies using Bayesian models [61, 62], simpler monitoring methods (C_{max} and C_{min} monitoring [25, 63] or only C_{min} [14] at each aminoglycoside administration), nomogram-tailored aminoglycoside dosages [15], pharmacist-driven aminoglycoside quality programmes [62, 64–67] or just compliance with the above-cited concepts (ODD, short duration, dose considerations) [17] were effective in reducing aminoglycoside nephrotoxicity.

Other protective factors have been recently reviewed [22, 68, 69]. Briefly, they can be classified into inhibitors of tubular accumulation of aminoglycosides targeting the megalin-related endocytic machinery (e.g. statins), co-treatment with renal protective drugs (e.g. antioxidants, free radical scavengers), treatments that improve the renal blood flow (e.g. calcium antagonists, platelet activating factor inhibitors) and miscellaneous others. Nearly all these studies were preclinical and, pending future clinical studies, none of these preventive strategies can be currently recommended.

2.6 Incidence

The incidence of aminoglycoside-associated nephrotoxicity depends on the definition of nephrotoxicity, the observation time window and the studied populations [70]. Altogether, a mean incidence of 20 % has been reported with a wide definition (>33 % decrease in CR_{CL} ± plasma creatinine increase ≥0.3 mg/dL), whereas the mean incidence is only 10 % if the definition is more restrictive (>50 % decrease in CR_{CL} ± plasma creatinine increase ≥0.5 mg/dL) [70]. Both definitions may overestimate aminoglycoside-associated nephrotoxicity, and the addition of criteria for tubular damage to the definition based on plasma creatinine lowers its incidence by 2- or 3-fold [26, 71]. More recently, a score designed to assess ARF, the RIFLE score [72] (Risk, Injury, Failure, Loss, End-stage kidney disease), found ARF in 24 % of patients receiving aminoglycosides [73]. However, aminoglycoside-attributed nephrotoxicity is somewhat difficult to assess properly because of frequent confounding factors associated with ARF [74, 75]. In patients with febrile neutropenia receiving aminoglycosides, severe sepsis accounted for the vast majority of ARF (>98 % of cases) according to a retrospective consensus of two physicians [76]. In critically ill patients, the challenge is even greater since ARF has multiple causes. ARF is

observed in 5–14 % of patients receiving aminoglycosides, according to the standard above-cited definitions [26, 77, 78]. To the best of our knowledge, only one study has assessed a 5 % risk of aminoglycoside-attributed nephrotoxicity in post-traumatic ICU patients [79]. Finally, there is a consensus that aminoglycoside-associated nephrotoxicity has decreased over the years due to better consideration of both precipitating and protective factors (see below) [70].

3 Aminoglycosides in Critically Ill Patients with Severe Sepsis or Septic Shock

3.1 Overview

The benefit-risk ratio of aminoglycosides is somewhat different for critically ill patients. Infections are more severe, involving bacteria that are less sensitive to standard antibacterial treatments and often in immunosuppressed patients. In addition, renal clearance of these patients is frequently altered. This complicates administration in these patients, particularly because C_{min} must remain under the toxicity threshold [80]. In addition, one must certainly avoid the fact that aminoglycosides decrease renal function since even such a small decrease may alter the prognosis of critically ill patients [81, 82]. Adoption of the ODD regimen may not be sufficient to change any nephrotoxicity risk because aminoglycoside doses increase in parallel with bacterial MICs [83]. This is arguably the case for patients with severe sepsis with reduced CR_{CL} [84]. Drusano et al. clearly illustrate the resulting illusory trade-off between aminoglycoside efficiency and toxicity [6]; targeting a high aminoglycoside C_{max} inevitably increased nephrotoxicity risk. However, an aminoglycoside duration of less than 6 days even at 10 mg/kg doses of netilmicin in critically ill patients with serum Cr < 150 μmol/L did not result in more nephrotoxicity complications compared with lower doses [85]. In general, if the short duration and ODD regimen are respected, high doses should probably still be considered [2].

