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REVIEW ARTICLE

Rational use of aminoglycosides—Review and recommendations by the Swedish Reference Group for Antibiotics (SRGA)

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Abstract

The Swedish Reference Group for Antibiotics (SRGA) has carried out a risk–benefit analysis of aminoglycoside treatment based on clinical efficacy, antibacterial spectrum, and synergistic effect with beta-lactam antibiotics, endotoxin release, toxicity, and side effects. In addition, SRGA has considered optimal dosage schedules and advice on serum concentration monitoring, with respect to variability in volume of drug distribution and renal clearance. SRGA recommends that aminoglycoside therapy should be considered in the following situations: (1) progressive severe sepsis and septic shock, in combination with broad-spectrum beta-lactam antibiotics, (2) sepsis without shock, in combination with broad-spectrum beta-lactam antibiotics if the infection is suspected to be caused by multi-resistant Gram-negative pathogens, (3) pyelonephritis, in combination with a beta-lactam or quinolone until culture and susceptibility results are obtained, or as monotherapy if a serious allergy to beta-lactam or quinolone antibiotics exists, (4) serious infections caused by multi-resistant Gram-negative bacteria when other alternatives are lacking, and (5) endocarditis caused by difficult-to-treat pathogens when monotherapy with beta-lactam antibiotics is not sufficient. Amikacin is generally more active against extended-spectrum beta-lactamase (ESBL)-producing and quinolone-resistant Escherichia coli than other aminoglycosides, making it a better option in cases of suspected infection caused by multidrug-resistant Enterobacteriaceae. Based on their resistance data, local drug committees should decide on the choice of first-line aminoglycoside. Unfortunately, aminoglycoside use is rarely followed up with audiometry, and in Sweden we currently have no systematic surveillance of adverse events after aminoglycoside treatment. We recommend routine assessment of adverse effects, including hearing loss and impairment of renal function, if possible at the start and after treatment with aminoglycosides, and that these data should be included in hospital patient safety surveillance and national quality registries.

Introduction

In the 1980s the use of aminoglycosides as monotherapy for Gram-negative sepsis was replaced by new cephalosporins, carbapenems, and fluoroquinolones with a broad-spectrum effect against Gram-negative bacteria and less toxicity than aminoglycosides. In recent decades, beta-lactam antibiotics have often

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been combined with an aminoglycoside for the treatment of severe sepsis/septic shock to broaden the antibacterial spectrum and achieve a rapid bactericidal and possible synergistic effect.

The Swedish Reference Group for Antibiotics (SRGA) has carried out a risk–benefit analysis of aminoglycoside treatment based on clinical efficacy, antibacterial spectrum, synergistic effect with beta-lactam antibiotics, endotoxin release, and toxicity. Our aim was to provide evidence-based guidelines for aminoglycoside use in Sweden. The guidelines are intended for use after adaptation to local resistance data by local drug committees. For example, changing the first-line aminoglycoside from gentamicin or tobramycin to amikacin requires training and well-developed decision support from the laboratory and infectious diseases specialists, to ensure that the advantages of amikacin are not outweighed by disadvantages of suboptimal dosing and increased adverse events during implementation of the change.

Antibacterial spectrum

Aminoglycosides have a broad antibacterial spectrum with good activity against staphylococci, Enterobacteriaceae, Pseudomonas, and Acinetobacter spp. [1,2]. Enterococci and streptococci are naturally low-grade-resistant to aminoglycosides. Aminoglycosides and beta-lactam antibiotics have a synergistic effect against many species of bacteria, which can be used in the treatment of infections where the intrinsic activity of the aminoglycoside is insufficient, e.g. Enterococcus faecalis and viridans streptococci. Aminoglycosides have insufficient activity against Pasteurella multocida, Stenotrophomonas maltophilia, and Burkholderia cepacia. Aminoglycosides have no effect against anaerobic bacteria, as an aerobic environment is required for efficacy. Moreover, the effect is decreased at low pH.

Differences among aminoglycosides

Aminoglycosides have similar antibacterial spectra against wild-type bacteria, with certain exceptions. Amikacin is a better alternative in the treatment of infections caused by Escherichia coli with non-susceptibility to cefotaxime, piperacillin–tazobactam, or ciprofloxacin, as associated resistance is much more common for gentamicin/tobramycin than for amikacin. Tobramycin has a slightly higher activity against wild-type Pseudomonas aeruginosa. Amikacin also offers good activity against Mycobacterium tuberculosis [1]. There is no established ranking of differences in toxicity between gentamicin, tobramycin, and amikacin, as studies are too small and too heterogeneous to show clear differences.

Indications

SRGA recommends that aminoglycoside therapy should always be considered in the following situations:

(1) In combination with broad-spectrum beta-lactams in patients with progressive severe sepsis or septic shock.
(2) Sepsis without shock, in combination with broad-spectrum beta-lactam antibiotics if the infection is suspected to be caused by multi-resistant Gram-negative pathogens.
(3) Pyelonephritis, in combination with a beta-lactam or quinolone until culture and susceptibility results are obtained, or as monotherapy in patients with a serious allergy to beta-lactam or quinolone antibiotics.
(4) Serious infections caused by multidrug-resistant Gram-negative bacteria when other alternatives are lacking,
    a. on the above indications (1–4) amikacin is preferred due to lower resistance among Enterobacteriaceae than for gentamicin/tobramycin,
    b. the choice of first-line aminoglycoside should be decided by local drug committees based on local resistance data.
(5) Endocarditis caused by difficult-to-treat pathogens when monotherapy with beta-lactam antibiotics are not sufficient.

