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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is there a role for glutamine supplementation in the management of acute pancreatitis?

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Abstract

There is no consensus about the effects of glutamine supplementation for acute pancreatitis. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified 15 systematic reviews including 31 randomized controlled trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded glutamine supplementation might decrease infectious complications in acute pancreatitis, but it is not clear if it affects mortality or length of hospital stay because the certainty of the evidence is very low.

Problem

Glutamine is an amino acid required for nucleotide synthesis, which makes it an important energetic substrate for cells with fast turnover, such as intestinal epithelium.

Given plasmatic glutamine is reduced in critical care patients and in those undergoing major surgery, it is considered an essential amino acid under stress.

Acute pancreatitis constitutes a potentially severe condition, in which these mechanisms are particularly relevant. So, a potentially beneficial effect of glutamine supplementation has been proposed. However, it is not clear if it leads to clinically relevant effects.

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
- Glutamine might decrease infectious complications in acute pancreatitis, but it is not clear whether it decreases mortality and length of hospital stay because the certainty of the evidence is very low.
- The conclusions of this summary disagree with many existing systematic reviews, and the main guidelines have not considered this question.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 15 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15] including 31 randomized controlled trials reported in 32 references [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] (one study is reported in two references [30],[31]).
What types of patients were included	The different trials included patients with severe acute pancreatitis classified according to the following criteria: Glasgow in two trials [17],[21], APACHE II in eight trials[19],[20],[25],[28],[29],[30],[38],[42],[46], RANSON in six trials [19],[24],[32],[38],[46],[47], severity index according to imagenologic criteria in four [19],[28],[38], [46], ATLANTA criteria in two [26] y [27], in one trial it was not reported what criteria was used [36].Four trials used a combination of the criteria above [19],[28],[38],[46]. It was not possible to extract the information about the severity criteria used in 13 trials from any systematic review identified.
What types of interventions were included	Eight trials evaluated glutamine supplementation associated to parenteral nutrition [17],[18],[19],[20],[25], [28],[32],[37], and 10 to enteral nutrition [21],[22],[23], [24],[26],[27],[29],[30],[34],[38]. Sixteen trials used glutamine alone [17],[18],[19],[20],[21],[25],[28],[32],[36],[37],[38],[39],[42],[45],[46],[47] and eight glutamine associated to other elements [22],[23],[24],[26],[27],[29],[30],[34]: six with arginine [22],[23],[24],[26],[29],[30], one with con tributyrin and antioxidants [29], two with fiber [22],[23], one with omega-3 [30],[31] and one with Bifidobacterium, Lactobacillus and Enterococcus [34]. It was not possible to extract the information about the glutamine supplementation used in eight trials from any systematic review identified. All of the studies compared against placebo or standard treatment.
What types of outcomes were measured	The main outcomes meta-analysed in the different reviews were: - Mortality (pooled in 13 systematic reviews). - Infectious complications (pooled in 12 systematic reviews). - Length of hospital stay (pooled in 11 systematic reviews). Other outcomes analysed in the different review were: plasma albumin level, plasma C-reactive protein level, surgical intervention rate, time until amylase returned to normal, hospitalization expenses, organ failure, length of intensive care unit stay, days on mechanical ventilation, feeding intolerance, systemic inflammatory response syndrome, change in white blood cells count, ventilator-associated pneumonia, abdominal pain, serious adverse events, side effects (ALT, AST, creatinine), serum amylase in patients undergoing ERCP (after 8 and 24 hours), pancreatitis in patients undergoing ERCP. The following subgroups were analysed in the different reviews: - Effect of high/low doses (more or less than 4.2 g/kg) on mortality in critical and surgical patients - Parenteral versus enteral glutamine.

Summary of findings

Information on the effects of glutamine for acute pancreatitis is based on 22 randomized controlled trials involving 1107 participants (nine trials did not provide data for meta-analysis). All of the trials reported mortality [16],[17],[18],[19],[20],[21],[22],[24],[25],[26],[27],[28],[29],[30],[32],[34],[35],[36],[38],[39],[41],[43], 20 trials (1063 participants) reported the outcome infectious complications [16],[17],[18],[19],[21],[22],[24],[25],[26],[27],[28],[29],[30],[32],[35],[36],[39],[41],[43],[45] and 18 trials (1018 participants) reported the outcome length of hospital stay [16],[18],[19],[21],[26],[27],[28],[29],[30],[32],[34],[35],[36],[38],[39],[41],[42],[43],[44].

The summary of findings is the following:

- It is not clear whether glutamine supplementation decreases mortality because the certainty of the evidence is very low.
- Glutamine supplementation might decrease infectious complications in acute pancreatitis. The certainty of the evidence is low.
- It is not clear whether glutamine supplementation decreases length of hospital stay because the certainty of the evidence is very low.

Glutamine supplementation for acute pancreatitis

Patients acute pancreatitis
Intervention glutamine supplementation
Comparison Placebo or standard treatment

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT GLUTAMINE	**WITH GLUTAMINE**		
	Difference: patients per 1000			
Mortality	129 per 1000	86 per 1000	RR 0.67 (0.47 to 0.97)	⨁◯◯◯[1 2 3] Very low
	Difference: 43 patients less per 1000 (Margin of error: 4 to 69 less)			
Infectious complications	293 per 1000	196 per 1000	RR 0.67 (0.55 to 0.82)	⨁⨁◯◯[1 3] Low
	Difference: 97 patients less per 1000 (Margin of error: 53 to 132 less)			
Length of hospital stay	16 days**	14.09 days	--	⨁◯◯◯[3 4] Very low
	Difference (MD): 1.91 days less (0.49 to 3.33 less)			

RR= Risk ratio.
MD= Mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT GLUTAMINE** is based on the risk in the control group of the trials. The risk **WITH GLUTAMINE** (and its margin of error) is calculated from relative effect (and its margin of error)
**Approximated mean based on representative trials [21],[38],[41].

