

Living friendly summaries of the body of evidence using epistemonikos (FRISBEE)

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Is antibiotic prophylaxis beneficial in acute pancreatitis: first update

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Resumen

Este resumen Epistemonikos (Living FRISBEE: Living FRIendly Summary of the Body of Evidence using Epistemonikos) es una actualización del resumen publicado en Agosto de 2014, basado en dos nuevas revisiones sistemáticas aparecidas en Enero y Febrero de 2015. Existe controversia sobre los efectos del uso de antibióticos profilácticos en pacientes con pancreatitis aguda. Utilizando la base de datos Epistemonikos, la cual es mantenida mediante búsquedas en 30 bases de datos, identificamos 18 revisiones sistemáticas que en conjunto incluyen 19 estudios aleatorizados. Los combinamos mediante un metanálisis y generamos tablas de resumen de resultados utilizando el método GRADE. Concluimos que el uso de antibióticos profilácticos podría disminuir la mortalidad y el tiempo de hospitalización en pacientes con pancreatitis aguda, pero la certeza de la evidencia es baja. La probabilidad que la aparición de nueva evidencia cambie lo que sabemos es alta.

Abstract

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in August 2014, based on two systematic reviews appeared in January and February 2015. There is controversy about the effects of prophylactic antibiotics in acute pancreatitis. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified 18 systematic reviews including 19 randomised studies overall. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded that prophylactic antibiotics may reduce mortality and length of hospitalization in patients with acute pancreatitis, but the certainty of the evidence is low. The probability that future evidence change what we know is high.

About the update

The article updates the August 2014 Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) (doi: 10.5867/medwave.2014.07.6004) by including two new systematic reviews that appeared after publication of the original article [1],[2].

The new evidence incorporated in this summary does not lead to a modification on the certainty of the evidence, the key messages or other considerations for decision-making. Notwithstanding, it is important to mention that our summary (consistent with the new reviews) is discordant with the results of the majority of previous systematic reviews and guidelines.

Key messages

- Antibiotic prophylaxis may reduce mortality and length of hospitalization in patients with acute pancreatitis, especially if administered early.
- In spite of the large number of systematic reviews and studies, which may suggest the subject is exhausted, the correct statement is there is not enough evidence yet.
- The likelihood that new evidence might change what we know is high. Any recommendation formulated at this moment should be reviewed in the light of new evidence..

Problem

Most cases of acute pancreatitis are mild but some patients develop a severe form of this condition characterized by organ dysfunction and/or local complications, such as pancreatic necrosis.

The initial stage is characterized by complications derived from the inflammatory systemic response, and in the second stage infectious complications might ensue with associated morbidity and mortality. Antibiotic prophylaxis has been proposed as an alternative to avoid the latter, but its use is controversial since it is also associated with adverse effects and antibiotic resistance.

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.

About the body of evidence for this question

<p>What is the evidence. (See evidence matrix in Epistemonikos later).</p>	<p>We found 18 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18] including 19 randomized controlled trials reported in 20 articles,[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38] and two observational studies [39],[40].</p> <p>This table and the summary in general are based on the randomized studies.</p>
<p>What types of patients were included.</p>	<p>Most studies included patients with necrotizing pancreatitis [19],[29],[32],[35], severe pancreatitis [27],[33],[34],[38], any of these [24],[28],[31],[37], or severe necrotizing pancreatitis [22],[26],[30].</p> <p>One study included patients with alcoholic pancreatitis plus two or more collections [21] and three old studies included patients based only on clinical and biochemical criteria [20],[23],[25].</p>
<p>What types of interventions were included.</p>	<p>All studies except one [27] used intravenous antibiotics.</p> <p>Two studies used ampicillin [20],[23], one ampicillin or lincomycin [25], six imipenem [19],[28],[29],[30],[37],[38], two meropenem [22],[36], one ciprofloxacin [24] and three used a combination of ciprofloxacin and metronidazole [26],[34],[35].</p> <p>Five studies allowed different antibiotic options [21],[22],[27],[31],[32].</p>
<p>What types of outcomes were measured.</p>	<p>All studies measured mortality, but only three reported length of hospitalization. Other outcomes reported were pancreatic or peripancreatic infection, fungal infection, surgical intervention need, non-pancreatic infection, sepsis.</p>

Summary of findings

This information is based on 19 studies including 1178 patients. All studies evaluated mortality but only three (153 patients) measured length of hospitalization.

