Analytic Reviews: Management of Aminoglycosides in the Intensive Care Unit
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Analytic Reviews: Management of Aminoglycosides in the Intensive Care Unit

Elizabeth A. Radigan, PharmD, BCPS1, Neil A. Gilchrist, PharmD, BCPS2, and Melissa A. Miller, PharmD, BCPS2

Abstract
Antibacterial resistance is increasing throughout the world, while the development of new agents is slowly progressing. In addition, the increasing prevalence of fluoroquinolone resistance may force many practitioners to choose an aminoglycoside agent in gram-negative regimens. Aminoglycosides are bactericidal agents with potent activity against gram-negative infections and activity against gram-positive infections when added to a cell wall active antimicrobial-based regimen. These agents may be dosed multiple times a day or consolidated as high-dose, extended-interval dosing to maximize pharmacokinetic and pharmacodynamic properties to achieve possible improved efficacy with reduced toxicity. Clinical application includes the treatment of bacteremia, endocarditis, health-care and nosocomial pneumonias, intra-abdominal infections, and others. Nephrotoxicity and ototoxicity are potential risks of aminoglycoside therapy that may be minimized with serum monitoring and short courses of therapy.

Keywords
aminoglycoside, gentamicin, tobramycin, high-dose, extended-interval

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Introduction
Gram-negative infections are an ongoing challenge for clinicians in the intensive care unit (ICU), with a limited number of antibacterials to choose from and even fewer potential agents in the pipeline. There are an increasing number of multiple drug-resistant gram-negative infections including Pseudomonas aeruginosa, Acinetobacter baumannii, and extended-spectrum β-lactamase (ESBL) producing Klebsiella pneumoniae.1-4 Fluoroquinolone resistance has steadily increased as the number of resistant isolates doubled from 1990 to 2000 in P. aeruginosa.5 In addition to antibacterial resistance, approximately 10% of patients admitted to the hospital report allergies to penicillin medications, limiting the clinicians’ choice of agents or weighing the risk of a potential serious adverse drug reaction.6 Due to an increasing trend in antibiotic resistance, especially fluoroquinolones, and relatively few antimicrobial selections, aminoglycosides will continue to have a major role among the antimicrobials used in many ICUs.

Aminoglycosides are useful agents in the ICU, with potent activity against gram-negative bacilli, rapid bactericidal activity, ability to interact synergistically with cell wall-active antibiotics (eg β-lactams), and predictable pharmacokinetics in some patient populations.7 A limitation that has precluded the empiric use of these agents in a majority of patients is the potential risk of nephrotoxicity. There are currently 9 aminoglycosides available in the United States market: gentamicin, tobramycin, amikacin, streptomycin, neomycin, kanamycin, paromomycin, netilmicin, and spectinomycin. Gentamicin, tobramycin, and amikacin are the focus of this article as they are the most widely prescribed.

Pharmacology
Aminoglycosides are bactericidal agents that bind irreversibly to the 30S bacterial ribosome subunit. This binding interferes with the reading of the genetic code, halts translation, and results in inhibition of protein synthesis with cell death.8 These agents have activity against a number of aerobic gram-negative bacilli, gram-positive cocci, and some mycobacteria strains. In general, resistance to aminoglycosides is present in Burkholderia cepacia and Stenotrophomonas maltophilia.

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Treatment of susceptible gram-positive infections may require the combination of a cell wall-active agent, such as a β-lactam, to allow for the introduction of the aminoglycoside into the bacteria cytoplasm, such as enterococci.

Gentamicin, tobramycin, and amikacin all have similar pharmacokinetic properties with a peak serum concentration at 30 to 60 minutes after an intravenous (IV) infusion and a terminal half-life of 1.5 to 3.5 hours in adult patients with normal renal function. The volume of distribution (Vd) is 0.2 to 0.3 L/kg, which closely resembles that of extracellular fluid, and allows for therapeutic concentrations in blood, bone, synovial fluid, and peritoneal fluid. Aminoglycosides have poor distribution into the lungs and central nervous system. Aminoglycosides are minimally bound to plasma proteins, and elimination of these agents occurs primarily via glomerular filtration as unchanged drug in the proximal tubule, which contributes to the nephrotoxicity of these agents.\(^8\)

Concentration-dependent killing and the postantibiotic effect (PAE) are 2 important pharmacodynamic properties related to aminoglycosides that clinicians should be familiar when prescribing these agents.\(^9\) Concentration-dependent killing refers to the relationship between drug concentration and antimicrobial effect. Optimal antimicrobial activity occurs with aminoglycosides when the peak serum concentration of drug in proportion to minimum inhibitory concentration (MIC) of bacteria achieves a ratio of at least 8:1 to 10:1.\(^10,11\) This concept of high peak concentrations has been incorporated into practice as high-dose, extended-interval dosing (HDED) of aminoglycosides. The PAE refers to the antimicrobial activity of antibiotics after serum concentrations have fallen below the MIC. Aminoglycosides have been found to have a PAE between 0.5 to 8 hours.\(^12\) This number can change depending on a number of factors including bacterial strain, duration of exposure, and concentration obtained by the aminoglycoside.

**Toxicity**

The toxicity concerns with gentamicin, tobramycin, and amikacin include nephrotoxicity, ototoxicity, and potential to induce neuromuscular blockade.

**Nephrotoxicity**

The mechanism of nephrotoxicity with aminoglycosides has been reviewed extensively by Mingeot-Leclercq and Tulkens.\(^13\) The primary mechanism occurs as a result of small, but significant amounts of drug absorbed in the epithelial cells of the proximal tubules. Aminoglycosides accumulate within the lysosomes of the epithelial cells resulting in impaired function of these organelles.\(^14\) Previous data have shown that nephrotoxicity may occur in 10% to 20% of patients exposed, with the potential for increased toxicity when combined with other nephrotoxic agents, such as vancomycin.\(^15\)

Clinical presentation typically occurs after 7 days of therapy as a nonoliguric renal failure caused by reduction in glomerular filtration rate secondary to acute tubular necrosis.\(^8\) In the majority of cases, nephrotoxicity is fully reversible after discontinuation of the aminoglycoside. In a study of 201 critically ill patients receiving gentamicin or tobramycin, treatment resulted in 69 cases of nephrotoxicity out of 240 courses of aminoglycoside therapy. Of note, renal function returned to baseline values in patients surviving their hospital stay. Some patients needed up to 90 days to return to their baseline kidney function.\(^16\) Risk factors for aminoglycoside-induced nephrotoxicity are listed in Table 1.\(^16-19\)