Contraindications

Aminoglycosides are strongly associated with oto- and nephrotoxicity. To reduce the overall frequency of these serious adverse effects, aminoglycoside treatment should be avoided in specific high-risk patients, and considered only if no other treatment alternative exists. These high-risk groups include patients with:

(1) Chronic renal impairment.
(2) Known hearing loss.
(3) Genetic predisposition to aminoglycoside-induced hearing loss.
(4) Concomitant treatment with other nephro- or ototoxic drugs.

Breakpoints for aminoglycoside susceptibility testing

Bacteria are defined as wild-type (WT) in the absence of acquired mechanisms of resistance. The bacteria are

Table I. Clinical breakpoints and epidemiological cut-off levels (ECOFF) for aminoglycosides.

Species	Clinical breakpoint S ≤ mg/l	Clinical breakpoint R > mg/l	ECOFF ≤ mg/l
Enterobacteriaceae			
Gentamicin	2	4	2
Tobramycin	2	4	2
Amikacin	8	16	8
Staphylococcus aureus			
Gentamicin	1	1	2
Tobramycin	1	1	2
Amikacin	8	16	8
Coagulase-negative staphylococci			
Gentamicin	1	1	0.5
Tobramycin	1	1	2
Amikacin	8	16	ND
Pseudomonas aeruginosa			
Gentamicin	4	4	8
Tobramycin	4	4	2
Amikacin	8	16	16
Acinetobacter spp.			
Gentamicin	4	4	4
Tobramycin	4	4	4
Amikacin	8	16	8

S, sensitive; R, resistant.

categorized as WT, applying the epidemiological cut-off level (ECOFF) of aminoglycosides. The clinical breakpoints will assume a once-daily dose with 5–7 mg/kg × 1 of gentamicin/tobramycin and 15–20 mg/kg of amikacin (Table I; http://mic.eucast.org/Eucast2/).

Prevalence of aminoglycoside resistance

In Sweden resistance is rare (< 1%) in Staphylococcus aureus, but occurs to varying degrees (1–10%) in Enterobacteriaceae (lower range for amikacin and higher range for gentamicin/tobramycin) and P. aeruginosa. Resistance is common (> 10%) among coagulase-negative staphylococci (CoNS). High-level aminoglycoside resistance (HLAR) is common (> 10%) among E. faecalis and Enterococcus faecium (Figure 1).

Globally, high frequencies of aminoglycoside resistance have been reported from most parts of the world among Gram-negative bacteria, including P. aeruginosa [3] and methicillin-resistant staphylococci (methicillin-resistant S. aureus (MRSA) and methicillin-resistant S. epidermidis (MRSE)).

Before treatment, enterococcal strains causing endocarditis should be investigated for HLAR, because synergy between aminoglycosides and beta-lactam antibiotics will not be expected in these strains. Gentamicin is used for detecting HLAR, defined as a gentamicin minimum inhibitory concentration (MIC) > 128 mg/l. The production of transferable (plasmid or integron) aminoglycoside-modifying enzymes (AME; acetylating, adenylating, or phosphorylating enzymes) causes partial cross-resistance between aminoglycosides because the respective aminoglycoside is a substrate of some, but not all, of these enzymes. Chromosomally mediated defective transport of aminoglycosides through the bacterial cell wall will cause resistance to all aminoglycosides, whereas increased activity of efflux pumps affects different aminoglycosides to various extents. Methylation of the RNA (transferable 16S rRNA methylases) confers resistance to all the aminoglycosides [4]. These transferable 16S rRNA methylases are commonly seen in strains with carbapenemases, such as New Delhi metallo-beta-lactamase (NDM)-producing Enterobacteriaceae. Resistance to amikacin might raise suspicions of 16S rRNA methylases, but AMEs,

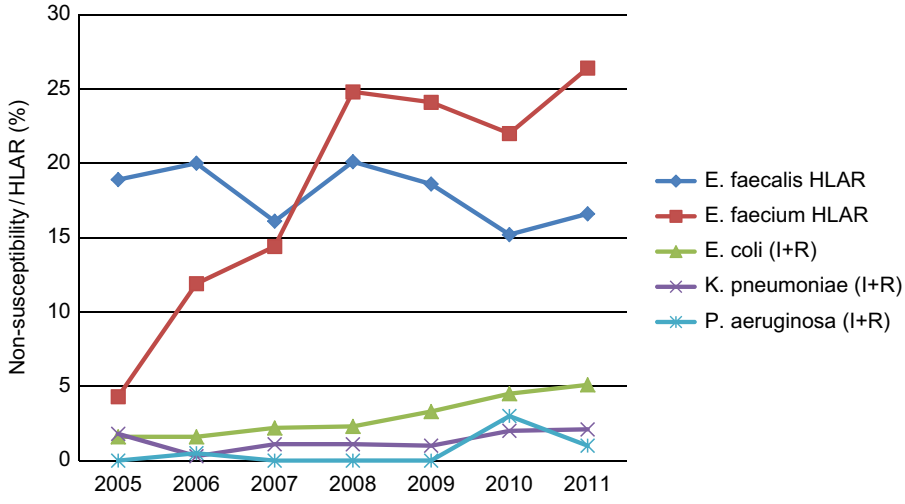

Figure 1. Aminoglycoside resistance among invasive isolates in Sweden 2005–2011. Source: EARSNet, http://www.smittskyddsinstitutet.se. HLAR, High level aminoglycoside resistance. Median and (range) of number of isolates/year: E. coli 3665 (3190–4123), K. pneumoniae 642 (280–825), P. aeruginosa 300 (149–342), E. faecalis 561 (492–707), E. faecium 286 (211–348).

as we see with extended-spectrum beta-lactamase (ESBL) strains, usually do not affect amikacin.

