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Gentamicin should remain part of the empirical sepsis regimen for adults

PERSPECTIVES

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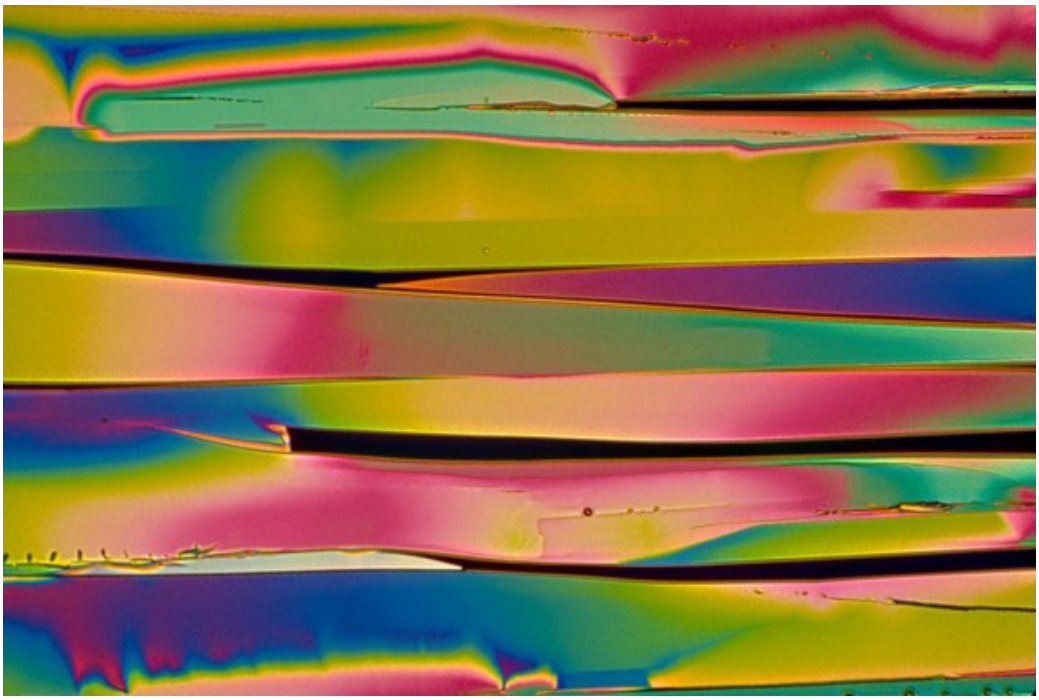
In the Norwegian guidelines, the combination of a narrow-spectrum beta-lactam antibiotic and aminoglycoside should remain the first choice for empirical antibiotic therapy for the majority of severe infections.



Aminoglycoside crystal structures. Illustrative photo: Dennis Kunkel Microscopy/Science Photo Library

Aminoglycosides in combination with narrow-spectrum beta-lactams have been used in Norway for several decades as empirical standard treatment for serious infections (including sepsis) originating from most infection foci (1) (Table 1). The majority of Norwegian patients receive this treatment for 1–3 days before switching to other antibiotics. This combination provides broad

antimicrobial coverage and has a more favourable ecological profile than relevant alternatives. Combination regimens also facilitate de-escalation, which is a core principle of antibiotic management.

Table 1

Sepsis and standard antibiotic therapy for various foci. From the national clinical guidelines for antibiotics in hospitals.

Sepsis and septic shock					
In cases of septic shock or strong suspicion of sepsis, antibiotics are initiated as quickly as possible, and within one hour. In patients without shock and with a lower suspicion of sepsis, additional diagnostics and observations can be performed before initiating antibiotics within three hours.					
Unknown focus:	Lower respiratory tract:	Urinary tract:	Abdomen:	Skin and soft tissue:	Septic shock:
Benzylpenicillin intravenously 2.4 g × 6 + gentamicin intravenously 6–7 mg/kg × 1	*Community-acquired* Benzylpenicillin intravenously 3 g × 4 + gentamicin intravenously 6 mg/kg × 1 *Hospital-acquired* Piperacillin/tazobactam intravenously 4/0.5 g × 4	Ampicillin intravenously 2 g × 4 + gentamicin intravenously 6–7 mg/kg × 1	Ampicillin intravenously 2 g × 4 + gentamicin intravenously 6–7 mg/kg × 1 + metronidazole intravenously 1.5 g × 1 loading dose, followed by metronidazole intravenously 1 g × 1	Cloxacillin intravenously 2 g × 6 + gentamicin intravenously 6 mg/kg × 1	Piperacillin/tazobactam intravenously 4/0.5 g × 1 loading dose, followed by piperacillin/tazobactam intravenously 4/0.5 g × 4 Loading dose is administered over 30 minutes. Subsequent doses are administered over 3 hours, and initiated immediately after the loading dose.