There is limited data on treatment and preventative strategies for aminoglycoside nephrotoxicity. Therapies that have been tried in animal models include calcium supplementation, calcium channel blocker therapy, and the administration of antioxidants. None of these interventions have been incorporated into practice due to limited human data.\(^20-23\) It is still unclear whether HDED administration of aminoglycosides may decrease the incidence of nephrotoxicity compared to traditional dosing. Nicolau and colleagues\(^24\) reported an incidence of 1.2% onset of acute kidney injury secondary to HDED aminoglycoside therapy in more than 2000 patients compared to a historical incidence of 3% to 5%. Common practice to limit nephrotoxicity includes monitoring serum aminoglycoside levels, monitoring serum creatinine levels, avoiding or minimizing concomitant therapy with other nephrotoxic agents, and minimizing duration of therapy. As we discuss clinical trials reporting rates of nephrotoxicity, it is important to note that most trials define nephrotoxicity as a rise in serum creatinine of 0.5 mg/dL or an increase of 50% compared to baseline, which makes it difficult to determine the severity of the nephrotoxic effect. For example, a patient with a rise in serum creatinine from 0.5 mg/dL to 1 mg/dL would be considered to have nephrotoxicity, as would a patient with an increase from 1 mg/dL to 3 mg/dL, although one patient may be considered to have more significant toxicity.

**Ototoxicity**

Aminoglycoside-induced ototoxicity can lead to both permanent hearing loss and vestibular dysfunction and is an important dose-limiting side effect to consider when using aminoglycosides. It has been reported that development of nephrotoxicity and ototoxicity are independent adverse effects.\(^17,25,26\) Some factors may predispose patients to ototoxicity, such as genetics\(^27,28\) and preexisting renal disease. Permanent hearing loss is due to loss of hair cells and neurons in the cochlea, which do not regenerate. Vestibular dysfunction is due to altered function of type 1 vestibular hair cells. Both are usually irreversible and are not related to serum aminoglycoside levels. Rates of cochlear and vestibular toxicity range from 0% to 62%\(^29-31\) and 0% to 19%\(^32,33\) respectively, and may vary based on the type of audiograms performed. Different frequencies of puretone audiometry testing and other types of audiologic assessment such as otoacoustic emissions have varying sensitivities for monitoring and detecting ototoxicity, as reflected in the wide ranges noted above. In addition, ototoxicity can occur without...
Table 1. Potential Aminoglycoside Risk Factors for Nephrotoxicity16-19

<table>
<thead>
<tr>
<th>Concurrent diuretic therapy</th>
<th>Frequency of aminoglycoside dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy</td>
<td>Male gender</td>
</tr>
<tr>
<td>Initial peak and trough serum levels</td>
<td>Comorbid disease state:</td>
</tr>
<tr>
<td>Baseline GFR &lt;60 mL/min per 1.73 m²</td>
<td>Liver disease, shock, diabetes</td>
</tr>
<tr>
<td>Use of other nephrotoxic drugs</td>
<td>Sodium levels</td>
</tr>
<tr>
<td>Iodinated contrast exposure</td>
<td>Daily area under the plasma concentration curve (AUC)</td>
</tr>
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</table>

**Neuromuscular Blockade**

Neuromuscular blockade is a rare but potentially dangerous side effect of aminoglycosides. This adverse effect has been reported most commonly with peritoneal irrigation with neomycin solution, however, case reports with other aminoglycosides given intravenously can be found. Limited data suggest that there is no increased risk of aminoglycoside-associated neuromuscular blockade with HDED. It may be prudent to weigh the risks versus benefit when considering aminoglycoside therapy in patients receiving neuromuscular blocking agents or patients with neuromuscular diseases, such as myasthenia gravis.

**Dosing Strategies**

**Traditional Versus High-Dose, Extended-Interval Dosing**

The bactericidal activity of aminoglycosides is concentration-dependent. They are dosed using the actual body weight of the patient. Traditional aminoglycoside dosing uses small doses (1-2 mg/kg) that are given multiple times per day, usually every 8 to 12 hours. Traditional dosing for serious gram-negative infections target peak gentamicin and tobramycin serum concentrations of 8 to 10 mcg/mL, and trough serum concentrations <2 mcg/mL. Amikacin dosing is much higher, typically 7.5 mg/kg given every 8 to 12 hours, with target peak serum concentrations of 30 to 40 mcg/mL and trough serum levels of <10 mcg/mL.

Aminoglycosides may also be given at a higher dose (5-7 mg/kg for gentamicin or tobramycin and 15-20 mg/kg for amikacin) and at an extended interval (every 24, 36, or 48 hours), which is often referred to as high-dose, extended-interval dosing (HDED). High-dose, extended-interval dosing allows for the achievement of similar area under the curve as multiple daily dosing. Studies have validated that HDED of aminoglycosides are at least as effective as multiple daily dosing and allow for optimization of the pharmacodynamic effects including concentration-dependent killing and PAE. An additional advantage may also be a reduced incidence of nephrotoxicity when given once daily versus multiple times per day. High-dose, extended-interval dosing of aminoglycosides has traditionally used a population-based dosing nomogram. In 1995, Nicolau and colleagues published their experience with the development of the Hartford Nomogram and it has become the most widely used nomogram for HDED of aminoglycosides. The Hartford Nomogram was designed to target peak serum concentrations 10 times the MIC of their institution’s most serious gram-negative pathogen, P. aeruginosa (median gentamicin MIC = 2 mcg/mL, median amikacin MIC = 4 mcg/mL). When using the Hartford Nomogram, patients are given a 7 mg/kg dose of gentamicin or tobramycin (15 mg/kg for amikacin) and a random serum level is obtained 6 to 10 hours after the first dose. This value is then plotted on their nomogram to determine the optimal dosing interval (Figure 1). The goal when using the Hartford Nomogram is to achieve maximal killing by achieving high peaks and undetectable serum trough concentrations in an effort to minimize the risk for nephrotoxicity and take advantage of the PAE. It is important to note that patients with the potential for variable aminoglycoside pharmacokinetics including pediatrics, pregnant women, patients with burns, patients with ascites, and patients undergoing dialysis were excluded during the development of this dosing nomogram.
Because the Hartford Nomogram was designed for their institution-specific MICs and multiple patient populations were excluded, some experts have questioned whether nomograms should even be used, particularly in critically ill patients. In 2002, Buijk and colleagues enrolled 89 critically ill patients to receive HDED gentamicin or tobramycin based on the Hartford Nomogram. Pharmacokinetic parameters including Vd were estimated for all patients. In this study, the authors found that the majority of the critically ill patients achieved a peak to MIC ratio of $\geq 10$. They also found that the pharmacokinetic profiles for dosing intervals only matched that of the Hartford Nomogram in 62% of cases. Patients with septic shock had a higher Vd and doses of 7 mg/kg were necessary in these patients to achieve the optimal peak to MIC ratio. The authors concluded that critically ill patients have highly variable pharmacokinetic profiles that do not always fit within the Hartford Nomogram and that individual pharmacokinetic monitoring may be warranted. Additionally, Wallace and colleagues evaluated the accuracy of 4 dosing nomograms including the Hartford Nomogram. They prospectively collected data from 90 hospitalized patients, 40% of which were admitted to the ICU, who received gentamicin therapy. Patients had either 2 or 3 gentamicin concentrations collected and individualized pharmacokinetic parameters were estimated to determine optimal dose and frequency to achieve a target peak level of 20 mcg/mL and a trough level of 0.2 mcg/mL. These individualized dosing regimens were then compared to the dose and frequencies recommended by 4 different dosing nomograms. The authors found a considerable difference in pharmacokinetic parameters when comparing individualized dosing to those of the dosing nomograms, and many of the patients did not achieve the peak level the nomogram was designed to produce. As a result, the authors advocate that dosing nomograms should be avoided and that individualized pharmacokinetic monitoring should be used.

