MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2016;16(Suppl 2):36463 doi: 10.5867/medwave.2016.6463

Is preemptive antifungal strategy a good alternative to empirical treatment in prolonged febrile neutropenia?

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Citation: Koch E, Rada G. Is preemptive antifungal therapy a good alternative to empirical treatment in prolonged febrile neutropenia?. *Medwave* 2016;16(Suppl 2):36463 doi: 10.5867/medwave.2016.6463
Publication date: 9/6/2016

Abstract

Patients with prolonged febrile neutropenia are at high risk of invasive fungal infection, so it has been standard practice to initiate empirical antifungal therapy in these cases. However, this strategy is associated with important toxicity, so diagnostic test-guided preemptive antifungal therapy has been proposed as an alternative. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified three systematic reviews including twelve studies overall. Four randomized controlled trials addressed the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded it is not clear whether preemptive strategy affects mortality because the certainty of the evidence is very low, but it might slightly decrease the use of antifungal agents in patients with prolonged febrile neutropenia.

Problem

During chemotherapy-induced neutropenia fever occurs frequently but clinical infection is documented in only 20-30% of febrile episodes [1]. Invasive fungal infections usually appear after the first week of prolonged neutropenia and empirical antibiotic therapy, and constitute an important cause of morbidity and mortality [2]. It has been standard practice to initiate empirical therapy for fungal infections in patients with prolonged febrile neutropenia, and this approach has been incorporated into several guidelines. Approximately 40–50% of patients are treated with antifungals using this empirical approach, whereas the estimated actual incidence of invasive fungal infection is around 10–15% [3]. As a result, many patients are potentially exposed to unnecessary toxic treatment and considerable financial burden. Diagnostic test-guided preemptive antifungal therapy, that is antifungal treatment instituted if indicators of possible invasive fungal are identified, has been proposed as an alternative treatment strategy in these patients.

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

- It is not clear whether preemptive strategy affects mortality because the certainty of the evidence is very low, but it might slightly decrease the use of antifungal agents in patients with prolonged febrile neutropenia.
- It is not possible to conduct an adequate balance between benefits and risks and costs, given the high level of uncertainty associated to the existing evidence.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified three systematic reviews [4],[5],[6]including twelve primary studies [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18] from which five correspond to randomized controlled trials [9],[10],[13],[15],[18]. One of the trials was excluded from this summary since it does not compare against empirical strategy [9]. This table and the summary in general are based on the four pertinent randomized controlled trials [10],[13],[15],[18].
What types of patients were included	Two studies included only adults [10],[15], one study included both adults and children [18] and one study did not report the age of the patients [13]. All studies included only patients with hematological malignancies. One study included only patients who received allogenic stem cell transplant [13], and the other three included patients undergoing chemotherapy or allogenic stem cell transplant [10],[15],[18].
What types of interventions were included	All studies used different criteria for starting antifungal therapy in the preemptive strategy, and different tests for early diagnosis of invasive fungal disease. Three studies used galactomannan test twice a week [10],[15],[18]; one study used nested PCR for *Aspergillus*[15] and one study non-nested PCR for *Aspergillus* and *Candida* [13]; only one study performed blood cultures[13]. All studies used imaging as diagnostic test; two studies performed chest computed tomography if serological tests were positive [15],[18], one study performed chest and abdomen computed tomography to all patients [13], and one study performed chest radiography followed by chest computed tomography[10].
What types of outcomes were measured	Different systematic reviews reported meta-analysis for the following outcomes: • Incidence of invasive fungal infection • Invasive fungal disease-related mortality • Overall mortality • Antifungal therapy use

Summary of findings

Information on the effects of preemptive strategy is based on four randomized controlled studies involving 988 patients [10],[13],[15],[18]. All of them provided information on the use of antifungal therapy, and three studies provided information on all-cause mortality [10],[13],[15]. The summary of findings is the following:

- It is not clear whether preemptive strategy affects mortality because the certainty of the evidence is very low.
- Preemptive strategy might slightly decrease the use of antifungal agents in patients with prolonged febrile neutropenia.

Preemptive therapy for prolonged febrile neutropenia

Patients Prolonged febrile neutropenia (more than or equal to three to five days)
Intervention Preemptive antifungal strategy
Comparison Empirical antifungal therapy

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH empirical antifungal therapy	**WITH preemptive antifungal strategy**		
	Difference: patients per 1000			
All-cause mortality	105 per 1000	116 per 1000	RR 1.11 (0.77 to 1.62)	⨁◯◯◯[1,2,3] Very low
	Difference: 11 patients more per 1000 (Margin of error: 24 less to 65 more)			
Use of antifungal agents	433 per 1000	402 per 1000	RR 0.93 (0.81 to 1.08)	⨁⨁◯◯[1,2,3] Low
	Difference: 31 patients less per 1000 (Margin of error: 82 less to 35 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 empirical antifungal therapy** is based on the risk in the control group of the trials. The risk **WITH preemptive antifungal strategy** (and its margin of error) is calculated from relative effect (and its margin of error)