- Antibiotic prophylaxis may reduce mortality and length of hospitalization in patients with acute pancreatitis, but the certainty of the evidence is low.

Antibiotic prophylaxis versus placebo in acute pancreatitis				
Patients	Acute pancreatitis			
Intervention	Antibiotics			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT antibiotics	WITH antibiotics		
	Difference: patients per 1000			
Mortality	133 per 1000	103 per 1000	RR 0.78 (0.58 to 1.06)	⊕⊕○○ ^{1,2} Low
	Difference: 29 patients less per 1000 (Margin of error: 56 less to 8 more)			
Length of hospitalization	19.7 days	14.1 days	MD -5.64 (-11.01 to -0.27)	⊕⊕○○ ^{1,2} Low
	Length of hospitalization was 5.64 days less (Margin of error: 11 days to 6 hours less)			
RR: Risk ratio MD: Mean difference Margin of error = 95% confidence interval. GRADE: evidence grades of the GRADE Working Group (see later in this article) * The risk in the group 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 There is important imprecision. The decision might vary substantially if the boundaries of the confidence interval are considered. Sample size well below <i>optimal information size</i> . ² There is important risk of bias in many studies. Matrix of evidence: Prophylactic antibiotics vs placebo for acute pancreatitis				

Other considerations for decision-making

To whom this evidence does and does not apply

- Most studies included patients with severe acute pancreatitis, based on radiological or clinical criteria. There is little direct evidence for less severe patients, but it is unlikely that a relevant clinical benefit exists in this group.
 - Most studies do not make distinction based on cause of pancreatitis, so this evidence is applicable to any etiology.
 - One review [2] presents an analysis of studies in which prophylaxis was administered early (first 72 hours after beginning of symptoms, or first 48 hours of hospitalization) concluding there is a larger and more certain benefit in this subgroup (relative risk for mortality 0.52 [95% confidence interval 0.29 to 0.95]; moderate certainty of the evidence). Unfortunately, the approach proposed by these researchers does not allow to clarify if it is a credible effect or not, since the whole group is needed in order to test this hypothesis.
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About the outcomes included in this summary

- This summary synthesizes the effects on mortality and length of hospitalization, which were considered as critical outcomes for decision-making by the authors of this article.
 - Other outcomes might be needed to make decisions in individual cases, but without more certainty about the direction and magnitude of the effect on mortality and length of hospitalization, it is unlikely that they would change the decisions.
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Balance between benefits and risks, and certainty of the evidence

- The certainty of the evidence is low, so it is difficult to estimate the balance between benefits and risks, which will probably change with new information.
 - The risks and costs of antibiotic prophylaxis are well known, and they affect both the individual and the population.
 - If there were a clinically relevant benefit in mortality, the balance would be inclined in favour of the intervention. If the benefit were only observed on length of hospitalization or other outcomes, the balance would not be as clear.
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Resource considerations

- The direct cost of prophylactic antibiotics and the indirect cost derived from their excessive use are high, especially in critical care units.
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Differences between this summary and other sources