Individualized pharmacokinetic dosing and monitoring is an alternative approach to nomogram-based dosing. This approach will often use the initial starting dose as described in HDED nomograms but will obtain 2 or more serum concentrations in the postdistributive phase (commonly 2 to 10 hours after the end of the infusion) to calculate patient-specific pharmacokinetics including Vd and half-life. Because of the large degree of interpatient variability in the ICU, this is becoming an attractive option for critically ill patients. By performing individualized pharmacokinetics, doses and dosing intervals can be altered to optimize therapy. Another potential advantage of this method as reported by Streetman and colleagues is the reduced potential for developing nephrotoxicity when individualized pharmacokinetic dosing is used. These investigators found a significant reduction in the incidence of nephrotoxicity in patients who received individualized pharmacokinetic monitoring as compared to those who did not (7.9% vs 13.2%, $P = .02$).

Ultimately, the choice between traditional dosing and HDED is often dependant on patient-specific characteristics and the type and site of infection in which it has been studied. When using HDED, the choice between nomogram-based dosing or individualized pharmacokinetic dosing in the critically ill patient is also dependent on patient-specific characteristics, specifically those affecting Vd and clearance, which occurs in patients with burns, trauma, sepsis, obesity, and renal dysfunction. These variables will be addressed in upcoming sections of the review.
As a general rule, alterations in Vd will require a change in the aminoglycoside dose that is needed, while changes in renal drug clearance will require a modification in the dosing frequency. When evaluating how these pharmacokinetic changes affect the dosing and monitoring of aminoglycosides in critically ill patients, it is easiest to separate them into specific patient populations.

**Burn patients.** The alterations in pharmacokinetics of patients with burns have been extensively studied. During the resuscitation phase after burn injury, patients generally have a decreased Vd and decreased renal drug clearance. This is followed by a hypermetabolic phase lasting several days to weeks in which Vd and renal drug clearance are markedly increased secondary to fluid resuscitation, fluid losses, decreased albumin, increased cardiac output, and renal elimination. The optimal dose and dosing interval of aminoglycosides in this patient population can be challenging. Based on their pharmacokinetic alterations, high-dose aminoglycoside therapy is common to achieve optimal peak serum concentrations. Because most HDED nomograms have excluded patients with burns, individualized pharmacokinetic monitoring should be used. Hoey and colleagues retrospectively evaluated 40 patients with burns who received gentamicin or tobramycin at 5 and 7 mg/kg IV as a single daily dose. Seventy percent of patients achieved the desired peak/MIC ≥10, however, 18% of the patient experienced a drug-free interval for ≥12 hours. The authors concluded that giving patients with burns a single, daily dose of aminoglycoside is not sufficient. They advocate for individualized therapeutic drug monitoring to assure that the appropriate peak to MIC ratio is achieved and that patients’ levels are not undetectable for extended periods of time. In another study by Conil and colleagues, they included 38 patients with burns in the secondary phase of the burns (>48 hours) who received amikacin 20 mg/kg IV once daily. Only 16% of patients achieved a peak to MIC ratio ≥8 and this was particularly evident in the patients with ≥15% burns or creatinine clearance >120 mL/min. Because of the challenges seen with dosing and monitoring of aminoglycosides in patients with burns, high doses with individualized pharmacokinetic monitoring appears to be most appropriate to optimize therapy in this patient population.

**Medical/surgical patients.** Medical and surgical ICU patients tend to have normal to increased Vd secondary to fluid resuscitation and/or having capillary leak syndromes. Renal function can be unchanged, increased, or decreased in this patient population. Medical ICU patients tend to have normal to decreased renal function secondary to advanced age, preexisting conditions such as chronic kidney disease, or because of acute kidney injury resulting from their medical illness. Critically ill surgical patients will often retain their baseline renal clearance or it may be increased secondary to an increase in cardiac output. Because of the increased Vd and variable changes in renal clearance seen in both medical and surgical patients, there is little consensus that any one aminoglycoside dosing method is optimal. Generally, critically ill patients with normal to increased renal clearance are most appropriate for HDED aminoglycoside regimens. For those patients with compromised renal function or requiring renal replacement therapy, HDED has not been well studied. Because of this, using traditional aminoglycoside dosing with the dosing interval modified based on the creatinine clearance of the patient is most appropriate in this population.

**Trauma patients.** Critically ill trauma patients tend to be young and hypermetabolic, similar to patients with burns. They often get massive fluid resuscitation causing an increased Vd and can have normal to increased renal clearance. Based on these pharmacokinetic changes in ICU trauma patients, a high-dose aminoglycoside regimen seems most appropriate. Finnell and colleagues retrospectively analyzed 49 trauma patients who received 7 mg/kg of gentamicin or tobramycin and had a creatinine clearance >40 mL/min to evaluate the validity of the Hartford Nomogram in this patient population. They found that 98% of the dosing intervals were in accordance with those predicted by the nomogram. Unfortunately, this study does not specify the percentage of patients who were in the ICU. Toschlog and colleagues examined 79 trauma patients who received HDED using the Hartford Nomogram, all of