Amikacin has a better activity against Escherichia coli resistant to cephalosporins (ESBL-producing), quinolones, and piperacillin–tazobactam because these strains less often carry genes that also inactivate amikacin. Among invasive isolates of E. coli from the Karolinska University Laboratory (Sweden) in 2011 ($n = 1022$), 5/1022 (0.5%) were resistant to amikacin, whereas 80/1022 (7.8%) were resistant to gentamicin (unpublished data). Among E. coli isolates with decreased susceptibility (intermediate (I) + resistant (R)) to cefotaxime, piperacillin–tazobactam, or ciprofloxacin, resistance was much more common to gentamicin than amikacin (Table II) (unpublished data).

Choice of aminoglycoside

In Sweden, the most frequently used aminoglycosides for bacterial infections are gentamicin and tobramycin, whereas amikacin is used to a lesser extent and mainly to treat tuberculosis [1]. In many countries with high levels of multi-resistance, amikacin is used to a larger extent as it is more active against ESBL-producing and quinolone-resistant E. coli than other aminoglycosides. This makes amikacin a better option in cases of suspected antibiotic resistance in Enterobacteriaceae, which is increasing globally. In 2011, the estimated Swedish consumption of intravenously administered aminoglycosides by defined daily dose (DDD) was about 34,400 for gentamicin, 40,600 for tobramycin, 6800 for amikacin, and 15 for netilmicin. The SRGA analysis has been limited to amikacin, gentamicin, and tobramycin.

Each decision on the use of a specific aminoglycoside should be based on the presence of risk factors for resistance in the individual case and the local epidemiology of antibiotic resistance.

Pharmacodynamics and pharmacokinetics

Aminoglycosides primarily affect bacterial protein synthesis and result in rapid concentration-dependent killing with a low release of endotoxin. Beta-lactam antibiotics with major affinity for penicillin-binding protein 3 (cefotaxime, ceftazidime, piperacillin, etc.) induce filament formation and slow killing of Gram-negative bacteria, accompanied by high endotoxin release, which is associated with a stronger inflammatory response than with carbapenems or aminoglycosides [5,6]. Aminoglycosides have been shown to reduce the beta-lactam-induced endotoxin release [7]. Animal studies of Gram-negative sepsis have shown better survival with beta-lactam antibiotics that induce low endotoxin release than beta-lactams inducing high endotoxin release; however, clinical studies have failed to show a similar advantage [8]. The antibacterial effect of aminoglycosides correlates best with peak serum concentrations in relation to MIC (C_{max}/MIC), which provides a strong rationale for once-daily dosing. Multiple dosing (2 times daily) is recommended for the use of aminoglycosides in combination therapy for complicated cases of endocarditis. In these cases, the main objective is to achieve synergy with cell wall-active antibiotics [9]. Available data indicate that the synergistic effect is mainly due to the beta-lactam facilitating penetration of the aminoglycoside into the cell, which suggests that once-daily dosing is preferable on these indications as well [10]. However, no clarifying, randomized studies have been found on this issue. To achieve an adequate C_{max} without causing drug accumulation and an increased risk of toxicity, the next dose should be withheld until a sufficiently low trough value has been reached in the serum concentration. Importantly, pharmacokinetics may display high intra-individual variability, especially in severely ill patients, including those with sepsis and septic shock, which requires frequent laboratory monitoring and reconsideration of the optimal dosage [11–13]. The variation in pharmacokinetics in these patients is at least partly explained by increased extracellular volume, reduced protein binding, and variable clearance. High loading doses of aminoglycosides and beta-lactam antibiotics may be necessary to avoid suboptimal plasma concentration profiles and treatment failure [14–17]. There is, thus, a parallel risk of overdose and drug accumulation after repeated dosing due to decreased renal clearance.

Table II. Resistance to amikacin and gentamicin among Escherichia coli isolates with non-susceptibility (I + R) to cefotaxime, piperacillin–tazobactam, or ciprofloxacin.

	Resistance[a] (%)	
Non-susceptibility (I + R)[a]	Amikacin	Gentamicin
Cefotaxime ($n = 66$)	4/66 (6%)	29/66 (44%)
Piperacillin–tazobactam ($n = 66$)	4/66 (6%)	16/66 (25%)
Ciprofloxacin ($n = 177$)	4/177 (2%)	58/177 (33%)

I, intermediate; R, resistant.
[a]Only 1 episode per patient has been included.

Aminoglycoside treatment for specific indications

Severe sepsis and septic shock

In a large observational study of patients with Gram-negative bacteremia, mortality was higher for patients on aminoglycoside monotherapy than for those on the combination with beta-lactam antibiotics, except

for those with infections in the urinary tract [18]. Beta-lactam antibiotics are often combined with an aminoglycoside for severe sepsis/septic shock to broaden the antibacterial spectrum and achieve rapid bactericidal, and possible synergistic, effects. A Cochrane analysis of sepsis studies conducted in 1966–2004, in which beta-lactam and aminoglycoside combination therapy was compared with monotherapy with beta-lactam, was unable to demonstrate any difference in survival [19]. It was concluded that the combination with aminoglycoside provided no advantage, but merely added a significant risk of nephrotoxicity. However, in this Cochrane meta-analysis, only a fraction of the patients had septic shock; the use of combination therapy in septic shock remains a subject of debate. In another meta-analysis that compared the combination of mainly beta-lactam and aminoglycoside with beta-lactam monotherapy in Gram-negative sepsis, no benefit in survival was demonstrated, except for a subgroup of patients with Pseudomonas sepsis [20]. A small prospective, observational study of patients with Klebsiella bacteremia reported increased survival in a subgroup of patients with septic shock who were treated with the combination of beta-lactam and aminoglycoside rather than beta-lactam monotherapy [21]. In a considerably larger observational study, Leibovici et al. failed to show increased survival for combined beta-lactam and aminoglycoside compared with beta-lactam monotherapy, except in a subgroup of neutropenic patients [18]. Most previous studies and meta-analyses on sepsis have not been able to clearly show increased survival as a result of combination treatment [18–20,22]. This may in part be explained by poor design or underpowered studies [23]. In a recent meta-analysis, Kumar and colleagues showed that combination therapy with 2 antibiotics, both with activity against causative bacteria, resulted in lower mortality from septic shock compared with treatment with only 1 effective antibiotic—but only in the most severe cases [24]. In contrast, among the less critically ill, combination treatment tended to be harmful [24].

