

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

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Are prophylactic antibiotics useful in chronic obstructive pulmonary disease?

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Abstract

Bacterial infections are one of the main causes of chronic obstructive pulmonary disease exacerbation, so the use of prophylactic antibiotics, especially macrolides, has been proposed in these patients. However, it is unclear whether antibiotics use is worth the risk and cost. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified five systematic reviews including eight randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded prophylactic antibiotics probably decrease exacerbations in chronic obstructive pulmonary disease, but have no effect on hospitalizations or mortality.

Problem

Exacerbations contribute substantially to morbidity and mortality in patients with chronic obstructive pulmonary disease. Since bacterial infections play a major etiologic role it has been proposed prolonged use of prophylactic antibiotics may reduce exacerbations. Apart from their antimicrobial role, it has been postulated that some antibiotics such as macrolides may also have an anti-inflammatory effect. On the other hand, the use of prophylactic antibiotics is associated with costs and adverse effects at both individual and population level.

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

- Prophylactic antibiotics probably reduce the risk of exacerbations, but they do not decrease hospitalizations or mortality in patients with chronic obstructive pulmonary disease.
- The risk of adverse effects of prophylactic antibiotics in patients with chronic obstructive pulmonary disease is not clear because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews [1],[2],[3],[4],[5], considering 10 primary studies [6],[7],[8],[9],[10],[11],[12],[13],[14],[15], including eight randomized controlled trials [6],[7],[8],[9],[10],[12],[13],[14]. This table and the summary in general are based on the latter.
What types of patients were included	All studies included patients with FEV1/FVC <70% with moderate to very severe disease. Three studies included patients with a history of exacerbations in the previous months [6],[10],[13].
What types of interventions were included	The antibiotic used was a macrolide in seven studies; azithromycin [6],[8],[10], clarithromycin [7] and erythromycin [9],[12],[14]; and a quinolone in only one study (moxifloxacin) [13]. Prophylactic antibiotics were administered continuously in five studies [6],[7],[9],[12],[14] and intermittently or pulsed in the other three [8],[10],[13]. Concomitant therapy was the following: inhaled corticosteroids alone in two studies [7],[12], theophylline plus inhaled anticholinergics in one study [14], inhaled corticosteroids plus inhaled anticholinergics and beta2 agonists in one study [6], inhaled corticosteroids plus inhaled beta2 agonists, inhaled anticholinergics and theophylline in one study [9], and concomitant therapy was not reported in three studies [8],[10],[13]. Seven studies used a placebo for comparison [6],[7],[9],[12],[13],[14].
What types of outcomes were measured	Different systematic reviews performed meta-analysis of the following outcomes: <ul style="list-style-type: none"> • exacerbations • mortality • hospitalizations • quality of life • time to first exacerbation • adverse effects

Summary of findings

Information on the effects of prophylactic antibiotics in chronic obstructive pulmonary disease is based on eight randomized trials that included 3,315 patients. It was possible to obtain information on exacerbations in seven studies [6],[7],[8],[9],[12],[13],[14], on hospitalizations in three [6],[8],[13], on mortality in four [6],[8],[10],[13] and on adverse effects in seven [6],[7],[8],[9],[12],[13],[14].

- Prophylactic antibiotics probably reduce exacerbations in patients with chronic obstructive pulmonary disease. The certainty of the evidence is moderate.
- Prophylactic antibiotics do not reduce the risk of hospitalization in patients with chronic obstructive pulmonary disease. The certainty of the evidence is high.
- Prophylactic antibiotics do not reduce mortality in patients with chronic obstructive pulmonary disease. The certainty of the evidence is high.
- The risk of adverse effects of prophylactic antibiotics in patients with chronic obstructive pulmonary disease is not clear because the certainty of the evidence is very low.

Prophylactic antibiotics for chronic obstructive pulmonary disease				
Patients	Chronic obstructive pulmonary disease			
Intervention	Prophylactic antibiotics			
Comparison	Placebo or no treatment			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT antibiotics	WITH antibiotics		
	Difference: patients per 1000			
Exacerbations	588 per 1000	428 per 1000	RR 0.73 (0.59 to 0.90)	⊕⊕⊕○ ¹ Moderate
	Difference: 160 patients less per 1000 (Margin of error: 57 to 243 less)			
Hospitalizations	407 per 1000	400 per 1000	RR 0.98 (0.90 to 1.07)	⊕⊕⊕⊕ High
	Difference: 7 patients less per 1000 (Margin of error: 41 less to 30 more)			
Mortality	86 per 1000	76 per 1000	RR 0.89 (0.71 to 1.13)	⊕⊕⊕⊕ High
	Difference: 10 patients less per 1000 (Margin of error: 25 less to 11 more)			
Adverse effects	394 per 1000	374 per 1000	RR 0.95 (0.83 to 1.08)	⊕○○○ ^{2 3} Very low
	Difference: 20 patients less per 1000 (Margin of error: 67 less to 32 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 antibiotics** is based on the risk in the control group of the trials. The risk **WITH antibiotics** (and its margin of error) is calculated from relative effect (and its margin of error).