Moreover, recent data showed improved prognosis in septic shock patients receiving aminoglycosides and β-lactams compared with β-lactams alone [9, 10]. As a result, many ICU teams keep using aminoglycosides in critically ill patients with sepsis even with altered renal function [6, 17, 25, 86]. Owing to aminoglycoside drawbacks, other teams give priority to the use of fluoroquinolones in association with β-lactams [6], whatever their potential for the induction of cross-resistance [87, 88]. To the best of our knowledge, no study evaluated the incidence and the reasons for these different options.

3.2 Critically Ill Patients Have a High Baseline Risk for Nephrotoxicity

3.2.1 Altered Baseline Renal Function

Chronic renal failure is a common risk factor for aminoglycoside nephrotoxicity [54, 89, 90]. Cosgrove et al. [24] and Radigan et al. [91] initially proposed a 50 mL/min or 60 mL/min CR_{CL} threshold, respectively, for the aminoglycoside-associated nephrotoxicity risk to occur. However, acute kidney injury (AKI; a recognized definition of ARF in ICU patients) may be more accurately assessed by the RIFLE score than by CR_{CL} [72]. For instance, altered renal function as assessed by Cosgrove et al. in their recent study of aminoglycoside-associated nephrotoxicity risk [24], would rather correspond to the R, I or F stages. Patients with chronic renal failure necessitating RRT are L or E. During the first 2 ICU days, the incidence of R, I or F scores is 35–45 %, [82, 92] highlighting the specific risk of critically ill patients. Sepsis is the main determinant of AKI, leading both to a true fluid hypovolemia (by frequent decreases in oral hydration and nutrition, fever, diarrhoea or vomiting in the days preceding ICU admission) and a relative hypovolemia (vasoplegic state, sedation, sepsis-specific increased capillary leakage) [55, 91]. Studies in humans reported that nephrotoxicity risk was correlated to the severity of sepsis [15, 55, 79, 90].

3.2.2 Sepsis-Specific Acute Kidney Injury

Several experimental studies reviewed by Zager et al. have demonstrated that the aminoglycoside-associated nephrotoxicity risk was synergistic not only with non-specific renal hypoperfusion factors but also with more specific ones such as endotoxemia and fever [20, 93, 94]. More recently, Lipcsey et al. compared four groups of pigs (endotoxemia + tobramycin, endotoxemia + physiologic serum, physiologic serum + tobramycin, physiologic serum alone) and suggested that the sepsis-induced hypoperfusion was predominant over the aminoglycoside-specific toxicity on the occurrence of ARF [95]. Lastly, very recent animal experimentations showed that bactericidal antibacterials resulted in a more severe and transient AKI than placebo [96].

3.2.3 Frequent Co-Morbidities

Critically ill patients often present with several risk factors such as diabetes mellitus, reduced renal function and low albumin concentration (see Table 1).

3.2.4 Association with Other Nephrotoxic Treatments

Even if resistant bacteria can develop in the entire hospital, they are often more concentrated in the ICU. In this context, the concomitant administration of other nephrotoxic antibacterials such as vancomycin or colistin [97] is common. In particular, the increased aminoglycoside-associated nephrotoxicity in the presence of vancomycin has been well described [23, 24, 98, 99]. Other treatments such as diuretics [100] or iodinated contrast media are also commonly used in critically ill patients. Some authors went so far as to avoid aminoglycoside administration on the day preceding iodinated contrast perfusion [101]. Finally, an exhaustive list of frequently administered nephrotoxic agents has been proposed by Pannu and Nadim [43], which should prompt caution when used in association with aminoglycosides [90].

3.3 Aminoglycoside Administration is a Complex Issue

In critically ill patients with sepsis, an 83 % variability in pharmacokinetic/pharmacodynamic (PK/PD) characteristics has been observed between two consecutive aminoglycoside administrations [102]. Target attainment for aminoglycoside is tricky [103].