<table>
<thead>
<tr>
<th><strong>Special Dosing Considerations in Critically Ill Patients</strong></th>
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<tr>
<td><strong>Increased volume of distribution</strong></td>
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<tr>
<td>Accumulation of fluid (resuscitation, trauma, etc)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
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<tr>
<td>Capillary leak syndromes (systemic inflammatory response syndrome)</td>
</tr>
<tr>
<td><strong>Increased clearance</strong></td>
</tr>
<tr>
<td>Hypermetabolic states (burns, trauma)</td>
</tr>
<tr>
<td>Increased cardiac output</td>
</tr>
<tr>
<td><strong>Decreased clearance</strong></td>
</tr>
<tr>
<td>Reduced renal perfusion</td>
</tr>
<tr>
<td>Decreased cardiac output</td>
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**Table 2. Pharmacokinetic Changes in Critically Ill Patients.**

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which were critically ill in the ICU. Fifty eight percent of patients in this study had a gentamicin or tobramycin level of <2 mcg/mL 10 hours after receiving 7 mg/kg, implying a marked increase in renal clearance of the drugs. This is of concern in that the patients may have undergone an extended drug-free interval that exceeds the coverage of the PAE predisposing the patients to therapeutic failure. Barletta and colleagues showed a similar result when they prospectively evaluated 19 critically ill trauma patients who received aminoglycoside therapy. All patients had a serum level drawn 4 and 8 hours after the end of a 30-minute infusion and population pharmacokinetic parameters were estimated for each patient. They found a high degree in variation from patient to patient. Estimated serum peak concentrations ranged from 13.1 to 26.1 mcg/mL and 4 of 19 patients were estimated to have undetectable serum drug levels for >12 hours. It appears that to optimize aminoglycoside dosing in critically ill trauma patients, they need high doses and individualized pharmacokinetic monitoring.

**Obese patients.** Obesity in critically ill patients is becoming increasingly more common and as many as 25% of patients in the ICU are obese. Obese patients have an increased Vd of aminoglycosides as compared with nonobese patients. This alteration in Vd has led to challenges in optimal dosing regimens. Aminoglycosides are traditionally dosed on the patient’s actual body weight. In obese patients, however, dosing with actual body weight tends to result in serum concentrations that are too high. To account for the change in Vd, a correction factor of 0.4 has been developed to account for excess body weight. For example, in obese patients weighing >20% of their ideal body weight (IBW), the aminoglycoside dosing weight (DW) can be calculated using the IBW and the actual body weight (ABW). One equation that can be used to determine the patients dosing weight is DW (kg) = IBW + 0.4 (ABW − IBW).

Obese patients do not appear to have alterations in aminoglycoside clearance and can be dosed at an appropriate interval as calculated by their creatinine clearance. The data for use of HDED of aminoglycosides in critically ill obese patients is lacking as they are generally excluded from such studies. With that said, obesity does not preclude patients from receiving HDED as it is used commonly in practice. The decision between using traditional aminoglycoside dosing versus HDED in critically ill obese patients should be based not only on their renal function, but also on the type and site of infection. Therapeutic drug monitoring should always be done in these patients to ensure appropriate drug levels are being targeted.

**Dosing During Renal Replacement Therapy**

In critically ill patients, renal failure requiring renal replacement therapy may occur secondary to a variety of reasons including preexisting renal disease, multiorgan failure, and shock. Because aminoglycosides are excreted by the kidney as unchanged drug, patients with renal failure are at significant risk for drug accumulation and development of nephrotoxicity. Aminoglycosides have a low molecular weight and are minimally protein bound, which allows them to be removed by both conventional hemodialysis and continuous venovenous hemofiltration. Dosing and monitoring of aminoglycosides during renal replacement therapy is a complex topic and one that is beyond the scope of this review. The readers are referred to other more comprehensive reviews for dosing and monitoring recommendations.

**Therapeutic Drug Monitoring**

Therapeutic drug monitoring (TDM) of aminoglycosides is essential not only to assess efficacy but also in the prevention of toxicity because of their narrow therapeutic index. Aminoglycosides are well known to be nephrotoxic; however, as mentioned previously, by using patient-specific TDM, the incidence of nephrotoxicity may be reduced. There have been many studies that have demonstrated positive clinical and economic outcomes when TDM is part of a clinical pharmacokinetic service. Bond and Raehl retrospectively reviewed patients who received pharmacist-managed aminoglycoside or vancomycin therapy (defined as a pharmacist under the authority of a physician initiating or adjusting aminoglycoside or vancomycin therapy and ordering of laboratory tests) as compared to physician-managed therapy. Patients who did not receive the pharmacist-managed drug therapy had 6.71% higher death rates, 12.28% increased length of stay, and accrued more drug and laboratory charges (8.15% and 7.80%, respectively). The literature supports a decrease in negative outcomes when a pharmacist is incorporated as either part of a clinical pharmacokinetics team or as part of the multidisciplinary team caring for critically ill patients.

**Types of Infection**

The decision to use an aminoglycoside in an ICU patient is multifactorial. In addition to assessing alterations in Vd and renal clearance as discussed previously, the site of infection, the pathogen, and its susceptibility have a significant impact on the management of aminoglycosides. The following section will address optimal aminoglycoside management in specific types of infections commonly encountered in critically ill patients.

**Sepsis/Bacteremia**

Antibiotic therapy for the treatment of septic shock/severe sepsis should be initiated as soon as possible, preferably no later than 1 hour following recognition of the syndrome. Although guidelines for severe sepsis support broad spectrum empiric therapy and recommend combination therapy when treating *Pseudomonas* infections or neutropenic patients for the first 3 to 5 days of therapy to ensure coverage of isolated organisms, the evidence for this practice is not strong. Although previous studies have reported that combination β-lactam plus amino-glycoside therapy may be beneficial due to in vitro synergism
and decreased development of resistance, a recent meta-analysis did not support a mortality benefit with the combined use of aminoglycosides and β-lactams as initial therapy for sepsis as compared to β-lactam monotherapy. Sixty-four trials with 7586 patients were included in the review, and of the 43 trials that reported mortality, there was no significant difference favoring combination or monotherapy. There was no benefit with combination therapy in patients with gram-negative infection or in patients with P. aeruginosa, and clinical failure was more common. In addition, those patients receiving combination therapy had significantly higher rates of nephrotoxicity, with the authors concluding a number needed to harm of 15 patients. This meta-analysis raises the question of the use of β-lactam plus aminoglycoside combination therapy in the treatment of infections related to severe sepsis.

Some clinicians, however, would argue that for the empiric treatment of infections in septic patients with risk factors for multidrug-resistant organism, the use of dual gram-negative therapy should be promoted to increase the likelihood that the isolated organism is covered by at least one of the initial agents. Once an organism has been isolated and is sensitive to one or both of the dual gram-negative therapies, the more toxic agent, such as the aminoglycoside, can be discontinued. The choice of antimicrobials used in individual institutions for the treatment of sepsis should depend on local antibiograms, and if used, dosing should be aggressive. In addition, the choice of HDED or multiple daily doses of aminoglycosides should depend on the site of infection, as discussed in future sections. For example, endocarditis should be treated with multiple daily doses in most cases, but HDED is preferred in patients with pneumonia, when appropriate.