Insufficient raw data on clinical outcomes

Critics of this use of aminoglycosides often refer to a meta-analysis from 2013, which concluded that combination therapy with beta-lactam antibiotics and aminoglycosides did not improve survival but increased the risk of kidney injury compared to beta-lactam monotherapy (2). However, this meta-analysis is not readily transferrable to the Norwegian context. It included many older studies in which aminoglycosides were dosed less effectively (too low) but were more toxic (three times daily over several days) than the current practice.

In 2015, the Norwegian Knowledge Centre for the Health Services (now the Division for Health Services in the Norwegian Institute of Public Health) published a systematic literature review on the use of aminoglycosides in sepsis (3). The report concluded that an aminoglycoside in combination with a beta-lactam antibiotic could increase the risk of kidney and therapeutic failure compared to beta-lactam monotherapy. However, there were no differences in overall mortality or incidence of severe adverse events. An important observation in the report was the low quality of studies available for review.

> ***«The combination of narrow-spectrum beta-lactam antibiotics and gentamicin covers most pathogens found in bloodstream infections in Norwegian hospitals»***

We performed an updated literature search with the assistance of Vestre Viken Hospital Trust's library service, and found similar limitations in the quality of studies, and in some cases, inconsistent results. The majority are retrospective observational studies or prospective cohort studies that show either no difference in mortality or reduced mortality with the combination of beta-lactam and aminoglycoside compared to beta-lactam monotherapy (4–6). It is therefore

difficult to draw definitive conclusions. We only found four randomised controlled trials (RCTs), three of which involve plazomicin, a newer aminoglycoside that is not currently available in Norway (7–9).

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) cautions against the use of aminoglycosides in monotherapy in systemic infections with foci outside the urinary tract, due to limited clinical documentation and recent pharmacodynamic studies. However, we have extensive clinical experience in Norway with the successful use of aminoglycosides in empirical regimens for serious infections. We therefore believe there are compelling reasons to continue the current practice.

Antimicrobial coverage

Early treatment with effective antibiotics reduces mortality in sepsis (10–12). Empirical antibiotic therapy must be tailored to local antimicrobial resistance. Data from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) show that the combination of narrow-spectrum beta-lactam antibiotics and gentamicin covers most pathogens found in bloodstream infections in Norwegian hospitals (13). In a Dutch study of patients with bacteraemia caused by Gram-negative bacteria, the coverage was found to be eight times higher for patients with a combination regimen of beta-lactam antibiotics and aminoglycoside compared to those who received beta-lactam antibiotic monotherapy (14). Although the coverage was significantly higher, there was no significant difference in mortality. This may be due to a considerably larger proportion of patients with septic shock in the group receiving aminoglycosides, making the groups not fully comparable.

Ecological impact

Aminoglycoside antibiotics are most effective against Gram-negative bacteria and exert a rapid bactericidal effect by inhibiting microbial protein synthesis (15). They are eliminated by glomerular filtration (> 95 %) and have limited transfer to the intestinal lumen. Consequently, they have limited effect on intestinal flora and are considered to be less conducive to resistance development than alternatives such as cephalosporins.

A correlation has been established between the use of broad-spectrum antibiotics and the incidence of antibiotic-resistant microbes and *Clostridioides difficile* infections (16). Reducing the use of such antibiotics in the Norwegian health service is an expressed medical and political goal (17). In Norway, the alternatives to gentamicin in empirical treatment of severe infections primarily include broad-spectrum third-generation cephalosporins and beta-lactams with beta-lactamase inhibitors.