¹ We downgraded the certainty of the evidence in one level for inconsistency. Some studies showed effect and others did not; I²=75%.

² We downgraded the certainty of the evidence in two levels for indirectness, because the studies measured adverse effects in too different ways.

³ We downgraded the certainty of the evidence in two levels for publication bias, since the sample of studies synthesized correspond to a small sample of the studies on adverse effects of macrolides or quinolones.

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 patients with moderate to severe chronic obstructive pulmonary disease. It is reasonable to extrapolate to patients at an earlier stage, for whom the expected benefit should be lower or non-existent.

About the outcomes included in this summary

- The outcomes selected for the summary of findings are those considered critical for decision-making by the authors of this article.

Balance between benefits and risks, and certainty of the evidence

- While there is a benefit on exacerbations, this does not translate into changes in hospitalizations or mortality, at least in the average patient.
- Moreover, there is uncertainty about adverse effects, based on studies summarized here, but it is reasonable to expect these would arise. The associated costs should also be considered, and the effects on antibiotic resistance at the population level.
- However, it is possible that in patients with frequent exacerbations, the benefit might be greater than risks and costs of this intervention.

What would patients and their doctors think about this intervention

- It is likely that most patients will prefer not to take antibiotics regularly in order to avoid having to occasionally take them in case of an exacerbation that would not impact on hospitalizations or mortality.
- Clinicians would probably incorporate the population factor of antibiotic resistance to the decision, so they might not be inclined to support this intervention.
- Some patients or their clinicians might be in favor of this intervention in case of frequent exacerbations, a history of severe exacerbations, or other factors that can make them put high value on the small expected benefit.

Resource considerations

- The cost of the intervention is probably not a determining factor in the clinical decision.
- It is not possible to adequately estimate the cost/benefit of this intervention due to the uncertainty about the costs of adverse effects, at both individual and population level.

Differences between this summary and other sources

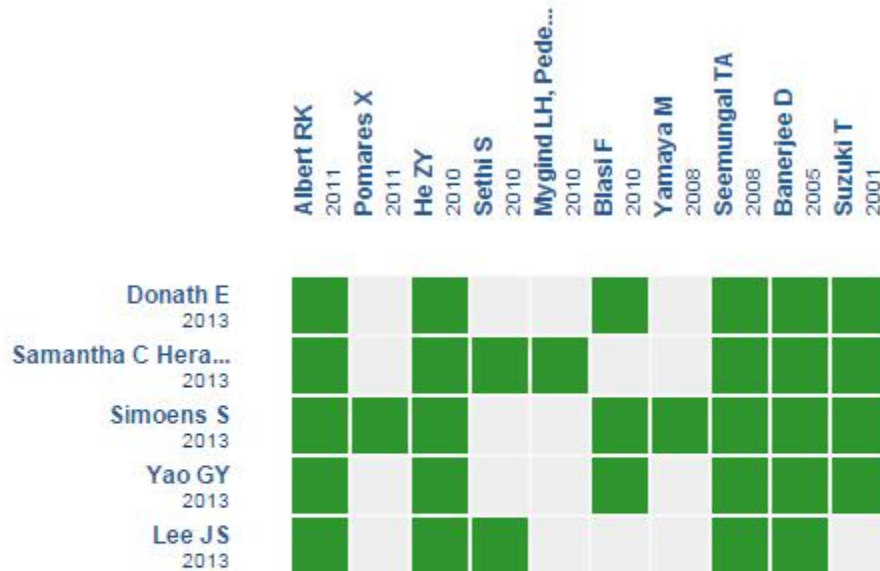
- Our summary is consistent with the systematic reviews identified.
- Our summary is in agreement with the main clinical guidelines, which differ slightly between them. The GOLD guideline states there is no role for prophylactic antibiotics, while the joint guideline of the American College of Chest Physicians and the Canadian Thoracic Society suggests their use in patients with moderate to severe disease who have a history of exacerbations in the past year despite optimal therapy [16],[17].

Could this evidence change in the future?

- The probability that future evidence change what we know about the benefits of prophylactic antibiotics in chronic obstructive pulmonary disease is very low, because of the certainty of the evidence.
- There is a high probability that future evidence give us better information about adverse effects, such as the ongoing Cochrane review that will synthesize the adverse effects of macrolides [18].

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**: [Prophylactic antibiotic therapy for chronic obstructive pulmonary disease](#)

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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