

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Is the addition of aminoglycosides to beta-lactams in cancer patients with febrile neutropenia needed?

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Abstract

It is still controversial if the combined use of beta-lactam antibiotics and aminoglycosides has advantages over broad-spectrum beta-lactam monotherapy for the empirical treatment of cancer patients with febrile neutropenia. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified three systematic reviews including 14 pertinent randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded the combination of beta-lactam antibiotics and aminoglycosides increases nephrotoxicity and it might increase mortality in febrile neutropenic cancer patients.

Problem

Patients with cancer have predisposition to infections that increase morbidity and mortality. Many factors contribute to this risk, including neutropenia and the anatomic barrier disruption due to the underlying disease or its treatment. This has led to the use of empirical antibiotics when infection is suspected in patients with fever, before isolating the pathogen or determining its sensitivity.

The combination of beta-lactams and aminoglycosides has been one of the most widely used treatment options. It aims to increase antimicrobial spectrum, and a synergistic effect has been proposed too, preventing the appearance of intra-treatment resistance. Currently, there are alternatives for beta-lactam monotherapy with wide coverage over gram positive and negative bacteria, which can be used to replace

combinations. Furthermore, the addition of aminoglycosides increases adverse effects risk, mainly renal toxicity.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- The addition of aminoglycosides to beta-lactams in cancer patients with febrile neutropenia reduces treatment failure but increases nephrotoxicity and it might increase mortality.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews [1],[2],[3], including 14 randomized controlled trials reported in 17 references [4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20].
What types of patients were included	Eleven studies [6],[7],[10],[11],[14],[15],[16],[17],[18],[19],[20] included adult population only and three studies [4],[8],[9] included adults and children. Six studies [6],[7],[8],[9],[14],[18] included patients with hematologic malignancy, one study [10] included patients with solid tumors and six studies [4],[11],[15],[17],[19],[20], included both. In three studies [4],[8],[14] patients with bone marrow transplantation were included. Most of the studies considered patients with moderate neutropenia (<1000 leukocytes/mm ³) and five studies [4],[6],[8],[9],[11] included patients with severe neutropenia.
What types of interventions were included	All included studies compared combination therapy (beta-lactam plus aminoglycosides) versus monotherapy with the same beta-lactam. All studies used a beta-lactam with antipseudomonic activity (piperaciline-tazobactam, cefepime, ceftazidime, cefoperazone and imipenem) and 12 of 14 studies [4],[6],[7],[10],[11],[14],[15],[16],[17],[18],[19],[20], used amikacine as aminoglycoside.
What types of outcomes were measured	The main outcomes were overall mortality, mortality related to infection, treatment failure and nephrotoxicity.

Summary of findings

The information about the effects of the association between aminoglycosides and beta-lactams in cancer patients with febrile neutropenia is based on 14 randomized controlled trials that included 2670 patients. Fourteen studies reported treatment failure, ten studies overall mortality [4],[6],[7],[9],[14],[15],[16],[18],[19],[20], seven studies measured mortality related to infection [4],[6],[9],[14],[15],[16],[18],[20] and eight studies reported nephrotoxicity [6],[7],[10],[11],[14],[17],[18],[19].

- The addition of aminoglycosides to beta-lactams in cancer patients with febrile neutropenia reduces treatment failure. The certainty of the evidence is high.
- The addition of aminoglycosides to beta-lactams in cancer patients with febrile neutropenia increases nephrotoxicity. The certainty of the evidence is high.
- The addition of aminoglycosides to beta-lactams in cancer patients with febrile neutropenia probably increases mortality, compared to monotherapy with the same beta-lactam. The certainty of the evidence is low.