Lungs

Intravenous. Infections that occur in the lungs including hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) can be difficult to manage in the critically ill patient and often require the empiric use of 2 gram-negative active antimicrobial agents to target multidrug-resistant (MDR) pathogens. At the present time, these choices include an antipseudomonal cephalosporin, carbapenem, or β-lactam/β-lactamase inhibitor, plus either an antipseudomonal fluoroquinolone or an aminoglycoside. Choice of a fluoroquinolone or aminoglycoside as the second empiric gram-negative agent should be based on institution-specific antibiograms, as suggested by Beardsley and colleagues.86

Distribution of aminoglycosides into lung tissue is not optimal. Infected airways, especially alveoli, are the site where much of the bacterial replication occurs in pneumonia. For this reason, alveolar lining fluid to serum concentrations may be a better measure of aminoglycoside penetration in pneumonia than whole-lung tissue (50%), bronchial secretions (20%-60%), and sputum (20%). In a small study evaluating the penetration of gentamicin into the alveolar lining fluid of critically ill patients with VAP, patients were all given gentamicin 240 mg (mean dose of 3.5 mg/kg) IV once daily.90 They found that the alveolar lining fluid to serum ratio was 32%, which accounted for a mean peak alveolar fluid lining concentrations of 4.24 mcg/mL 2 hours after administration, and mean peak serum concentration of 13.39 mcg/mL at 0.5 hours. However, the authors concluded that for the treatment of pneumonia caused by gram-negative pathogens with reduced susceptibility, higher doses of gentamicin would be required to optimize alveolar concentrations.

Knowing that the penetration of aminoglycosides into the lungs is poor, use of HDED over multiple daily dosing in appropriate patients allows for higher peak concentrations to achieve the target peak to MIC ratio. As stated previously, a peak to MIC ratio of at least 8:1 optimizes bactericidal activity. Kashuba and colleagues showed that if the optimal peak to MIC ratio can be achieved in patients with gram-negative nosocomial pneumonia within the first 48 hours using HDED aminoglycoside therapy, this resulted in faster temperature and leukocyte count resolution. A recent study in 638 adult patients with nosocomial pneumonia examined the use of obtaining antibiotic concentrations and MICs early in therapy to determine whether dose alterations could impact outcomes. A small number of patients were started on an aminoglycoside, amikacin 15 mg/kg IV every 24 hours, and were considered to be at their pharmacodynamic goal if the peak to MIC ratio was greater than or equal to 8 mcg/mL. Despite patients with sepsis, hypotension, and/or end organ dysfunction being excluded from the study, this data showed that optimal dosing of antibiotics including β-lactams, fluoroquinolones, and aminoglycosides can improve clinical outcomes. Some additional randomized, controlled clinical trials published in English since 1995 involving intravenous use of aminoglycosides in the initial treatment of adults with HAP, VAP, or HCAP are summarized in Table 3.

For most patients receiving aminoglycosides for treatment of pneumonia, the use of HDED and monitoring in accordance with the Hartford nomogram (or equivalent) is acceptable. An initial timed level following the first dose should be obtained, and then trough serum levels should be drawn with every third to fourth dose (goal trough: undetectable), or more often in patients with acute changes in renal function or Vd. As discussed previously, some critically ill patient populations with pneumonia may benefit from individualized dosing based on pharmacokinetic parameters, such as 2 levels drawn at least 4 hours apart following the first dose. Having a trained clinical pharmacist involved in the dosing and monitoring of these specific patient populations is strongly encouraged. To minimize the potential for toxicity, if the isolated pathogen is susceptible to the antipseudomonal cephalosporin, carbapenem, or β-lactam/β-lactamase inhibitor and the aminoglycoside, and the patient is clinically improving, discontinuation of the aminoglycoside should be considered.

Inhaled. Due to the limited penetration of aminoglycosides into the lung when given intravenously and risk of systemic toxicity, administering aminoglycosides via aerosolization offers a potentially safe and efficacious mode of delivery.
Comparable efficacy between regimens.

Brun-Buisson et al

Total AE: 23.9% and 13.9% in the PTZ vs CTZ groups, respectively.

Increased serum creatinine levels: 6.8% vs 5.5% in the PTZ vs CTZ groups, respectively.

Clinical response (cure or improvement) in clinically evaluable: 63.9% PTZ AMK \( (n = 83) \) vs 61.5% CTZ AMK \( (n = 26) \).

Crude and attributed mortality rates were 30.7% and 6.8% vs 22.2% and 11% in the PTZ vs CTZ groups, respectively.

AMK 7.5 mg/kg q 12 h combined with PTZ \( (n = 88) \) vs CTZ \( (n = 36) \). AMK was given for at least 10 days in patients with PA, and at least 5 days in all other patients.

Table 3. Summary of Select Randomized, Controlled Clinical Trials in VAP, HAP, and HCAP that Included Aminoglycosides as Part of the Initial Treatment Regimen