[1] We downgraded the certainty of the evidence in two levels for mortality and length of hospital stay, and in one level for infectious complications because many studies had risk of bias. In the case of mortality, the two trials providing more information (50% weight in the meta-analysis) did not show benefit.
[2] We downgraded the certainty of the evidence in one level because of imprecision, since the confidence interval included the possibility of a small benefit.
[3] We downgraded the certainty of the evidence for publication bias, according to a highly indicative funnel plot in the mortality meta-analysis, which included the larger proportion of usable trials.
[4] We downgraded the certainty of the evidence in two levels because of inconsistency (I^2=75%).

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 in this summary applies to patients with severe acute pancreatitis, by any definition. Even though glutamine has been evaluated in a wide range of critical care patients, this summary only addresses the effect on acute pancreatitis, and does not apply to critical care patients with other conditions.

About the outcomes included in this summary

- The outcomes selected for the summary of findings table (mortality, infectious complications and length of hospital stay) were considered as critical for decision-making by the authors of this article. They coincide with the outcomes addressed in most systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

- The certainty of the evidence is low or very low, so any estimation of benefit-risk is unreliable. If observed benefit were true, it would be an intervention with a favorable benefit-risk ratio for severe acute pancreatitis patients.
- Even though there might be adverse effects in selected patients (e.g. hepatic encephalopathy), these are minimal, so this factor is not relevant for decision-making.

What would patients and their doctors think about this intervention

- It is an intervention of uncertain benefit, but without relevant adverse effects. Clinicians putting more value on the unproven benefit might be inclined to use it, especially in a context without resources constraints.
- Some clinicians might be disinclined to use this intervention since the main guidelines do not provide a recommendation for this question.

Resource considerations

- It is an intervention that might increase costs, especially associated to a formula. It is not possible to provide an adequate cost-benefit balance given the uncertainty of the evidence. If we consider a possible benefit on infectious complications, but not on mortality or length of hospital stay, it would be a situation where the balance between benefit and cost is highly dependent on the direct cost of glutamine in the specific context.

Differences between this summary and other sources

- There is a large number of systematic reviews addressing this question, which denotes the interest and lack of clarity on the topic, mainly because limitations of primary studies.
- The conclusion of this summary disagrees with some of the main reviews. For instance, the systematic review including more pertinent primary studies [1], shows a clear benefit on mortality

and infectious complications, without paying much attention to limitations on the certainty of the evidence.

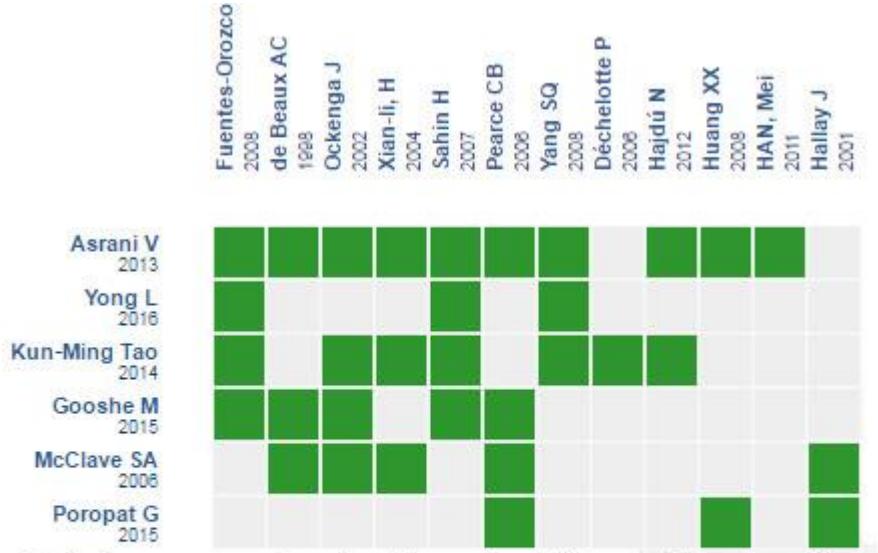
- On the other hand, this summary agrees with a recent Cochrane review [10] regarding the limitations on the certainty of the evidence. However, this review only included a low proportion of the studies identified in this summary (6 of 31).
- The main guidelines, such as those of the American Gastroenterology Association, the American College of Gastroenterology, and the joint guideline of the International Association of Pancreatology and the American Pancreatic Association do not address glutamine supplementation as part of their recommendations [48],[49],[50],[51].

Could this evidence change in the future?

- The probability of future evidence changing what we know is high, considering the poor certainty of the evidence.
- According to the WHO International Clinical Trials Registry Platform there are at least two unpublished trials. They might provide relevant information [52],[53].
- None of the reviews identified included an important proportion of the trials identified by this summary. A new systematic review including more studies could shed light on the topic too.

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:** [Glutamine supplementation for acute pancreatitis]

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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