1 The certainty of the evidence was downgraded in one level because of risk of bias, since most studies have high risk of bias (e.g. lack of blinding), including those with more weight in the meta-analysis.
2 The certainty of the evidence was downgraded in one level because of indirectness, since the empiric strategy is initiated earlier than in current practice. On the other hand, there is important variability on the tests that are part of the preemptive strategy.
3 The certainty of the evidence was downgraded in one level because of imprecision. The confidence interval considers both the possibility of a clinically important benefit on mortality and an increase in the risk of dying. We did not downgrade the certainty of the evidence for the outcome 'use of antifungal agents' because the confidence interval is narrow, even though the no-effect line is crossed.

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 included in this summary is applicable to patients with hematological malignancies undergoing stem cell transplant or chemotherapy, presenting febrile neutropenia and remaining febrile despite empirical antibiotic treatment.

About the outcomes included in this summary

- All-cause mortality and use of antifungal therapy were selected as critical outcomes for decision-making by the authors of this summary.
- We did not include the outcome invasive fungal infection because it was considered less important than the selected outcomes when choosing a treatment over the other, and also because of the susceptibility to risk of bias derived from lack of blinding.

Balance between benefits and risks, and certainty of the evidence

- Because of the high level of uncertainty it is not possible to assess risk/benefit properly.
- Preemptive strategy might decrease antifungal therapy use, and also the potential associated adverse effects. However this information must be taken with caution for decision-making because of the very low certainty of the evidence about mortality.

What would patients and their doctors think about this intervention

- Physicians and patients who prefer to avoid the risk of adverse effects above the uncertain benefit of the empirical therapy, will probably choose the preemptive strategy.
- It is particularly important to inform the patient about the uncertainty associated with this decision.

Resource considerations

- Because of the high uncertainty it is not possible to assess cost/benefit properly.
- Preemptive strategy costs vary depending on the tests selected for invasive fungal infection diagnosis. The costs of empirical therapy also vary depending on the antifungal agent selected.
- Even if the existing evidence about the effects were more certain it would be desirable to formally assess cost-efectiveness. The characteristics of this type of decision will be different depending on where it is implemented.

Differences between this summary and other sources

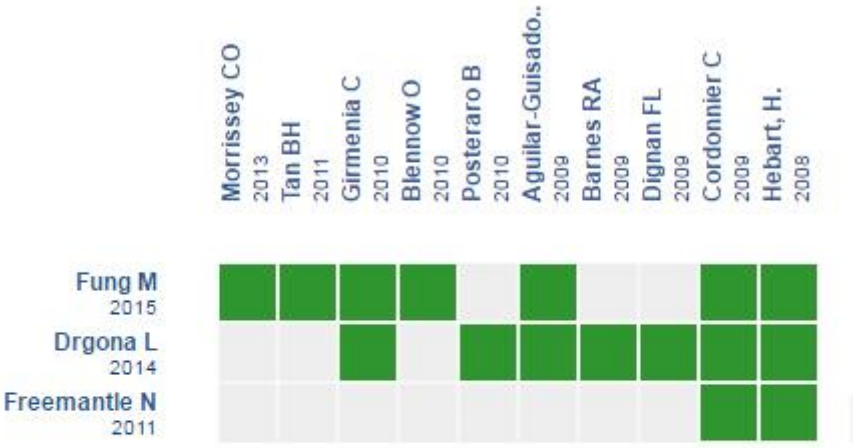
- The conclusions of our summary partially agree with the systematic reviews identified. The more recent and complete review [6] concludes preemptive antifungal strategy is a reasonable alternative to empirical treatment in terms of outcomes and costs. However, our summary puts more emphasis on the associated uncertainty of the existing evidence.
- Our summary agrees with the guideline of the Infectious Diseases Society of America [1] which considers preemptive antifungal strategy as an acceptable alternative to empirical treatment in clinically stable neutropenic patients that still have fever after four to seven days of broad-spectrum antibiotics, and have no evidence of fungal infection (serological tests, chest and paranasal computed tomography without fungal infection, and absence of fungal agents such as*Candida* or *Aspergillus* on cultures). They suggest starting antifungal agents if any of the tests is positive. Most of the evidence identified in this summary was not available in 2010 when the guideline was published.

Could this evidence change in the future?

- The probability that future studies would change the conclusions of this summary is high, considering the uncertainty of the existing evidence.
- There are no new or ongoing trials answering this question, based on a search of trials published after the search date of the more recent review identified, and a search in the the International Controlled Trials Registry Platform of World Health Organization. One of the included studies is still open, so new data might emerge [19].

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:** Preemptive antifungal strategies in febrile neutropenia

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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