The same authors recently published a retrospective analysis of a large prospectively collected cohort of patients in septic shock (>4600 patients), in which patients were compared with controls using an advanced matching technique based on so-called propensity analysis [25]. This study showed an increase in survival for patients with septic shock when a beta-lactam was combined with an aminoglycoside, fluoroquinolones, or macrolides/clindamycin [25]. The advantage of the combination treatment in this study was valid for most, but not all, beta-lactam antibiotics, excluding beta-lactam antibiotics with an effect on Pseudomonas (carbapenems, anti-pseudomonal cephalosporins) in which no significant mortality benefit was observed. With the exception of carbapenems and anti-pseudomonal cephalosporins, combination therapy of beta-lactam antibiotics and aminoglycoside may increase survival in progressive severe sepsis and septic shock. As multidrug-resistant Gram-negative bacteria have become increasingly common in many countries, the risk of treatment failure when using monotherapy with a beta-lactam antibiotic in patients with severe sepsis has increased. Combination therapy with aminoglycosides might therefore be needed to broaden the spectrum of antibacterial effect [26–28]. For example, Craig, in a recent review of aminoglycosides, recommends that aminoglycosides should be administered in combination with beta-lactam antibiotics or fluoroquinolones in patients with septic shock or hypotension as high, once-daily doses and very rarely for more than 5–6 days [29].

In Sweden, it has become practice to give a single dose of aminoglycoside in combination with beta-lactam antibiotics in severe infections. Many clinicians claim they have had good experiences with the single dose, which can be given for several reasons, e.g. to broaden the spectrum, achieve a synergistic effect, more rapidly eliminate bacteria with less endotoxin release, and reduce the risk of resistance. However, to our knowledge, no randomized controlled trials exist that examine the effect on mortality, morbidity, ecology, and toxicity in various infections. Therefore, from an evidence-based perspective, it is difficult to evaluate this procedure.

Pyelonephritis and other foci of infection

A meta-analysis of randomized controlled trials on the efficacy of monotherapy with aminoglycosides compared with non-aminoglycosides included 37 studies, of which 26 were studies of urinary tract infection [30]. Both clinical and bacteriological treatment failure was slightly, but significantly, more common in monotherapy with an aminoglycoside [30]. In total, fewer adverse events were reported in the aminoglycoside group, but several cases with renal involvement were noted [30]. The authors found support for recommending monotherapy with an aminoglycoside in urinary tract infections but not in infections with other foci [30]. A return to the use of benzylpenicillin in combination with aminoglycosides has been recommended for bacterial infections of unknown origin to reduce the use of cephalosporins and quinolones, as this combination is less likely to select resistant bacteria [31]. However, this recommendation would imply monotherapy with an

aminoglycoside in Gram-negative sepsis, which is supported by literature evidence only in Gram-negative bacteremia with a urinary focus [18,30,32]. For progressive severe urosepsis/septic shock, monotherapy with an aminoglycoside will not suffice, as these patients ideally should receive treatment with 2 effective antibiotics (see above: Sepsis) [24].

It is not yet known whether the 5–7 day monotherapy with an aminoglycoside is as effective as longer aminoglycoside treatment of pyelonephritis and complicated urinary tract infections. However, urine concentrations of aminoglycoside are above the MIC for most Gram-negative rod bacteria at least 4 days after the last dose of aminoglycoside. This favours shorter treatment as it reduces the risk of adverse events [29].

Aminoglycoside therapy may also be indicated in cases of severe lung infections caused by P. aeruginosa [26,27]. In ventilator-associated pneumonia, inhaled aminoglycosides can provide an alternative route of administration to avoid renal toxicity and ototoxicity [33].

Two meta-analyses have shown aminoglycosides to have an inferior clinical effect compared with beta-lactam antibiotics in the treatment of Gram-negative infections with an abdominal focus [34,35]. Treatment with an aminoglycoside (plus clindamycin) was associated with a higher risk of renal impairment than was monotherapy with beta-lactam antibiotics.

Endocarditis

Aminoglycoside treatment of endocarditis is largely based on older studies [36–38]. The strongest documentation of the effect of combination therapy with an aminoglycoside is related to endocarditis caused by enterococci. In endocarditis due to streptococci, the main reason for using combination therapy has been to shorten the length of treatment, but no clinical trials have definitely supported the use of combination therapy for S. aureus endocarditis [35]. The Endocarditis Working Group (EWG) of the Swedish Society of Medicine has recently (2012) updated guidelines [39]. The group recommends a once-daily dosage in most cases of endocarditis, except a twice-daily dosage in difficult-to-treat cases of endocarditis such as enterococcal endocarditis and valvular prosthesis endocarditis. There are no documented differences between gentamicin, netilmicin, tobramycin, and amikacin for endocarditis except for E. faecium, when netilmicin and tobramycin should not be used. This is because E. faecium has a naturally occurring enzyme that prevents synergy with all aminoglycosides, except gentamicin, streptomycin, and amikacin. The EWG of the Swedish Society of Medicine recommends 3 mg/kg/day of gentamicin/tobramycin as endocarditis treatment in general; the exception is 5 mg/kg of gentamicin/tobramycin once daily for the first days of treating S. aureus endocarditis. No recommendations are available for amikacin. The trough concentrations should be below 1 mg/l, and peak concentrations at least 3–5 mg/l after administration of gentamicin/tobramycin 1.5 mg/kg twice daily (= 3 mg/kg/day).