> ***«Aminoglycoside antibiotics are most effective against Gram-negative bacteria and produce a rapid bactericidal effect by inhibiting microbial protein synthesis»***

National and international action plans to combat antibiotic resistance recommend measures to reduce the overall use of antibiotics, and in particular agents associated with an increased incidence of microbes producing extended-spectrum beta-lactamases (ESBLs). This was also the advice in the report by the European Centre for Disease Prevention and Control (ECDC) following their visit to Norway in 2018 (18). From a microbial ecological perspective, the use of cephalosporins and beta-lactam/beta-lactamase combinations should be limited to situations where agents that are less conducive to resistance development, such as gentamicin, are not recommended.

Adverse effects of aminoglycosides

Acute kidney injury is a known adverse effect of aminoglycosides. The risk of kidney injury increases with prolonged use and multiple-daily dosing (15). However, it is uncertain whether short-term use and once-daily dosing pose an increased risk of kidney injury. Two recent studies from Scotland and Denmark, respectively, found no evidence of increased risk of kidney injury with short-term use (1–4 days) (4, 19).

In the period from 2012 to 2021, the use of aminoglycosides in Norway increased by 30 % measured by the defined daily dose (DDD) (Hospital Pharmacy Drug Statistics, SLS database). During the same period, 33 aminoglycoside-related adverse effects were reported to the Adverse Reactions Register at the Norwegian Medical Products Agency (Norwegian Medical Products Agency, data obtained 29 March 2022). Twenty of the cases related to systemic treatment of severe bacterial infections in adults. Despite the likely extensive underreporting of adverse effects, the data do not raise concerns regarding the use of gentamicin in accordance with guideline recommendations.

EUCAST recently changed the dosing recommendation for higher doses of aminoglycosides (6–7 mg/kg) based on clinical breakpoints and expected clinical efficacy. This adjustment has been incorporated into the Norwegian guidelines. In collaboration with the National Centre for Antibiotic Use in Hospitals, a broadly composed expert group recently devised a protocol for the safe use of aminoglycosides (20). The recommendation highlights the need for early concentration measurements in selected patient groups, including patients over the age of 80.

Patients can safely be given a single dose of aminoglycoside as part of the initial empirical regimen for severe infections. Increased vigilance for adverse effects should, however, be exercised, particularly when systemic aminoglycoside therapy is to continue for more than three days.

Mortality

One multi-centre RCT has been conducted in the last decade comparing the use of gentamicin or tobramycin in combination with benzylpenicillin versus meropenem in patients (n = 297) with neutropenic fever. The study showed a slight increase in mortality in the combination therapy group (3.4 % versus 0 %). A minority of patients had documented bacteraemia (16 %), and none of the deaths were related to infection with Gram-negative bacteria (21).

In a meta-analysis from 2019, the efficacy of combination therapy with beta-lactam antibiotics and once-daily dosed aminoglycosides was compared to beta-lactam antibiotic monotherapy for severe infections. No difference in mortality was found in relation to the use of aminoglycosides (22). We consider this meta-analysis to be particularly relevant for the Norwegian context, as it only included studies with once-daily dosed aminoglycosides.

Experiences from Scandinavian countries with similar resistance patterns and use of aminoglycosides are important. A retrospective observational study of bacteraemia by St Olav's Hospital, Trondheim University Hospital in 2019 showed significantly reduced mortality when using empirical antibiotic therapy in accordance with national guidelines, compared to discordant therapy (23). Most indications suggested combination regimens with a narrow-spectrum beta-lactam antibiotic and an aminoglycoside (21). A Swedish study of community-acquired sepsis showed that patients who received a single dose of gentamicin along with a beta-lactam antibiotic upon admission had significantly lower mortality than the group who received beta-lactam antibiotic monotherapy (24).

Gentamicin should be continued

There is limited clinical research of a high methodological quality on the use of aminoglycosides in combination therapy with narrow-spectrum beta-lactam antibiotics for severe infections. In our literature review, there was no evidence that clinical outcomes were worse in such a regimen

compared to alternatives. On the contrary, our review suggests that the combination regimen is safe at population level (19), provides good coverage against relevant microbes (13, 24) and is less conducive to resistance development than relevant alternatives.

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