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Design</th>
<th>Patients</th>
<th>Dosing Regimen</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Lerma et al(^4)</td>
<td>Open-label, prospective, multicenter, RCT.</td>
<td>n = 124. Adult mechanically ventilated patients with nosocomial PNA in MICU or SICU.</td>
<td>AMK 7.5 mg/kg q 12 h combined with PTZ ( (n = 88) ) or CTZ ( (n = 36) ). AMK was given for at least 10 days in patients with PA, and 3-4 days in all other patients.</td>
<td>Clinical response (cure or improvement) in clinically evaluable: 63.9% PTZ + AMK ( (n = 83) ) vs 61.5% CTZ + AMK ( (n = 26) ). Crude and attributed mortality rates were 30.7% and 6.8% vs 22.2% and 11% in the PTZ vs CTZ groups, respectively.</td>
<td>Total AE: 23.9% and 13.9% in the PTZ vs CTZ groups, respectively. Increased serum creatinine levels: 6.8% vs 5.5% in the PTZ vs CTZ groups, respectively.</td>
<td>Comparable efficacy between regimens.</td>
</tr>
<tr>
<td>Brun-Buisson et al(^4)</td>
<td>Open, multicenter, RCT.</td>
<td>n = 204. Conducted in 27 ICUs in France. Adult patients with VAP.</td>
<td>AMK 7.5 mg/kg q 12 h combined with PTZ 4.5 gm IV q 6 h ( (n = 98) ) or CTZ 1 g IV q 6 h ( (n = 99) ). AMK was given for at least 10 days in patients with PA, and at least 5 days in all other patients.</td>
<td>Clinical cure (per protocol) 51% in the PTZ AMK ( (n = 104) ) vs 36% in the CTZ + AMK ( (n = 107) ). 30-day mortality 18.4% and 22.2%, respectively.</td>
<td>AE in 18% and 22%, respectively.</td>
<td>Comparable efficacy between regimens.</td>
</tr>
<tr>
<td>Sieger et al(^5)</td>
<td>Open, multicenter, RCT.</td>
<td>n = 211. Conducted in 22 centers. Adult patients with HAP.</td>
<td>Meropenem (1 g IV q8 h) monotherapy ( (n = 104) ) vs CTZ 2 gm IV q 8 plus TOB 1 mg/kg IV q 8 ( (n = 107) ). TOB could be discontinued if the isolated pathogen was susceptible to CTZ.</td>
<td>Clinical response in 89% ( (n = 63) ) of meropenem vs 72% ( (n = 58) ) of CTZ + TOB patients ( P = .04 ).</td>
<td>AE occurred in 22% and 19% of patients, respectively.</td>
<td>Meropenem is more efficacious than the combination of CTZ plus TOB in the initial treatment of HAP.</td>
</tr>
<tr>
<td>Joshi et al(^6)</td>
<td>Open, multicenter, RCT.</td>
<td>n = 300. Conducted in 25 centers. Adult patients with LRTI.</td>
<td>PTZ + TOB ( (n = 155) ) vs CTZ + TOB ( (n = 145) ). TOB was administered as 5 mg/kg per day in 3 divided doses, and for patients with PA, was continued for the duration of study.</td>
<td>Clinical success in evaluable PNA patients only: 7.7% PTZ ( (n = 70) ) vs 52% CTZ ( (n = 42) ) ( P = .046 ). Mortality in all randomized patients: 7.7% PTZ vs 17% CTZ, ( P = .03 ).</td>
<td>No renal AE noted.</td>
<td>PTZ + TOB was more effective than CTZ + TOB in patients with nosocomial LRTI.</td>
</tr>
<tr>
<td>Joshi et al(^7)</td>
<td>Double-blind, multicenter RCT.</td>
<td>n = 449. Adult patients with nosocomial PNA.</td>
<td>PTZ + TOB ( (n = 222) ) vs IMP + TOB ( (N = 215) ). TOB was administered as 5 mg/kg per day in 3 divided doses, and for patients with PA was continued for the duration of study.</td>
<td>Clinical cure rate in evaluable patients was 68% in PTZ ( (n = 98) ) vs 61% in IMI ( (n = 99) ) groups ( P = .256 ). Mortality was 10% in PTZ ( (n = 222) ) vs 8% in IMI ( (n = 215) ) ( P = .41 ).</td>
<td>Serious AE occurred in 19% of PTZ vs 19% of IMI-treated patients. No renal AE were reported.</td>
<td>Comparable efficacy between regimens.</td>
</tr>
<tr>
<td>Rubinstein et al(^8)</td>
<td>Open, prospective, multicenter RCT.</td>
<td>N = 580. Adult with nosocomial PNA ( (n = 297) ), sepsis, or severe upper UTI. 29 centers in 13 countries.</td>
<td>CTZ monotherapy vs CTX/TOB. TOB was administered as 3-5 mg/kg per day, with dose and interval modified to obtain peak of 6-12 mcg/mL and trough &lt;2 mcg/mL.</td>
<td>Clinical cure (PNA only): 58% CTZ monotherapy ( (n = 159) ) vs 46% CTX/TOB ( (n = 138) ) ( P = .09 ). Clin response (PNA only) 73% vs 65%. Mortality was similar between groups.</td>
<td>AE related to study drug: 11 patients CTZ vs 15 patients CTX/TOB ( P = .32 ). 9 of 15 CTX/TOB patients had nephrotoxicity ( P = .001 ).</td>
<td>For empiric treatment of serious nosocomial infections, CTZ is more effective than CTX/TOB.</td>
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Abbreviations: AE, adverse events; AMK, amikacin; CTX, ceftriaxone; CTZ, cefazidime; HAP, hospital-acquired pneumonia; HCAP, health care-associated pneumonia; IMI, imipenem/cilastatin; IV, intravenous; LRTI, lower respiratory tract infection; PA, Pseudomonas aeruginosa; PNA, pneumonia; PTZ, piperacillin/tazobactam; RCT, randomized controlled trial; TOB, tobramycin; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
Animal data shows there may be faster bacterial killing when aminoglycosides are given via inhalation. Although initial data in cystic fibrosis patients showed no ototoxicity or nephrotoxicity in patients receiving inhaled tobramycin, more recent case reports have shown some risk of toxicity in adults, particularly in patients with renal dysfunction. Inhaled aminoglycosides have been studied in prevention of VAP and treatment of VAP, showing positive results. In a small pilot study by Hallal and colleagues, inhaled tobramycin (TOBI), administered in doses of 300 mg twice daily, as compared to intravenous tobramycin in patients with VAP caused by P. aeruginosa or Acinetobacter spp, was considered safe and effective. The 5 patients that received TOBI had clinical resolution of VAP, whereas 2 of the 5 patients with intravenous tobramycin were failures. Mohr et al retrospectively reviewed 22 patients with VAP that received tobramycin 300 mg inhaled twice daily (n = 16) or amikacin 400 mg-1000 mg inhaled twice daily (n = 6), and there were no reported renal or pulmonary toxicities.

The pharmacokinetics of inhaled and intravenous amikacin have also been studied in a simulated mechanical ventilation model in healthy participants. Intravenous doses of amikacin 15 mg/kg were compared to nebulized amikacin in 40, 50, and 60 mg/kg doses, and the resulting peak serum concentrations were 48 mcg/mL, 8.2 mcg/mL, 9.2 mcg/mL, and 9.2 mcg/mL, respectively. Although these nebulized doses of amikacin are higher than those clinically used in the treatment of pneumonia, they verify that some systemic exposure is likely in patients undergoing mechanical ventilation. More studies are needed to determine whether inhaled aminoglycosides should be regularly considered as an option in treatment of pneumonia.