Adverse events and toxicity

Shortly after streptomycin – the first aminoglycoside – was introduced in the 1940s, side effects reported were ototoxicity, nephrotoxicity, and neuromuscular blockade. Although new aminoglycosides were developed, the safety profile remained largely the same. Between 1969 and August 2011, 311 cases with a total of 416 adverse events thought to be associated with aminoglycoside therapy were registered in the Swedish side-effect registry, SWEDIS. Nineteen of the cases had a fatal outcome. Most adverse events were reported in 1978–1991. The aminoglycoside most commonly associated with adverse events was gentamicin (63%), followed by tobramycin (16%), netilmicin (16%), amikacin (4%), and streptomycin (2%). Importantly, the differences in frequency largely reflect differences in clinical use. Despite the well-known ototoxicity of aminoglycosides, patients are rarely followed-up with audiometry.

Nephrotoxicity

Nephrotoxicity occurs in approximately 10–25% of patients treated with aminoglycosides [40,41]. The usual risk factors include advanced age, prior renal impairment, dehydration, concomitant exposure to other nephrotoxic drugs (e.g., amphotericin B, vancomycin, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), cisplatin, cyclosporin, and iodinated contrast agents), and prolonged or repeated periods of treatment and high dose [41–43]. Typically, nephrotoxicity will manifest itself as a secretory dysfunction without a change in urine volume but with increased excretion of proteins, enzymes, glucose, potassium, calcium, and phospholipids after only a few days of treatment [44]. The mechanism is a proximal tubular epithelial cell death, which in turn is partly caused by direct and indirect mitochondrial effects [45], a functional change in the cellular components involved in fluid transport, and direct vascular effects [41]. When the kidneys can no longer compensate for the toxic effects, there is an increase in the plasma

concentrations of creatinine and urea. This typically occurs after about 1 week of treatment and is therefore a late sign [44]. An earlier sign may be an increased trough concentration of aminoglycoside [46]. If the dose is adjusted or the treatment discontinued when an increase in creatinine is observed [40], tubular cells will usually regenerate and renal function will be restored.

Clear evidence of the nephrotoxic effect of a single dose of aminoglycoside in severe sepsis or septic shock with early renal impairment has yet to be described. In intensive care unit (ICU) patients with varying renal function but a creatinine clearance (CrCl) of >30 ml/min, no additive renal toxicity was caused by aminoglycoside treatment [47]. Experiments have failed to detect any additional effect of a high single dose of tobramycin on experimental animals whose kidneys are significantly harmed by the sepsis-induced inflammatory response [48].

Among the aminoglycosides, neomycin has the most pronounced nephrotoxic effect, and streptomycin the least. For other substances, there is no universally accepted classification, and studies are often too small and too heterogeneous to show clear differences [49–53]. Gentamicin has, however, a more nephrotoxic effect in animal studies. It is excreted less and reabsorbed more than tobramycin, netilmicin, and amikacin [54]. In studies comparing once-daily dosing with more than 1 dose per day, the outcome has essentially shown no significant difference or an advantage related to once-daily dosing [43,55–59]. A reduction in nephrotoxicity with once-daily dosing is mainly due to the fact that renal tissue uptake of aminoglycosides is not directly proportional to the serum level, appearing instead to be saturable at a transient high level [60,61].

Ototoxicity

Aminoglycosides damage the vestibule of the ear and the cochlea. Unlike renal toxicity, this is considered irreversible. Aminoglycosides can be detected in the inner ear a short time after the dose is administered systemically [62]. Elimination is slow, however, and aminoglycosides can be measured in hair cells up to 11 months after treatment, as revealed by animal experiments [63]. The risk of deafness is related to the cumulative dose, and increases with repeated courses and prolonged exposure [64]. The mechanism of ototoxicity has long been controversial. Recent research points to the production of damaging oxygen free radicals [65,66], which may be prevented or modified in the future with antioxidants, and mitochondrial dysfunction. The size of the permanent damage depends on the extent of hair cell loss. In the West, it was previously expected that as many as 20% of patients treated with aminoglycosides would develop a measurable hearing loss, which in 2–5% was clinically significant [67–70]. Hearing damage is usually dose-dependent and related to renal function, but apparently it can develop after only a single dose and with serum concentrations within the reference range (case reports in SWEDIS; Swedish Adverse Drug Reactions Register). Although all aminoglycosides can damage the labyrinth and cochlea, gentamicin, and even more so streptomycin, seems to damage vestibular function. The relative incidence [of toxicity] appears to be equal for tobramycin, gentamicin and amikacin [67]. Vestibular dysfunction will usually first manifest itself in nystagmus, dizziness, nausea, and vomiting [71]. As compensatory mechanisms occur relatively quickly, labyrinth lesions may easily be overlooked. A few patients do not develop compensatory mechanisms [72]. Patients with cochlear complications often complain of tinnitus and a pressure sensation in the ear, but deafness may come suddenly without warning and months after treatment [73]. The high frequencies are lost first, which can be determined using high-frequency audiometry before hearing loss in the vocal frequencies is a fact.

Despite rigorous control of aminoglycoside concentrations, it is difficult to prevent aminoglycoside-induced ototoxicity. No significant reduction in toxicity has been observed when changing from repeated daily dosing to once-daily dosing [58,59, 74,76]. The most common genetic predisposing factor for aminoglycoside-induced hearing loss is the A1555G mutation in the mitochondrial genome. It makes the mitochondrial rRNA structurally similar to the 16S rRNA of E. coli, with increased vulnerability to aminoglycosides as a result [77,78]. The mutation has been detected in a number of families around the world, but it also occurs sporadically. Typical of patients with A1555G is an aminoglycoside-induced, bilateral hearing loss without vestibular damage [79]. Hearing loss may occur among these patients even without exposure to aminoglycosides [80]. Information regarding the prevalence of the mutation in the Swedish population is lacking. In a Danish study, the background for non-syndromic hearing loss in 2.4% of the patients was determined to be the A1555G mutation [81]. In Spanish, Chinese, and Arab-Israeli patient material, corresponding figures rise to 15–30% with variable penetrance [73,82–85]. In a recent British study this mutation was found in 1/385 of a healthy population [86]. As preventive measures, we recommend that risk factors for clinically significant hearing loss be identified, including heredity, advanced age, renal impairment, dehydration, and other nephrotoxic drugs.