3.3.1 Volume of Distribution (Vd)

In the study by Rea et al., the 41 % individual Vd variability was explained by a highly variable haemodynamic and inflammatory state, which is the hallmark of critically ill patients with sepsis [102]. Inflammation is responsible for the increased capillary permeability. A more or less aggressive fluid resuscitation is required according to the severity of sepsis [104–107]. The weight gain secondary to aggressive intravenous fluid resuscitation [108] and the consecutive hypoalbuminaemia [109] have been shown to be associated with an increased Vd. In contrast, the presence of an ARF has been shown to either reduce or increase the Vd [28, 110, 111]. Other factors such as cirrhosis [105] or the degree of respiratory failure [109] have also been associated with Vd variations. Because of increased Vd, target attainment often cannot be achieved with normal aminoglycoside doses in patients with septic shock [78, 80, 112], trauma [107, 113, 114], or in surgical [115] or medical [102] ICU patients. Even larger doses exceeding the common recommendations (24 mg/kg amikacin) failed to reach this objective [116]. To further add to the complexity of critically ill patient management, Vd can normalize during the ICU stay in parallel with the treatment of sepsis [107, 117, 118] so that subsequent doses of aminoglycosides will need to be continuously adapted.

3.3.2 The Elimination Rate Constant (Ke)

In patients with septic shock, the elimination rate constant (Ke) can be increased and therefore result in concentrations of aminoglycosides lower than the MIC during a time window exceeding the duration of post-antibiotic effect [114]. Conversely, Ke can be decreased in the case of altered renal clearance or cirrhosis [105]. Ke is generally intimately related to CR_{CL}, and patients with severe sepsis, including those with ARF, [86] follow this rule. However, as in patients with febrile neutropenia [119], CR_{CL} accounts for approximately one-half of the aminoglycoside Ke in septic shock [46, 120, 121]. CR_{CL} can be approximated by Cockroft's method [122] but also by the Chronic Kidney Disease–Epidemiology (CKD-EPI) method, which could be more accurate in patients with extreme bodyweights [123]. No study at this time has correlated the latter to the specific aminoglycoside Ke. Up to 70 % of the Ke can be accounted for by the addition of severity markers such as the haemodynamic state, the ventilatory supply parameters (a positive end expiratory pressure can impair renal arterial flow) [109] or the global response to physiologic stress [124]. Still, a large inter-individual variability persists.

3.3.3 The Aminoglycoside Area Under the Concentration-Time Curve

The AUC reflects the global exposure to aminoglycosides. Begg et al. proposed to introduce AUC in a TDM programme to reduce aminoglycoside-associated nephrotoxicity [16]. However, this cannot be applied to critically ill patients since Ke, Vd and therefore AUC will be highly variable in this subset of patients [57]. Despite these limitations, the proposed AUC target for critically ill patients is between 70 mg · h/L (efficacy threshold) and 120 mg · h/L (toxicity threshold) [23, 32, 57].

3.4 Current Recommendations for Aminoglycoside Administration

3.4.1 General Recommendations

Dose and administration regimen: First, it must be outlined that current recommendations for patients with sepsis may not apply to septic shock or severe sepsis [102]. The ODD regimen reduced nephrotoxicity in critically ill patients with gentamicin [125, 126], tobramycin [34] and isepamicin. Beyond the ODD concept, which was only implemented in 25 % of North American patients in the year 2000 [127], the HDOD schedule for aminoglycoside administration should be preferred [70]. The objective for C_{max} is to reach ten times the MIC of the most resistant

bacteria involved in the infection [6, 40, 108, 128]. Generally, 5 mg/kg/day tobramycin or gentamicin, or 15 mg/kg/day amikacin can achieve this objective [91, 108]. However, in healthcare-associated infections in which more resistant bacteria are frequently observed, a more aggressive dose should be considered, i.e. 7 mg/kg/day gentamicin or tobramycin, [6, 16, 129] or 20–25 mg/kg/day amikacin [16, 130]. These recommendations would not apply to patients with previously altered renal function since, to the best of our knowledge, no study specifically addressed the HDOD issue in this subset of patients. The site of infection should also be considered since HDOD is more relevant in pulmonary or meningeal infections in which aminoglycoside penetration is reduced. Conversely, aminoglycoside administration in two to three equally divided doses remains indicated in the treatment of endocarditis [4, 91]. However, studies assessing aminoglycoside efficiency according to the site of infection did not separate infections according to their degree of severity. Moreover, different TDM or administration regimens have not been studied according to different infection sites [4, 91].