**Kidney**

Aminoglycosides can be used in the treatment of pyelonephritis and urinary tract infections (UTIs) in critically ill patients, often as alternative agents in patients with multiple allergies to β-lactams, fluoroquinolones, and sulfa-containing antimicrobials. Urinary tract infections acquired in the ICU occur-lactams, fluoroquinolones, and sulfa-containing antimicrobials. Urinary tract infections (UTIs) in critically ill patients, often as alternative agents in patients with multiple allergies to β-lactams, fluoroquinolones, and sulfa-containing antimicrobials. Urinary tract infections acquired in the ICU occur particularly in patients with renal dysfunction. In patients being treated with aminoglycosides synergistically in combination with a cell wall-active agent in the treatment of many types of bacterial endocarditis is recommended. Both gentamicin and streptomycin have been studied in endocarditis with similar efficacy. The use of streptomycin is reserved for strains of enterococcal species resistant to gentamicin due to limited availability of serum monitoring of streptomycin. When gentamicin is prescribed for the treatment of endocarditis, the usual synergy dose is 3 mg/kg per day divided into doses, adjusted for renal dysfunction. The goal peak is 3 to 4 mcg/mL and the goal trough <1 mcg/mL.

In the treatment of native valve staphylococcal endocarditis, gentamicin can be added to standard therapy for the first 3 to 5 days per the Infective Endocarditis guidelines published in 2005; however, this practice has been challenged by a recent publication. Cosgrove and colleagues evaluated the safety of a subset of 116 patients that received low-dose gentamicin in the study published by Fowler et al in 2006, comparing daptomycin monotherapy versus standard therapy (antistaphylococcal penicillin or vancomycin) plus initial low dose gentamicin in patients with Staphylococcus aureus endocarditis and bacteremia. They concluded that the use of low-dose gentamicin, when treating S aureus bacteremia and native valve endocarditis, is nephrotoxic. They also state that due to limited data supporting the use of gentamicin in the treatment of native valve S aureus endocarditis, it should not be used. For the treatment of prosthetic valve staphylococcal endocarditis gentamicin is recommended for combination therapy for the first 2 weeks of therapy.

In the treatment of enterococcal endocarditis, the use of aminoglycosides is more clearly defined. In patients being treated for native or prosthetic valve enterococcal endocarditis, an aminoglycoside should be used for the entire 4- to 6-week course of therapy, because synergy is required for susceptible strains of Enterococcus to be killed. Gentamicin should be administered in multiple, divided daily doses, adjusted for renal function. If high-level resistance to gentamicin is reported, streptomycin should be administered if susceptible. Management of patients on streptomycin can be more difficult due to lack of routine serum concentration monitoring in laboratories, and therefore must be sent out for special testing. For patients...
receiving streptomycin, it should be dosed at 15 mg/kg per day, intravenously or intramuscularly, divided into 2 equal doses, adjusted for renal function, with a goal peak of 20 to 35 mcg/mL and trough <10 mcg/mL.114

Treatment of endocarditis caused by streptococci may also involve administration of an aminoglycoside. For treatment of native valve endocarditis caused by highly-penicillin-susceptible streptococci (MIC ≤ 0.12 mcg/mL), the use of an aminoglycoside is not necessary. Gentamicin may be combined with either ceftriaxone or penicillin, to allow for a shortened 2-week course of therapy in appropriate patients.120,121 The 2-week course of therapy should not be used in patients with cardiac or extracardiac abscess or in those patients with a creatinine clearance of less than 20 mL/min. When treating native valve streptococcal endocarditis that is relatively resistant to penicillin (MIC > 0.12 to ≤ 0.5 mcg/mL) or prosthetic valve endocarditis that is penicillin-susceptible, gentamicin should be combined with either ceftriaxone or penicillin for the first 2 weeks of therapy. Finally, for prosthetic valve streptococcal endocarditis that is relatively or fully resistant to penicillin (MIC > 0.5 mcg/mL), gentamicin should be combined with either ceftriaxone or penicillin for the full 6 weeks of therapy. Gentamicin may be administered in the traditional synergy dosing regimen (daily in 3 equally divided doses), however, when treating streptococcal endocarditis, it may alternatively be administered as a 3 mg/kg IV dose once daily.114 This may be convenient for patients if they are receiving ceftriaxone once daily for the treatment of streptococcal endocarditis.

Central Nervous System

Bacterial meningitis is an infectious disease emergency that requires immediate management and control of infection. Acute bacterial meningitis is associated with significant morbidity and mortality, therefore it is prudent to administer antimicrobial therapy as soon as possible.122 Empiric antimicrobial therapy should be chosen based on the patient’s age and other risk factors and then targeted based on cerebral spinal fluid (CSF) gram stain results, blood cultures, and CSF cultures.123 In adults, aminoglycosides are not a component of the empiric antimicrobial regimen for the treatment of bacterial meningitis, however, they are recommended as a component of standard therapy when Enterococcus species, an uncommon cause of meningitis, is isolated. When pathogens are susceptible, the addition of an aminoglycoside to standard β-lactam therapy may also be considered in patients with Listeria monocytogenes, Streptococcus agalactiae, and P. aeruginosa.122 They may also be considered in patients with MDR gram-negative pathogens, when treatment options are limited. It should be noted that no placebo-controlled trials in patients with bacterial meningitis have been published that evaluate the use of specific antimicrobial agents.

Adults being treated with gentamicin or tobramycin for bacterial meningitis should be dosed at 5 to 7 mg/kg per day or with amikacin at 15 to 20 mg/kg per day, with serum concentration monitoring to target appropriate peak and trough levels.

Aminoglycosides may be administered using multiply daily dosing or as HDED. If administered daily in 3 equally divided doses, peaks should be 8 to 10 mcg/mL and troughs <2 mcg/mL. For HDED, peaks are generally not measured and troughs should be undetectable or <1 mcg/mL. In experimental meningitis, HDED of aminoglycosides is as effective as traditional dosing regimen.124 Although bactericidal activity at 72 hours was identical in this study, there was a benefit at 8 hours of greater bacterial killing in the experimental HDED, supporting the concentration dependant properties of aminoglycosides.

The penetration of aminoglycosides in the CSF is poor, even with meningeal inflammation, and therefore levels obtained would not be high enough to use aminoglycosides as monotherapy against most pathogens.125 To obtain better CSF concentrations of aminoglycosides, they may be administered intraventricularly in some patients.123 This can be accomplished in neurosurgical patients with meningitis that have intraventricular catheters, such as an external ventriculostomy or shunt reservoir, in place. Based on specific susceptibility patterns, gentamicin 4 to 8 mg/day, tobramycin 5 to 20 mg/day, or amikacin 5 to 50 mg/day could be administered by the intraventricular route in appropriate patients.123 The exact doses of aminoglycosides and other antimicrobials administered intraventricularly are not supported by detailed human data. Rodriguez-Guardado and colleagues described a subset of neurosurgical patients with MDR Acinetobacter meningitis with intraventricular catheters in place, and 16 of 51 patients received some form of aminoglycoside, which was often added to therapy based on susceptibility results.126 Of the 16 patients, 9 received combination therapy with a carbapenem plus an aminoglycoside (5 received intrathecal only and 4 received intravenous plus intrathecal), 4 received combined intravenous therapy with imipenem or ceftazidime plus an aminoglycoside, 1 received intravenous amikacin monotherapy, and 2 received a cephalosporin plus intravenous and/or intrathecal aminoglycoside. Intrathecal doses of aminoglycosides were 10 mg/24 hours for tobramycin or gentamicin, and 20 mg/24 hours for amikacin. The initial intravenous dose of amikacin was 500 mg every 8 hours. Mortality in the 9 patients who received combination therapy with a carbapenem plus an aminoglycoside was 22% versus 0% to 42% in patients that received other monotherapy or combined therapies. Other publications have also reported the use of intrathecal amikacin in the treatment of serious gram-negative meningitis.127-131 Nationally, as our hospital pathogens become more resistant, the use of aminoglycosides may become more important in the treatment of bacterial meningitis.