Aminoglycoside plus beta-lactam for febrile neutropenia in cancer				
Patients	Patients with cancer and febrile neutropenia			
Intervention	Aminoglycoside plus beta-lactam combined therapy			
Comparison	Monotherapy with beta-lactam antibiotics			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT aminoglycoside	WITH aminoglycoside		
	Difference: patients per 1000			
Treatment failure	451 per 1000	374 per 1000	RR 0.83 (0.71 to 0.98)	⊕⊕⊕⊕ High
	Difference: 77 patients less per 1000 (Margin of error: 9 to 131 less)			
Nephrotoxicity	20 per 1000	45 per 1000	RR 2.25 (1.23 to 4.09)	⊕⊕⊕⊕ High
	Difference: 25 patients more per 1000 (Margin of error: 5 to 61 more)			
Total mortality	62 per 1000	83 per 1000	RR 1.34 (0.95 to 1.90)	⊕⊕⊕⊕ ^{1,2} Low
	Difference: 21 patients more per 1000 (Margin of error: 3 less to 56 more)			
RR: Risk ratio. Margin of error = 95% confidence interval (CI). GRADE: evidence grades of the GRADE Working Group (see later in this article)				
* The risk WITHOUT aminoglycosides is based on the risk in the control group of the trials. The risk WITH aminoglycosides (and its margin of error) is calculated from relative effect (and its margin of error)				
1 We downgraded the certainty of the evidence because the primary studies had serious risk of bias.				
2 We downgraded the certainty of the evidence for imprecision.				

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented applies to adult population with cancer and febrile neutropenia secondary to chemotherapy or bone marrow transplantation. Most studies included severe febrile neutropenic inpatients.
-

About the outcomes included in this summary

- Critical for decision-making outcomes included in this summary were selected according to the opinion of the authors.
-

Balance between benefits and risks, and certainty of the evidence

- Treatment failure and nephrotoxicity are outcomes that could change mortality, being the latter the most critical outcomes for decision-making. The addition of aminoglycosides would increase it, but the certainty of the evidence is low.
-

Resource considerations

- It is a low cost intervention for patients and health systems. However, adverse effects could increase the costs. It is not possible to make a proper balance without better certainty about the effects on mortality.
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Differences between this summary and other sources

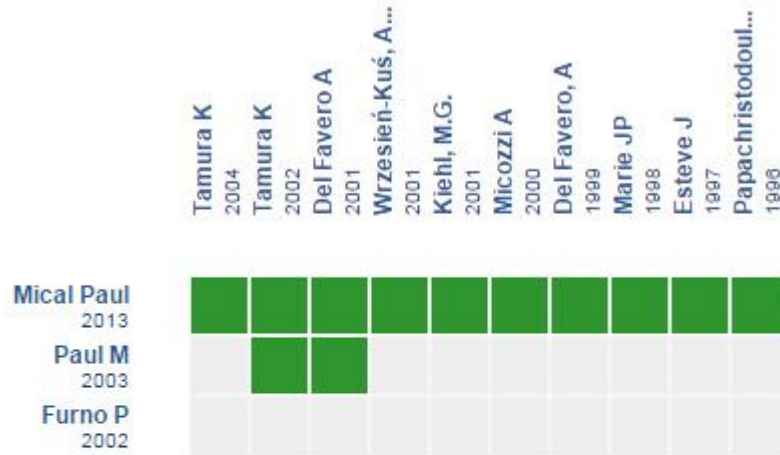
- The conclusions of this summary are consistent with the systematic reviews identified.
 - This summary partially agrees with the guideline of the Infectious Disease Society of America [21], which recommends use of combined therapy in cases of hemodynamic instability, gram-negative bacteria confirmed in blood culture and in patients that received antibiotics in the last 90 days.
-

Could this evidence change in the future?

- The probability that new studies change the conclusions about the effects of combined therapy on mortality in patients with febrile neutropenia is high because of the low certainty of the evidence.
 - We did not find ongoing trials that could properly answer the clinical question of this summary.
-

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.

The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.

The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.

The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version**: [Beta-lactam versus the same beta-lactam plus aminoglycoside for febrile neutropenic cancer patients](#)

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here <http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest

The authors do not have relevant interests to declare.

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