Duration: With the HDOD regimen, a maximum of 5 days of aminoglycosides is recommended, [6, 91] along with limitation of the use of concomitant nephrotoxic treatments [91].

Monitoring: Traditionally, simple monitoring of plasma aminoglycoside concentrations has been used and the dosing interval was determined according to CR_{CL} [91]. It proved to be efficient in reducing nephrotoxicity when rigorously performed [17]. However, C_{max} monitoring remains controversial since some authors advocate it only for immunosuppressed patients, for patients receiving more than 10 days of aminoglycosides or for bacteria MICs ranging from 8 to 16 mg/L [56]. Recent French recommendations consider C_{max} monitoring only after the first infusion in patients with severe sepsis [131]. The C_{max} objective is also different according to what recommendation is considered, varying from 20–25 mg/L to 30–40 mg/L for gentamicin, tobramycin or netilmicin, [131] and 60 mg/L for amikacin [129]. As soon as the MIC has been provided (which unfortunately often takes longer than the duration of aminoglycosides), aminoglycoside doses should be tapered. C_{min} monitoring is more consensual as it is clearly related to nephrotoxicity [56]. However, monitoring of C_{min} only for aminoglycoside treatment of more than 5 days or in the case of altered renal function has recently been recommended [131]. The specificity of patients with severe sepsis with fluctuating renal function has not been taken into account by these recommendations. The C_{min} objectives vary from 0.5 mg/L [131] to 1 mg/L [130] or 2 mg/L for gentamicin, tobramycin or netilmicin, and from 2.5 mg/L [131] to 5 mg/L for amikacin [56].

3.4.2 Obese Adult Intensive Care Unit (ICU) Patients

Obese adults represent up to 25 % of ICU patients [132]. Using total bodyweight (TBW) for aminoglycoside administration purposes could lead to an overestimation of the dose and it has been proposed to use alternative body-size patient descriptors such as ideal bodyweight (IBW). The dose is calculated according to dosing weight (DW), assuming that $(DW; kg) = IBW + 0.4\ (TBW - IBW)$. Recently, Pai et al. suggested that the lean bodyweight, which can be deduced from TBW, would be more accurate than IBW to reach C_{max} objectives in obese or even severely underweight patients [123]. In obese patients, the PK/PD objectives are unchanged so that HDOD remains recommended unless renal function is altered, which automatically leads to tailoring of the doses.

3.4.3 ICU Patients Needing Renal Replacement Therapy

Ten percent of patients in the ICU need RRT [82]. Aminoglycoside treatment for this group of patients is different depending on whether the patients present with chronic renal insufficiency already treated by RRT or with an ARF needing urgent RRT. The risk of ototoxicity prevails for the former whereas the issue of long-term renal recovery is much more relevant for the latter. In both cases, the objectives regarding aminoglycoside efficiency (C_{max} and AUC >70 mg · h/L) or toxicity (AUC <120 mg · h/L) remain identical [57, 133, 134].

