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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are new antibiotics better than beta-lactams for non-critical inpatients with community-acquired pneumonia?

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Abstract

Treatment for community-acquired pneumonia in immunocompetent adults is mainly empirical. Beta-lactam antibiotics have been traditionally considered first-line therapy. New antibiotics could be more effective but the evidence is not clear until now, and its use could entail greater costs, an increase in bacterial resistance and other adverse effects. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified six systematic reviews including 36 randomized trials addressing this question. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded new antibiotics are not better than beta-lactam antibiotics for the treatment of non-critical inpatients with community-acquired pneumonia in relation to clinical failure or adverse effects.

Problem

Community-acquired pneumonia is a highly prevalent disease which affects people of all ages, carrying a high morbimortality and costs, especially at extreme ages of life. Since decades, beta-lactams have been considered the first-line of empirical therapy. With the arrival of new families of antibiotics, like macrolides, azalides, ketolides and quinolones, the use of beta-lactams as first-line therapy has been put into question and the use of new antibiotics has increased. In this context, it becomes necessary to assess the effects of beta-lactams in comparison with the alternatives.

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
- New antibiotics are not better than beta-lactam antibiotics for non-critical inpatients with community-acquired pneumonia in relation to clinical failure or adverse effects.
- The use of beta-lactam antibiotics in community-acquired pneumonia probably leads to no difference in mortality when compared to the new antibiotics.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6], including 36 randomized controlled studies reported in 37 references [7],[8],[9],[10], [11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24], [25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38], [39],[40],[41],[42],[43]. One of the studies is reported in two papers [25],[39].
What types of patients were included	Most of the studies included only patients with community-acquired pneumonia. One study included 10% of patients with health care-associated pneumonia [17], and five studies also included a variable percentage of patients with different respiratory conditions [15],[22],[26],[36],[41]. Thirteen studies included only inpatients [11],[14],[17],[19],[21],[22], [24],[27],[28],[36],[37],[42],[43], eight studies included inpatients and outpatients [13],[15],[18],[20],[32],[33],[39],[40], and sixteen studies did not report place of management [7],[8],[9],[10],[12],[16],[23],[25], [26],[29],[30],[31],[34],[35],[38],[41]. Seven studies included critical patients [7],[10],[19],[20],[31],[32],[37] and 23 studies did not report the severity of illness [8],[9],[11],[13], [15],[16],[17],[21],[22],[23],[24],[26],[29],[30],[33],[34],[35],[36], [38],[40],[41],[42],[43].
What types of interventions were included	In five studies the beta-lactam used was a combination of penicillin with a beta-lactamase [13],[21],[32],[33],[34], eleven studies used a cephalosporin[8],[16],[18],[24],[26],[28],[29],[31],[37],[42],[43], three studies considered the use of a beta-lactam with a beta-lactamase inhibitor or a cephalosporin [19],[20],[27], and the remaining seventeen studies used a penicillin. Only one study used imipenem [17]. Three studies admitted the simultaneous use of a beta-lactam with a different antibiotic [18],[19],[20]. In seven studies the comparison used was a macrolide [12],[21],[23], [29],[35],[41],[43], one study compared with a quinolone or a macrolide [33] and the remaining 29 studies compared only with a quinolone.
What types of outcomes were measured	The outcomes reported by the identified systematic reviews were: Mortality, mortality with intention-to-treat, mortality in older than 65 years, clinical success, clinical success with intention-to-treat, clinical failure, clinical failure with intention-to-treat, clinical failure in pneumococcal pneumonia, clinical failure in atypical pneumonia, clinical failure in pneumonia caused by Legionella pneumophila, microbiological success, microbiological failure, adverse effects, gastrointestinal adverse effects, adverse effects that requires discontinuation of therapy, serious adverse effects, adverse effects with intention-to-treat, and length of hospital stay.