Aminoglycoside treatment should be minimized or even avoided in these patient categories.

Unfortunately, aminoglycoside use is rarely followed up with audiometry, and in Sweden we have currently no systematic surveillance of adverse events after aminoglycoside treatment. We recommend routine assessment of adverse effects, including hearing loss and impairment of renal function, if possible at the start and after treatment with aminoglycosides. These data should be included in hospital patient safety surveillance and national quality registers.

Neuromuscular blockade

The neuromuscular blockade caused by aminoglycosides is manifested as an acute muscular paralysis and apnoea, and can be treated with calcium and neostigmine. The phenomenon is now rare and in descending order coupled with neomycin, kanamycin, amikacin, gentamicin, and tobramycin. It is associated with anaesthesia, other neuromuscular-blocking drugs, and patients with myasthenia gravis, spinal injuries, chronic obstructive pulmonary disease, and tuberculosis [87–90]. As the clinical importance of this side effect remains the subject of debate, guidelines for aminoglycoside use in spinal units can differ greatly between countries [91].

Dosing and treatment duration

Increasing evidence suggests that aminoglycosides should be administered on a once-daily basis for patients without renal impairment to achieve optimal killing and reduce toxicity [29,92,93]. In 9 meta-analyses, aminoglycoside dosing every 24 h was compared with conventional dosing every 8 or 12 h [55,56,76,94–98]. Five of the meta-analyses showed a small, but statistically significant, better clinical effect of dosing every 24 h. Three meta-analyses showed a lower incidence of nephrotoxicity when doses were administered every 24 h. The meta-analyses showed the same occurrence of ototoxicity or a trend towards lower ototoxicity with once-daily dosing. During short courses of treatment, nephrotoxicity seems to develop later with 24-h dosing intervals than with 8- or 12-h dosing intervals. However, if aminoglycoside treatment continues for more than 10–14 days, once-daily or multiple daily doses do not seem to differ with regard to nephrotoxicity [29]. In a Dutch study of 89 ICU patients with a suspected or confirmed infection, 7 mg/kg gentamicin or tobramycin was given if CrCl was >30 ml/min [47]. A C_{max}/MIC ratio >10 was achieved in most patients, but patients with septic shock and renal dysfunction displayed abnormal pharmacokinetics. In 12 patients, impaired renal function (increase in CrCl >45 μmol/l) was reported, and of these, 6 had received only 1 dose of aminoglycoside [47]. Two of the patients with renal impairment died of septic shock; the other could be followed up and had reversible renal impairment [47]. In a larger observational study of 2184 patients treated with gentamicin 7 mg/kg every 24 h if renal function was normal (every 36 h at CrCl 59–40 ml/min and every 48 h at CrCl of 39–20 ml/min) [99], the median duration of treatment was 3 days, and only 27 (1.2%) patients developed renal insufficiency (>0.5 mg/dl increase in serum creatinine from baseline) and 3 (0.1%) had signs of vestibular damage based on symptoms and status [99]. One of the patients with vestibular damage received this after only 1 dose of aminoglycoside. As audiometry was not performed, and no data were reported on symptomatic hearing loss, underreporting may exist. The recommendations of a dose every 24 h apply only to up to 5–6 days of treatment [44,92,100]. In a recent 3-armed study, patients with severe sepsis or septic shock were given amikacin once daily at a dose of 15 mg/kg, 25 mg/kg, or 30 mg/kg, where 76% of patients with 30 mg/kg reached the recommended C_{max} (60 mg/l). With 25 mg/kg and 15 mg/kg, only 39% and 0%, respectively, reached the recommended C_{max}. The higher doses did not lead to greater nephrotoxicity [17].

Our conclusion is that there is enough evidence to recommend once-daily dosing of aminoglycosides (except twice-daily dosing in difficult-to-treat cases of endocarditis), which should be high in septic shock and very rarely for more than 5–6 days.

The treatment must always be kept as short as possible to reduce the risk of toxicity. Pharmacokinetic studies show that 25–30 mg/kg of amikacin and 7 mg/kg of gentamicin/tobramycin should be used for maximum effect in septic shock (C_{max}/MIC ratio of 10). Importantly, this refers to recommended loading doses; dose 2 should be given after 24 h to patients without renal impairment, but the dose and dosing interval must always be guided by serum concentration determinations.

There is still a knowledge gap regarding the target concentration at 8 h after the increased loading doses in septic shock (see below). Alternatively, in patients with septic shock and signs of renal impairment, we suggest waiting to administer the second dose of aminoglycoside until the 24-h concentration has been analyzed and reported from the laboratory to avoid toxic accumulation of the aminoglycoside. This highlights the need for laboratories to provide an analytical service on an acute basis 7 days a week.

Dosage in renal impairment

As evident from above, the daily dose needs to be adjusted in patients with impaired renal function. However, reducing the size of individual doses poses the risk that peak concentrations might be sub-therapeutic, whereas prolonged dosing intervals could ensure that the bactericidal serum levels will be reached after each new dose. Lower trough levels with a prolonged dosing interval should also reduce the risk of toxic effects, but there is a general lack of documentation that long dosing intervals (48 h or more) would effectively prevent microbial recovery. The obvious conclusion is that the use of aminoglycosides is complicated or even inappropriate in patients with severe renal impairment [101]. The longer half-life and prolonged elimination rate in renal insufficiency means that serum levels are quite stable over time and almost mimic continuous infusion, which increases the risk of aminoglycoside toxicity because of higher tissue uptake [60,102]. Unfortunately, serious infections are common in patients with renal failure, so aminoglycosides are still given to these patients in situations where no obvious antibiotic alternatives exist.