DRRT: Historically, common practice included the administration of a post-dialysis dose of aminoglycosides in patients receiving DRRT, [57, 98, 134] but it was recommended only half the usual dose be administered [135]. These recommendations are still relevant in current therapeutic guidelines such as the Dictionnaire Vidal in France [176] ("for patients necessitating hemodialysis, administer a loading post-dialysis dose of 5 to 7.5 mg/kg amikacin then monitor serum amikacin concentration"). However, it appeared that obtaining an adequate aminoglycoside peak level was uncertain with such doses [133]. A new aminoglycoside injection within 48–72 h was considered potentially inappropriate [136]. The alternate schedule of small doses every 8 h is not adequate regarding peak levels. Ash and Millikan were the first to propose another approach consisting of aminoglycoside administration during and just after dialysis. However, aminoglycoside doses (1.5 and 0.8 mg/kg, respectively [137]) were still too small to attain modern peak objectives. More recently, a pre-dialysis aminoglycoside administration schedule was studied [57, 133, 134, 138]. A 40 % decrease of aminoglycoside AUC was observed in comparison with a post-dialysis administration [138]. In addition, aminoglycosides could be administered once a day [139]. Sowinski et al. developed an experimental simulation of aminoglycoside infusions in

non-sepsis patients with chronic renal insufficiency [133]. They demonstrated the advantage conferred by pre- versus post-dialysis administration in terms of PK/PD benefit-risk balance, even though the objective of this study (C_{max} of aminoglycoside >8 mg/L) was still too low for patients with severe sepsis [133]. Despite the lack of studies, a pre-dialysis dose for aminoglycosides seems to better fit with modern objectives, enabling high C_{max} values with a reduced C_{min} and AUC avoiding further nephrotoxicity.

CRRT: During CRRT, whatever the epuration modality (continuous arterio-venous haemodialysis [140], continuous arterio-venous haemofiltration [141], continuous veno-venous haemofiltration with low [10 mL/mn] [142] or high [20 mL/mn] [143] filtration rate), aminoglycoside clearance is dependent mainly upon the membrane adsorption characteristics, the ultrafiltration rate and CRRT modalities (continuous haemofiltration [144], continuous haemodialysis [145] or continuous haemodiafiltration [146]). Determining what percentage of aminoglycoside is removed by CRRT remains a hazardous prediction (18–50 % according to different studies [140, 141, 143]). The dosing interval is therefore highly variable (18–60 h) [145]. Paramount is the fact that all the studies leading to these recommendations reported low gentamicin, tobramycin (1–3 mg/kg/day) or amikacin (10 mg/kg/day) doses [145]. Recently, Roberts et al. reported that a 6 mg/kg gentamicin dose every 48 h in patients with severe sepsis treated by extended daily diafiltration reached both efficiency (C_{max}/MIC ratio of ≥10 for MIC = 1 or AUC from time zero to 24 h [AUC_{0-24}] >70 mg · h/L) and renal tolerance (AUC_{0-24} <120 mg · h/L and minimal C_{min}) objectives [143]. Bogard et al. proposed adding tobramycin (6 mg/kg) and amikacin (15–20 mg/kg) to these dosing recommendations [147]. Yamamoto et al. also pointed that conventional recommendations [146] should be customized for patients presenting with severe sepsis or septic shock in order to avoid suboptimal dosing. They recommended using up to 20 mg/kg amikacin in patients receiving CRRT provided that the dosing interval was calculated and adapted [146]. They also pointed that the unbound drug fraction in plasma, which is directly related to albumin concentration, should also be considered for dose adjustment [146]. Akers et al. reported the same risk of suboptimal dosing in burn patients in the ICU [148].

4 Optimization of Aminoglycoside Administration in Critically Ill Patients

4.1 Therapeutic Drug Monitoring (TDM): Description, Historical Aspects, Classification and Relevance

Looking back to the 1970s when Chambers recommended a dose of 0.8–1.2 mg/kg/day divided into two to four perfusions a day illustrates how far we have come [149]. Because of inadequate C_{max} concentrations [150], the next 30 years were dedicated to comparing ODD vs. MDD administrations for sepsis of various degrees of severity [6, 15, 17, 61, 85, 103]. The ODD was successfully implemented in critically ill patients, resulting in a subsequent improvement in clinical and microbiological outcomes [83].

