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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is a short-course antibiotic treatment effective for streptococcal tonsillopharyngitis in children?

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Abstract

Acute bacterial tonsillopharyngitis in children has been classically treated with long courses of antibiotic, usually 10 days, with the intention to prevent the occurrence of complications. However, it has not been clarified whether a shortened treatment could be equally effective in fulfilling that purpose. To answer this question, we searched in Epistemonikos database, which is maintained by screening multiple databases. We identified five systematic reviews including 59 randomized trials overall. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded that a shortened antibiotic regimen is probably similar, or with minimal differences, to a longer course, and might not make any difference regarding complications related to Streptococcus group A infection.

Problem

Traditionally, bacterial tonsillopharyngitis in children, mainly caused by *Streptococcus*, has been treated with long antibiotic courses (10 days) with the purpose of eradicating *Streptococcus* group A and consequently preventing its complications. However, it is unknown whether a shortened treatment can be equally effective to accomplish that same purpose, probably reducing costs, possible adverse effects and improving adherence to treatment.

Methods

We used Epistemonikos database, which is maintained by screening multiple 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

- A shortened antibiotic regimen is probably similar, or with minimal differences, to a longer course, and might not make any difference in the rate of complications related to Streptococcus group A infection.
- It is unclear whether a shortened antibiotic course reduces adverse effects because the certainty of the evidence is very low.
- Considering the evidence and other potential benefits of shortened antibiotic therapy, such as reduced costs and improved adherence, the benefit/risk analysis is in favor of intervention.

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] including 59 primary studies, reported in 54 references (some articles report more than one study) [6],[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],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59]. All of the studies correspond to randomized controlled trials. We excluded from the analysis those trials whose long course of antibiotics lasted less than 10 days [33],[58],[59]. We included trials that involved only pediatric patients, whose age was 18 years or less [6],[7],[8],[9],[10],[12],[13],[14],[15],[19],[21],[23],[24],[25],[30],[31],[32],[37],[41],[43],[44],[45],[46],[48],[49],[50],[52],[53],[56],[57], and trials that enrolled adults too, if they were analyzed independently [34]. That is, 36 randomized trials, reported in 31 references.
What types of patients were included	Patients who participated in the trials included in this review correspond in their entirety to pediatric patients (between six months and 18 years). All trials included only patients with clinically compatible symptoms and microbiological diagnosis of Streptococcusgroup A (by culture or rapid test). One trial also included Anti-streptolysin O antibodies (ASO) as a possible test for the microbiological certification of Streptococcusgroup A [34].
What types of interventions were included	All included trials compared the use of shortened antibiotic treatment (three to seven days) versus a standard 10-day antibiotic treatment. Only five trials [15],[24],[34],[37],[46] used the same antibiotic as standard and shortened treatment. One of these used cefaclor [15], one cefuroxime [24], one cefetamet [34], one cefpodoxime [37] and one penicillin V [46]. Nineteen trials used a macrolide as a shortened treatment; sixteen compared it to a beta-lactam [13],[14],[19],[23],[30],[31],[41],[43],[44],[48],[49],[50],[52] and three to a macrolide [32],[56],[57]. Sixteen trials used a beta-lactam as a shortened treatment; all were compared to a beta-lactam [6],[7],[8],[10],[12],[15],[21],[24],[25],[34],[37],[45],[46],[52],[53]. One trial compared the use of a macrolide or beta-lactam versus a standard penicillin treatment [9]. One trial allowed the use of analgesics as cointervention [15], two did not allow the use of concomitant analgesics [23],[34], and the rest did not report cointerventions. In all trials, except one [34], an early follow-up was conducted between days 0 to 15 once completed the antibiotic treatment. The majority [6],[7],[9],[10],[12],[13],[19],[21],[23],[25],[30],[31],[37],[41],[43],[44],[45],[52],[53],[56] also report having a late follow-up of variable duration with up to one year of follow-up after treatment.
What types of outcomes were measured	The identified systematic reviews grouped the outcomes as follows: 1. Duration of the symptomatology. 2. Clinical success, defined as cessation of symptomatology once completed the antibiotic therapy. 3. Early clinical failure, defined as the presence of fever and/or persistent pharyngeal pain within two weeks after completion of antibiotic treatment.

	4. Late clinical failure, defined as the presence of persistent fever and/or odynophagia two weeks after completion of antibiotic treatment. 5. Clinical cure, defined as cessation or significant attenuation of symptomatology at the end of therapy, associated with the eradication of group A Streptococcus. 6. Microbiological eradication of group A Streptococcus. 7. Suppurative and non-suppurative complications. 8. Adverse effects of the antibiotic therapy such as diarrhea, gastrointestinal discomfort, rash, fungal infections. 9. Dropout rate due to adverse effects. 10. Rate of compliance with antibiotic treatment. 11. Recurrence, defined as the growth of a strain other than group A Streptococcus after eradication at the end of antibiotic therapy. 12. Relapse, defined as the growth of the same strain of Streptococcus group A, after its microbiological eradication.