Aminoglycosides are eliminated relatively efficiently in both peritoneal dialysis and haemodialysis. The most commonly used dosage regimen for intermittent haemodialysis is to administer a reduced dose of aminoglycoside during the final hour of haemodialysis (1–2 mg/kg). In between haemodialysis sessions, elimination is very slow, with a half-life of up to 2 days and considerable variation between patients. For this reason, supplementation with half the normal daily dose may seem justified. Although this would mean that peak concentrations are relatively low (and potentially sub-therapeutic), exposure over time will inevitably be higher for these haemodialysis patients than for patients with normal renal function. Therefore, other regimens have been discussed for intermittent haemodialysis and have been tested to a very limited extent, e.g. administering a higher dose just before the start of haemodialysis [103,104]. However, this has not yet been evaluated for therapeutic outcome. It should be remembered that aminoglycoside treatment in haemodialysis patients is almost always given in combination with other antibiotics, which may be important for the overall antimicrobial effect.

For patients with peritoneal dialysis, the same reduced intravenous doses might be used as for patients with haemodialysis, whereas higher doses can be given directly into the dialysate in the case of peritonitis. Patients with peritoneal dialysis are dependent on the small residual renal function and are therefore particularly vulnerable to even limited nephrotoxicity [105]. Continuous renal replacement therapy (CRRT) is the most commonly used renal replacement therapy in ICU patients. With CRRT, clearance of aminoglycosides varies greatly with the applied CRRT modality and flow rates, but clearance will correlate with the total haemodialysis and haemofiltration flow if adjusted for the effect of replacement fluid administered before the filter [106]. Typically, the clearance will be in the range of 15–70 ml/min, which should be compared with a normal clearance of 100–120 ml/min. For amikacin, a loading dose of 10–15 mg/kg has previously been proposed for CRRT patients [104]. However, a recent study demonstrated that even a loading dose of 25 mg/kg reached the target peak concentration of 64 mg/l in only 69% of the patients [15]. Pharmacokinetic modelling predicted that loading doses of 10 or 15 mg/kg would fail to reach the target peak concentration in all patients. In the same study, the median time to reach the target trough concentration of 5 mg/l was 34 h, despite CRRT with high flows. Assuming similar pharmacokinetics for other aminoglycosides, these data suggest that previously recommended doses have often been too low, that increased loading doses should be used in severely ill patients, regardless of CRRT treatment, and that adequate dosing requires prolonged dosing intervals tailored to measured trough concentrations.

In summary, the use of aminoglycosides in patients with renal dysfunction is extremely difficult because the antibacterial effect is related to high peak concentrations, whereas reduced renal clearance requires extended dose intervals to avoid nephrotoxicity. This, however, may allow bacterial regrowth. Although commonly used, reduced dose levels might only infer a risk of additional renal impairment without achieving an antibiotic effect. However, little is known as to what extent the latter is a problem with combination therapy.

Dosing in patients with obesity

Aminoglycosides are water-soluble drugs with low protein binding, a volume of distribution which roughly corresponds to the extracellular body fluids, and with an individual elimination capacity correlating well with the glomerular filtration rate (GFR).

Overweight due to obesity is dominated by fat, but also includes tissue components with a greater water content to which aminoglycosides are easily distributed. The distribution volume is therefore greater in obese patients than in patients of normal weight. Dose requirements in obesity are better understood for aminoglycosides than for most other antibiotics [108–110], but uncertainty still remains concerning the appropriate dose adjustments. When total body weight is considered in the dose calculation, it is clear that

significant obesity leads to an overestimation of both renal elimination capacity and apparent volume of distribution of water-soluble drugs. Patients with severe obesity therefore need a smaller dose when expressed as mg/kg actual weight. One approach to this is to use a standard mg/kg dose, but calculated for an adjusted body weight. It has been suggested that the adjusted body weight should be calculated as the patient's ideal weight (based on sex, height, and age) + 40% of the difference between the patient's current weight and ideal weight. It is unclear from what degree of obesity this reduction should apply; in cases of mild obesity, dosages should probably be calculated for a weight closer to the patient's actual weight.

Formulae for ideal weight and corrected weight follow.

$$\text{Ideal weight (males)} = 50\ \text{kg} + 0.9\ \text{kg per cm height over 152 cm}$$

$$\text{Ideal weight (women)} = 46\ \text{kg} + 0.9\ \text{kg per cm height over 152 cm}$$

$$\text{Adjusted weight (severe obesity)} = \text{ideal weight} + 0.4 \times (\text{current weight} - \text{ideal weight})$$

Although the use of adjusted body weight has been criticized [105], the key message is that a standard dose expressed as mg/kg body weight should not be used without individual concern. Of course, serum concentrations should be monitored in obese patients. Importantly, the situation is not identical for patients with high body weight due to increased muscle mass or for patients with extensive oedema due to chronic or acute disease. Since the volume of distribution is then increased, the initial dose should be based on actual bodyweight. However, for these patients, too, the indication for serum concentration measurements is stronger than for other patients.

Monitoring

Concentration determination of aminoglycosides is recommended as a routine procedure, but the indication for monitoring varies greatly between patients. Haemodynamically unstable patients, patients with large fluid shifts, and patients with dynamic changes in renal function should be subject to frequent concentration measurements, even daily. Middle-aged or younger patients with normal renal function and no reason to suspect an increased volume of distribution can be monitored less frequently, e.g. 1–2 times/week. Patients with a normal volume of distribution and renal function who are subjected to a once-daily dosing regime will usually reach the pharmacokinetic/pharmacodynamic target after repeated doses. Therefore, concentration measurements should focus on the early detection of accumulation, and should measure concentrations 8 or 24 h after the new dose (see below) [101]. The latter is even more important in elderly patients whose renal function and sensitivity to adverse events vary widely, even without underlying renal disease [101,109–111]. Post-dose concentrations, i.e. peak concentrations, should be monitored in more unstable patients to ensure that antimicrobial concentrations are reached, preferably with a C_{max}/MIC ratio >10.