The question of the intensity of monitoring needed to provide adequate aminoglycoside treatment was then raised. A simple empiric determination of aminoglycoside dose (an intervention classified as no TDM by Slaughter and Cappelletty [70]) or the availability of routine serum aminoglycoside concentrations for linear dose adjustment (classified as low TDM [70]) were considered inadequate, [151] particularly in the case of altered renal function [103]. They were progressively supplanted by nomograms such as the one developed at the Hartford hospital [152]. The Hartford nomogram has been used by different ICU teams [78, 113, 114]. On the one hand, this nomogram was based on more stringent C_{max} objectives and more accurate patient weight, while on the other hand, aminoglycoside clearance and the subsequent interval between doses was based on CR_{CL}. However, nomograms proved to be inconsistent in detecting an increase in aminoglycoside clearance [103] such as is frequently observed during septic shock [113, 114]. After the limits of nomograms were first suggested in the 1980s [153, 154], Buijk et al. showed that nomograms failed to accurately predict the dosage interval in 62 % of ICU patients [78]. More recently, the treatment of severe infections with MIC at 2 mg/L confirmed the limits of nomograms [155].

A significant turning point occurred in the years 1990–2000. Based on the large PK variability observed in critically ill patients, the individualization of aminoglycoside dosage was developed. Despite the description of the linear dose adjustment based on AUC by Begg et al. [16], no study specifically addressed this method in the ICU. Conversely, an additional aminoglycoside concentration dosage in the interval between C_{max} and C_{min} was studied in critically ill patients [34, 78, 80, 102, 104, 117, 156]. Vd was deduced from C_{max}, while the timing of aminoglycoside reinjection was deduced from CR_{CL} based on the intermediate dosage (classified as high TDM [70]). Another method initially described by Sawchuk and Zaske in burns units needed several serum samples during the post-distribution phase of aminoglycoside administration [154, 157]. It proved to be very robust, even in patients with extreme parameter values such as ICU patients [158]. However, to the best of our knowledge, it has not been widely used in ICUs, probably because the need for several dosages was considered too constraining.

Lately, in the 1990s the Bayesian approach was used for aminoglycoside administration in critically ill patients [56, 159] (classified as high TDM [70]). This approach relies upon *a priori* values of a particular patient population. It only requires one concentration measure to accurately estimate *a posteriori* aminoglycoside dose adjustment along with the dosing interval for reinjection [103]. This method allows the estimation of different parameters influencing the aminoglycoside serum concentration [56]. However, a large intra-individual variability such as the one observed in patients with severe sepsis required that the *a priori* subpopulation was an ICU population. Beyond this restriction, the large variability maintains a relative uncertainty even when all co-variates are taken into account [103, 109]. To date, it has not proven efficient to reduce nephrotoxicity [103] even if trends for lesser nephrotoxicity were suggested [61, 161]. Finally, it has been suggested that complex pharmacological models may become futile if the clinical environment of patients does not allow appropriate adjustments (such as the time-consuming computation of adequate dose and timing of administration [16]). In this context, the nurses- and doctors-to-patient ratios onto the ICU may be determinants unless external PK/PD monitoring services are provided [65, 66, 160].

4.2 Contribution of TDM to Aminoglycoside Efficiency in Critically Ill Patients

An improvement of septic parameters has been demonstrated with a nomogram-guided administration compared with a routine aminoglycoside administration in patients with mild to moderate sepsis but not specifically in patients with severe sepsis [16]. Further studies assessing post-nomogram methods, such as the Sawchuk and Zaske method or Bayesian models, failed to translate improvement of PK/PD parameters into clinical benefit [25, 103, 121, 161]. Zaske et al. first reported the benefit of his method on mortality in a non-randomized study of burn patients with sepsis [162]. In the ICU, Hickling et al. compared a pharmacokinetic method (based on three plasma concentrations measured after the loading dose) with a nomogram-based method. While the former method provided better target attainment for aminoglycoside concentrations, no effect was observed on mortality in this small-size study ($n = 27$) [121]. More recently, an amikacin dosage individualization using amikacin pharmacokinetic parameters estimated from the serum concentration-time data of individual patients resulted both in good resolution of the sepsis (94 %) and eradication of the causative bacteria (85 %). However, because there was no control group, the specific impact of the TDM could not be assessed [117].