Summary of findings

The information about the effects of beta-lactam antibiotics for the treatment of non-severe community-acquired pneumonia is based on 36 randomized trials including 11,662 patients. Nineteen studies reported mortality [11],[12],[14],[15],[17],[21],[22],[27],[28],[31],[32],[33],[36],[37],[39],[40],[41],[42],[43], 32 reported clinical failure [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[21],[22],[23],[24],[26],[27],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43], 18 reported microbiological failure [11],[14],[15],[17],[21],[22],[24],[30],[31],[32],[33],[36],[37],[39],[40],[41],[42],[43] and 23 studies reported adverse effects [[11],[12],[13],[14],[15],[17],[18],[19],[20],[21],[22],[27],[28],[30],[31],[32],[36],[37],[39],[40],[41],[42],[43]. The summary of findings is the following:

- Beta-lactam antibiotics in non-critical adult inpatients with community-acquired pneumonia probably leads to no difference in mortality when compared to the new antibiotics. The certainty of the evidence is moderate.
- New antibiotics are not better than beta-lactam antibiotics for non-critical adult inpatients with community-acquired pneumonia in relation to clinical failure. The certainty of the evidence is high.
- New antibiotics are not better than beta-lactam antibiotics for non-critical inpatients with community-acquired pneumonia in relation to adverse effects. The certainty of the evidence is high.
- The use of beta-lactam antibiotics in non-critical adult inpatients with community-acquired pneumonia probably leads to no difference in microbiological failure when compared to the new antibiotics. The certainty of the evidence is moderate.

Beta-lactam antibiotics in non-critical inpatients with community-acquired pneumonia

Patients Immunocompetent non-critical adult inpatient with community-acquired pneumonia
Intervention Beta-lactam antibiotics
Comparison Other antibiotics (macrolides or quinolones)

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH other antibiotic	WITH beta-lactam		
	Difference: patients per 1000			
Mortality	28 per 1000	25 per 1000	RR 0.87 (0.63 to 1.20)	⊕⊕⊕◯[1,2] Moderate
	Difference: 3 patients less per 1000 (Margin of error: 10 less to 6 more)			
Clinical failure	223 per 1000	228 per 1000	RR 1.02 (0.95 to 1.1)	⊕⊕⊕⊕[2] High
	Difference: 5 patients more per 1000 (Margin of error: 11 less to 22 more)			
Adverse effects	256 per 1000	251 per 1000	RR 0.98 (0.88 to 1.10)	⊕⊕⊕⊕[2] High
	Difference: 5 patients less per 1000 (Margin of error: 31 less to 26 more)			
Microbiological failure	119 per 1000	147 per 1000	RR 1.24 (0.99 to 1.56)	⊕⊕⊕◯[1,2,3] Moderate
	Difference: 28 patients more per 1000 (Margin of error: 1 less to 66 more)			

Margin of error = confidence interval 95%.
RR: Relative Risk.
GRADE: grade levels of evidence of the GRADE Working Group (see later in this article).

* The risks **WITH other antibiotic** are based on the risk in the control group of the studies. The risk **WITH beta-lactam antibiotic** (and its margin of error) is calculated from the relative effect (and its margin of error).

1. The certainty of evidence was downgraded because of a wide confidence interval.
2. Some studies include a small percentage of outpatients, or non-community-acquired pneumonia, or patients with a different pulmonary condition like asthma or decompensated chronic obstructive pulmonary disease. Nevertheless, the certainty of evidence was not downgraded since it is unlikely that this factor had substantially influenced the final results.
3. This outcome is highly sensitive to lack of blinding of both participants and outcome assessors, which occurred in some studies.

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

- This evidence applies to the management of non-critical adult inpatients with community-acquired pneumonia. It does not apply to health care-associated pneumonia, to severe pneumonia, to pediatric patients or to inmmunocompromised patients.

About the outcomes included in this summary

- We mainly considered clinically relevant outcomes like mortality, treatment failure and adverse effects. We also considered microbiological failure because of its relevance in epidemiological surveillance and in the pharmacological analysis of the effectivenes of the different family of antibiotics.
- We did not find enough data to assess length of hospital stay.