Patient data

An appropriate individual medical assessment of the analytical result requires information about the patient's dosage regimen and when the sample is taken in relation to the last dose (indicated by the exact time of the dose). In addition, renal function, body weight, treatment indication, and route of administration are of great value for proper assessment of the analytical results. The assay itself is based on immunoquantification and is relatively quick. As the result of analysis may directly affect decision-making related to the next dose, it should be available electronically or by phone before the next dose is planned.

Sampling

Typically, a sample will be taken (less than 1 h) before a new dose, and 30 min after intravenous infusion or injection. This specific time for a 'post-dose sample' is derived from early clinical studies in which the peak concentration was measured 45 min after intramuscular injection.

In once-daily dosing, the concentration in a sample taken 8 h after the dose may guide the next dose. However, the target interval for 8-h samples is uncertain (see below), and is lacking not only for the more aggressive, high doses listed above (see also below) [101], but also for the relatively low dosages used in the treatment of endocarditis [112].

Analysis

Most of the literature on this subject indicates that trough concentrations of gentamicin and tobramycin (in 2 or 3 times daily dosing) should be less than 2 mg/l before the next dose. Otherwise the risk of toxic side effects will increase, and the dosing interval would therefore need to be extended. With normal renal function and once-daily dosing, virtually all of the previous dose will be eliminated in 24 h. In other words,

very low concentrations are expected for the trough value, and the actual exposure over the day is difficult to assess. Because the total exposure is related to the risk of side effects (see above), low trough levels (<1 mg/l) should be aimed for during longer (several weeks) treatment courses. For amikacin, the recommended trough level is <5 mg/l [113].

Trough levels that increase during treatment on the same dose is a strong signal for decreased renal filtration capacity. For gentamicin or tobramycin and a dose of 4–5 mg/kg/day, 8-h concentrations above 3–4 mg/l indicate slow elimination and a too high dose in relation to elimination capacity and 24-h dosing. In other words, the dosing interval should then be extended. No guidelines exist for 8-h concentrations after 7 mg/kg of gentamicin or tobramycin, as well as 8-h recommendations for amikacin concentrations.

The recommended C_{max}

MIC ratios are 8–10 according to the literature [17]. This level (gentamicin/tobramycin C_{max} >7 mg/l) will almost always be reached for wild-type Enterobacteriaceae in patients with a normal distribution volume by giving the entire daily dose of gentamicin/tobramycin (4.5–7mg/kg) at one time. However, in divided daily doses or an abnormal distribution volume, it is sometimes difficult to reach. The more aggressive loading dose of amikacin recently proposed in the literature (25 mg/kg/day) for severe sepsis/septic shock results in the majority of patients (70%) having concentrations >64 mg/l after a new dose, equivalent to 8 times higher levels than the breakpoints for Enterobacteriaceae and Pseudomonas [14]. Note that only about half of the patients with severe sepsis or septic shock were able to eliminate the amikacin dose of 25 mg/kg in 24 h [14]. According to information provided by the manufacturer of amikacin, patients who receive a dose of 15 mg/kg reach post-dose values of around 50 mg/l.

Future developments

The sampling procedure described above is relatively simple and applies to Swedish laboratories. Limiting of monitoring to trough and top concentrations has only been criticized for giving too rough an estimate of actual patient exposure. It also has its origins in studies of divided daily doses. Other countries, e.g. Australia, recommend that single concentration measurements be used in combination with patient-specific characteristics (e.g. dose, weight, renal function) in pharmacokinetic models to predict more precisely the dose required to reach a given exposure (area under the curve, AUC) [101]. It remains to be clinically demonstrated whether this will lead to more effective and safer treatment. For unstable sepsis patients, however, day-to-day variations in renal function significantly reduce the predictive value of such single concentration determinations.

Knowledge gaps

The SRGA literature review has identified specific areas where more clinical data are required:

(1) Risk–benefit: Combination therapy with beta-lactam and aminoglycoside compared with monotherapy with beta-lactam antibiotics in severe sepsis without shock.
(2) Risk–benefit: Combination therapy with beta-lactam and aminoglycoside compared with monotherapy with carbapenem in severe sepsis with and without shock.
(3) Risk–benefit: Beta-lactam antibiotic combined with a single-dose aminoglycoside compared with combination therapy with multiple daily aminoglycoside doses in severe sepsis with or without shock.
(4) Risk–benefit: Combination therapy with beta-lactam and aminoglycoside compared with monotherapy of beta-lactam antibiotics for endocarditis, without septic shock, caused by S. aureus and viridans streptococci with low MIC for the beta-lactam antibiotic used.
(5) Ecology: Will addition of a single dose of aminoglycoside reduce the risk of resistance occurring? Monitoring target ranges for 8-h post-dose samples with higher daily doses.
(6) Monitoring: Will population pharmacokinetic modelling enable safer treatment for individual patients?
(7) Security: How can we better identify individuals who are at increased risk of ototoxicity?
(8) Dosage: How much can the dose interval be prolonged in patients with renal impairment without risking bacterial regrowth or the development of resistance?
(9) Dosing: What is the optimal dosing regimen for intermittent haemodialysis—before, or at the end of each treatment?
(10) Treatment duration: Effect on mortality, morbidity, ecology, and toxicity in various infections using a single dose of aminoglycoside in combination with beta-lactam antibiotics in severe infections.

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