4.3 Contribution of TDM in Reducing Nephrotoxicity in Critically Ill Patients

HDOD administration of aminoglycosides in critically ill patients is supported by the PK/PD advantages in terms of efficiency and cost effectiveness [163]. However, despite scarce clinical [85, 164] and biological data (decrease in nephrotoxicity assessed by patterns of urinary enzymes) [34], HDOD did not specifically prove a reduction of nephrotoxicity in critically ill patients [91]. It has been calculated that the cost of providing TDM averages $US302 per patient whereas the mean cost of an episode of nephrotoxicity was $US9851 [165]. TDM should then become cost effective whenever at least 10 % of nephrotoxicity is observed in a standard population of patients [61, 62, 70]. Less than 10 % might be considered in an ICU population where the cost associated with nephrotoxicity is certainly higher. Even if HDOD regimen *per se* may decrease the necessity for TDM [70], it is plausible that critically ill patients represent a subpopulation exceeding this threshold. A few studies conducted on sepsis demonstrated a significant benefit of different levels of TDM on nephrotoxicity [14, 15, 17, 25, 54, 63, 64]. In contrast, only one study of high-level TDM of aminoglycosides showed a reduction of nephrotoxicity in critically ill patients, yet its design did not ensure that nephrotoxicity reduction was solely due to TDM. Moreover, patients with basic alteration of renal function defined by CR_{CL} <60 mL/mn were excluded, limiting the conclusions of this study [117]. Interestingly, studies focusing on high-level TDM in critically ill patients needing RRT are missing.

5 Conclusion

There has been extensive research describing nephrotoxicity of aminoglycosides. The vast majority was carried out in patients with mild to moderate sepsis, and an extrapolation of these data to critically ill patients is not easy. These patients exhibit more severe sepsis and more important variability of their PK/PD parameters. Moreover, in these patients the pressure on renal function is increased by many factors such as septic shock *per se*, other nephrotoxic drugs and the direct effect of bacterial toxins. It would make sense to speak about aminoglycoside-associated AKI (AGAAKI) rather than aminoglycoside nephrotoxicity. With the AGAAKI risk and the clinical benefit of aminoglycosides being both potentially more important in this subset of patients, the question remains whether optimization could be relevant or not and at which level. To date, no aminoglycoside TDM has really proven its efficiency inside the ICU. In this particular context, TDM should probably be provided by a dedicated antibiotic team

[166] and combine both reliability and feasibility at the bedside. Many ICU characteristics (urgent care, high workload, several healthcare workers involved in the process of care) are major limiting factors for the success of TDM. The threshold above which TDM should become cost effective and then prompt realistic optimization remains to be determined. Indeed, many questions remain unresolved for critically ill patients needing aminoglycoside treatment. Among critically ill patients, who are the most susceptible to develop AGAAKI? Those presenting with dehydration and pre-renal failure [167]? Could biomarkers help in early detection of AGAAKI? Are aminoglycoside doses used for critically ill patients responsible for more nephrotoxicity than in other subgroups of patients? How often and why ICU physicians prefer alternative options to aminoglycosides in their patients (fluroquinolones for example)? What is the ideal aminoglycoside schedule of administration in patients necessitating RRT and, in particular, must aminoglycosides be administered before or after DRRT? What are the amounts and determinants of mass transfer of aminoglycosides during RRT? What should be the determinants of the timing of aminoglycoside re-injection during CRRT or DRRT? Will patients suffering from an initial tubular necrosis at the time of aminoglycoside administration recover in the same manner compared with patients not receiving aminoglycosides? So many issues remain that need to be addressed in future studies.

Acknowledgements No sources of funding were used to prepare this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this review.

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