Balance between benefits and risks, and certainty of the evidence

- The evidence here presented shows it is unlikely that there is a difference between beta-lactam antibiotics and the new antibiotics (quinolones and macrolides) for clinically relevant outcomes.
- Furthermore, it is unlikely there are differences in adverse effects between beta-lactam antibiotics and the new antibiotics.

What would patients and their doctors think about this intervention

- Considering the evidence presented in this summary, when making the decision of which antibiotic to choose for the empirical management of the community-acquired pneumonia other elements should be taken into account like local epidemiology of respiratory bacteria, the possibility of selecting reisistant pathogens with broad spectrum antibiotics, pharmacokinetic and pharmacodynamic of each drug, costs, simplicity of administration route and frequency, drug availability and therapy adherence.

Resource considerations

- In general, the use of beta-lactam antibiotics is a cheaper alternative when compared to the new antibiotics. Considering the evidence here presented, in which there would be no difference between these families of antibiotics, it is reasonable to prefer beta-lactan antibiotics.
- Anyway, beta-lactam antibiotics are a broad family of drugs which also includes some high-cost alternatives. This review does not compare the effectiveness of each beta-lactam, therefore any cost-benefit analysis is limited.
- The development of microbiological resistance and the association with adverse effects like Clostridium difficile diarrhea, should also be taken into account when making a cost-benefit analysis [44].

Differences between this summary and other sources

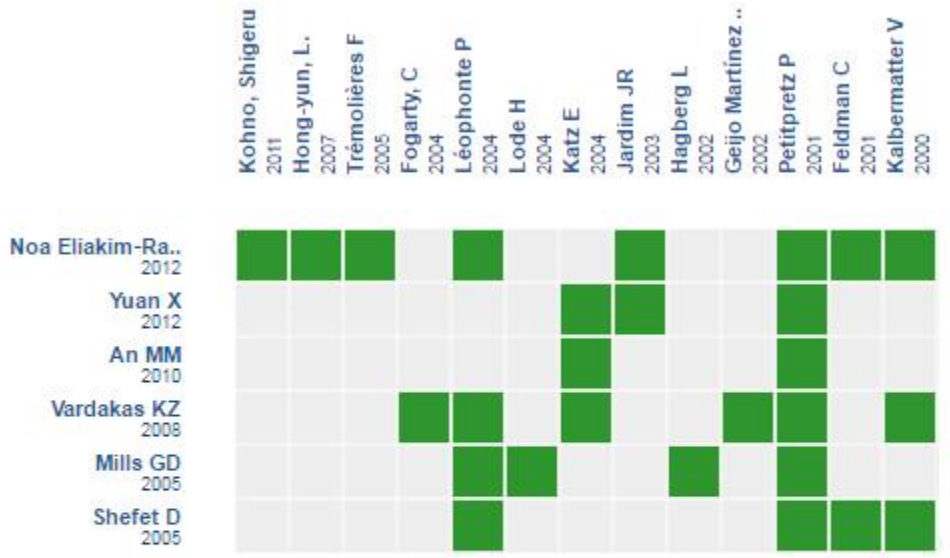
- The results here presented are similar to the conclusions of the main systematic reviews analysed in this review.
- The main community-acquired pneumonia guidelines propose different empirical treatments for this disease. This difference probably considers the local microbiology and the prevalence of beta-lactam resistant Streptococcus pneumoniae. The CONSENSUR II [45] guideline for Latin America proposes the use of beta-lactam antibiotics as the first-line therapy for inmunocompetent non-critical adult inpatients, while the IDSA-ATS guideline [46] recommends the use of a respiratory quinolone or a beta-lactam plus a macrolide. Our findings does not support there is a difference on the effects of these strategies.

Could this evidence change in the future?

- The likelihood that future evidence changes the main conclusions of this summary is low due to the certainty of the evidence.
- We did not identify unpublished or ongoing studies for this question in the WHO International Clinical Trials Registry Platform. Furthermore, we consider unlikely that new studies aiming to assess the effectivenes of beta-lactam antibiotics appear, due to the current amount and certainty of evidence for this question.

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 antibiotics compared with non-beta lactam antibiotics for non-severe community acquired pneumonia in adults requiring hospitalization

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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