Summary of findings

Information on the effects of shortened treatment of bacterial tonsillopharyngitis in children is based on 36 randomized trials. All of the trials (15,869 patients) reported microbiological eradication; three trials (8,135 patients) complications of group A *Streptococcus* [9],[44],[45] and 21 trials [6],[7],[10],[12],[13],[19],[21],[23],[29],[30],[31],[37],[41],[43],[44],[45],[52],[53] (7,997 patients) measured the adverse effects of therapy. The summary of findings is as follows:

- A shortened antibiotic course probably results in little or no difference in the *Streptococcus* group A eradication rate for bacterial tonsillopharyngitis in children, compared to a longer course. The certainty of the evidence is moderate.
- A shortened antibiotic course might not make any difference in the complications related to *Streptococcus* group A infection, compared to a longer course. The certainty of the evidence is low.
- It is unclear whether a shortened antibiotic course reduces adverse effects because the certainty of the evidence is very low.

Shortened antibiotic course for tonsillopharyngitis in children				
Patients	Pediatric patients (6 months to 18 years) with group A streptococcal infection			
Intervention	Shortened antibiotic course (3 to 7 days)			
Comparison	Standard antibiotic treatment (10 days)			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH standard duration treatment	**WITH shortened duration treatment**		
	Difference: patients per 1000			
Eradication	846 per 1000	838 per 1000	RR 0.99 (0.95 to 1.03)	⊕⊕⊕◯ [1,2] Moderate
	Difference: 8 patients less per 1000 (Margin of error: 42 less to 25 more)			
Complications	3 per 1000	1 per 1000	RR 0.55 (0.17 to 1.81)	⊕⊕◯◯ [1,3] Low
	Difference: 2 patients less per 1000 (Margin of error: 2 less to 2 more)			
Adverse effects	46 per 1000	81 per 1000	RR 1.74 (1.31 to 2.32)	⊕◯◯◯ [1,4] Very low
	Difference: 35 patients more per 1000 (Margin of error: 14 to 61 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 **WITH standard duration treatment** is based on the risk in the control group of the trials. The risk **WITH shortened duration treatment** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded because the trials have risk of bias.
[2] Although a good part of the evidence is indirect (they do not compare the same type of antibiotic in the shortened and standard regime), the table presents the analysis of the five trials that used the same antibiotic both in the shortened and the standard duration course [15],[24],[34],[37],[46].
[3] The certainty of the evidence was reduced due to imprecision, since the confidence interval is wide.
[4] The certainty of the evidence was reduced in two levels due to the indirect nature of the information, because all trials reporting adverse effects compared different antibiotics in the standard and the shortened treatment.

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

- All the trials included in this summary addressed a pediatric population with the diagnosis of group A *Streptococcus* tonsillopharyngitis.
- This evidence does not apply to adults, nor to children with a different etiology of tonsillopharyngitis, nor other sort of infections caused by group A *Streptococcus*.

About the outcomes included in this summary

- The critical outcomes for decision-making were selected based on the opinion of the authors of this summary.

Balance between benefits and risks, and certainty of the evidence

- There would be no differences in the eradication rate of group A *Streptococcus* when using a shortened antibiotic course, and there might be no difference in the complication rate, although the certainty of the evidence about complications is low. It is important to emphasize that these were very rare in both groups.
- Considering the evidence and other potential benefits of shortened antibiotic therapy, such as reduced costs and improved adherence, the benefit/risk analysis is in favor of the intervention.

What would patients and their doctors think about this intervention

- The evidence presented in this summary should lead most patients and clinicians to lean in favor of shortened treatment.
- However, the existence of international recommendations in favor of a standard treatment could dissuade some clinicians.

Resource considerations

- Shortening the duration of antimicrobial treatment leads to lower costs for patients, so it is probably a cost-effective intervention.

Differences between this summary and other sources

- This summary is consistent with the findings of the identified systematic reviews.
- The conclusions of this summary disagree with some of the major international clinical guidelines on the treatment of tonsillopharyngitis in children [60],[61],[62], that still recommend a 10-day antibiotic regimen since there is no proof of the non-inferiority of a shortened antibiotic treatment in the prevention of complications of group A *Streptococcus*.

Could this evidence change in the future?

- The probability of future evidence changing the conclusions of this summary, about the effectiveness of a shortened antibiotic course compared to a 10-day treatment for tonsillopharyngitis in children, is low given the certainty of the evidence currently available.
- No additional ongoing trials evaluating this question were identified, so new relevant information is unlikely to appear in the short term.

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:** Short-course antibiotic treatment for tonsillopharyngitis

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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