- The number of systematic reviews that have addressed this question is particularly large. This reflects the relevance of the question but also the existing uncertainty that arises from the body of primary studies, which have risk of bias and imprecision.
 - Even though no systematic review includes all of the studies identified in the matrix of evidence, the estimates of the more recent systematic reviews are similar to ours (in effect, relative risk 0.74 for mortality [95% confidence interval 0.50 to 1.07] in the more complete review [18]). The interpretation provided by most reviews is that there is "no effect". However, despite the large volume of systematic reviews and studies, which might suggest that the question is exhausted, the correct statement is "there is not enough evidence".
 - One of the more recent reviews [1] presents an analysis that includes two observational studies in the meta-analysis [39],[40]. The inclusion of evidence coming from observational studies when there is a substantial body of evidence originating from randomized trials is inadvisable, as is pooling their results. The authors of this new review approach this problem by presenting a separate analysis by design. Unfortunately, it is confusing instead of clarifying.
 - The main guidelines incorporate a relatively low proportion of the existing evidence and their recommendations slightly vary [41],[42],[43]. For instance, the American Gastroenterology Association states it is not possible to make a recommendation (and it
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might be used in some cases) [42] and the American College of Gastroenterology makes a strong recommendation against the use of prophylactic antibiotics [41].

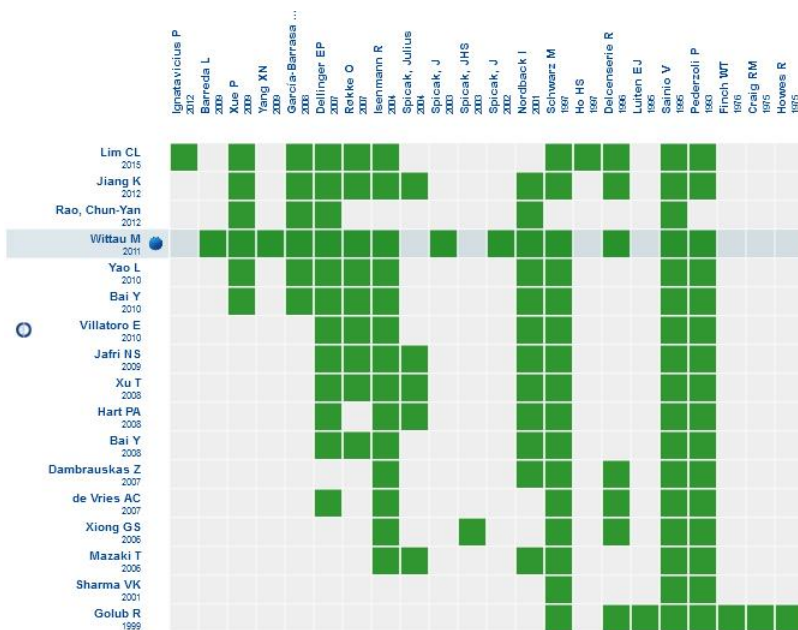
- It is important to bear in mind that GRADE makes a distinction between the certainty of the evidence for guidelines and systematic reviews. For the former it refers to the confidence in the estimates of effect, for the latter refers to the level of confidence on the estimate in order to support a particular decision [44].

Could this evidence change in the future?

- The probability of new evidence changing what we know is high. Any recommendation formulated at this moment should be reviewed in the light of new evidence.
- We are not aware of ongoing studies answering 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..



Comenzando desde cualquier revisión sistemática, Epistemonikos construye una matriz basada en las conexiones existentes en la base de datos (la revisión desde la cual se construyó la matriz aparece resaltada). El autor de la matriz puede seleccionar la información pertinente para una pregunta específica de salud (típicamente en formato PICO) de manera de desplegar el conjunto de información para esa pregunta. Las filas representan las revisiones sistemáticas que comparten al menos un estudio primario, y las columnas muestran los estudios. Los recuadros en verde corresponden a estudios incluidos en las respectivas revisiones.

Follow the link to access the interactive version: [Prophylactic antibiotics vs placebo for acute pancreatitis](http://dx.doi.org/10.5867/medwave.2014.06.5997).

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.

Potential conflicts of interest

The authors do not have relevant interests to declare.

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