Febrile Neutropenia

The use of aminoglycosides in combination with third generation cephalosporins or antipseudomonal penicillins has been studied extensively in the management of febrile neutropenia. Guidelines published by the Infectious Disease Society of America in 2002 reviewing the use of antimicrobials in neutropenic patients with cancer suggest these patients can be treated with β-lactam monotherapy or β-lactam plus aminoglycoside
combination therapy.\textsuperscript{132} However, a meta-analysis published by Paul and colleagues in 2003 suggests that monotherapy may be preferred.\textsuperscript{133} The authors of this meta-analysis included 47 trials comparing $\beta$-lactam monotherapy to $\beta$-lactam plus aminoglycoside combination therapy in patients with fever and neutropenia. The primary outcome was all-cause mortality, and there was no significant difference found between monotherapy and combination therapy for this endpoint. Rates of superinfection, treatment failure, and adverse effects were also assessed. Monotherapy resulted in lower rates of treatment failure and adverse events, while rates of superinfection were similar. These results suggest that monotherapy with a broad-spectrum $\beta$-lactam is favored over combination with an aminoglycoside.

Dosing of aminoglycosides in trials evaluating the treatment of febrile neutropenia was traditionally done using multiple daily doses; however, more recent literature has used HDED such as gentamicin 5 mg/kg daily and amikacin 20 mg/kg daily.\textsuperscript{134,135} The safe and effective use of HDED aminoglycosides as compared to multiple daily doses in patients with febrile neutropenia has also been confirmed in previous studies.\textsuperscript{136-139} Therefore, if patients with febrile neutropenia are prescribed an aminoglycoside, the decision of HDED or multiple daily dosing should be based on individual patient characteristics, such as renal function and age. Based on data showing that HDED is safer in many patient populations and is equally as efficacious to multiple daily dosing in febrile neutropenic patients, this approach should be preferred in appropriate patients if an aminoglycoside is used.

Other

\textit{Intra-abdominal.} Aminoglycosides, originally as monotherapy, and later in combination with anti-anaerobic agents, were once considered the gold standard in the treatment of intra-abdominal infections. A meta-analysis published in 2002 reviewed all prospective randomized controlled trials that included aminoglycosides as agents in the treatment of intra-abdominal infections.\textsuperscript{140} Forty-seven trials, all of which compared aminoglycoside-based regimens to other antimicrobial regimens and were published between 1981 and 2000, were included in the analysis. With all trial data combined, there were a total of 7772 patients, 66\% (5182) of whom were clinically evaluable, with intra-abdominal infections sources including appendicitis, intra-abdominal abscess, hepatobiliary, peritonitis, perforations, and others. As expected, the majority of patients also received surgical therapy. The aminoglycosides used in the majority of trials were gentamicin and tobramycin, with no studies using HDED, and the anti-anaerobic agent used most frequently was clindamycin, rather than metronidazole. The majority of comparator regimens included cephalosporins, carbapenems, or penicillins. An odds ratio of less than 1 favored the aminoglycoside-based regimens, and the odds ratio for all clinically evaluable patients included in the meta-analysis was 1.194 ($P = .04$), which favors the comparator regimens. When separately evaluating only more recent trials published from 1990 to 2000 (n = 3169), the odds ratio further supported the comparator regimens (OR 1.438, $P = .001$). Thirty-three of the 47 included studies used some form of aminoglycoside concentration monitoring, but this was not discussed further in most trials. Nephrotoxicity was reported in 42 trials, which occurred in 2.3\% of patients; however, ototoxicity was reported in only 5 trials with an incidence of 1.2\%.

A more recent meta-analysis published in 2007 reported on the effectiveness of aminoglycoside plus clindamycin therapy versus $\beta$-lactam monotherapy for the treatment of intra-abdominal infections.\textsuperscript{141} Based on the results of the 28 randomized, controlled clinical trials evaluated, the authors found that $\beta$-lactam monotherapy was more effective and that aminoglycoside plus clindamycin therapy carries a higher risk of nephrotoxicity but a lower risk of antibiotic-associated diarrhea. There was no difference in all-cause mortality or attributed mortality between treatment groups.

The use of aminoglycosides in the treatment of intra-abdominal infections is no longer favored over alternatives that are more efficacious and may pose a lower risk of toxicity and do not require serum monitoring. Another disadvantage of aminoglycosides that may be clinically significant, thereby favoring $\beta$-lactams in the treatment of intra-abdominal infections, is the decreased action of aminoglycosides in infected abdominal tissue due to a low pH environment.

\textit{Bone/joint.} Parenteral aminoglycosides have not been studied extensively in the treatment of osteomyelitis; however, aminoglycosides are often included as a component of cement or beads used during orthopedic procedures. This topic is beyond the scope of this article and will not be discussed further.

In patients with prosthetic joint infections, aminoglycosides may be used to target specific pathogens such as enterococcus but are not used empirically.\textsuperscript{142} They may be given in multiple daily doses or as HDED. Due to the extended length of therapy required to adequately treat prosthetic joint infections, aminoglycosides are not as practical as other antimicrobials with improved side-effect profiles.

Conclusion

Aminoglycosides continue to serve as a clinically useful class of antibacterials in the ICU. In particular, gentamicin, tobramycin, and amikacin have an important role in the treatment of a broad spectrum of infections including bacteremia, endocarditis, health care and nosocomial pneumonias, and urinary tract infections. Practitioners choosing to prescribe one of these agents should understand the respective dosing methods and appropriate patient populations to select for these agents. Nephrotoxicity and ototoxicity are the major side effects occurring with the use of these agents and may be reduced by close monitoring of drug serum levels and minimizing the duration of aminoglycoside therapy.

Declaration of Conflicting Interests

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