ARTICLE CITATION:


ABSTRACT:

In cirrhotic patients with gastrointestinal bleeding, antibiotic prophylaxis decreases the incidence of infections but most randomized trials have not shown an increase in survival. The aim of this meta-analysis was to assess the efficacy of antibiotic prophylaxis in the prevention of infections and its effect on survival rate in cirrhotic patients with gastrointestinal bleeding. Four end points were assessed: infection, bacteremia and/or spontaneous bacterial peritonitis (SBP), incidence of SBP, and death. For each end point, heterogeneity and treatment efficacy were assessed by Der Simonian and Peto methods. Five trials including 534 patients, 264 treated with antibiotic prophylaxis for 4 to 10 days and 270 without, were identified. Mean follow-up was 12 days. Antibiotic prophylaxis significantly increased the mean percentage of patients free of infection (32% mean improvement rate, 95% confidence interval [CI]: 22-42, P <.001), bacteremia and/or SBP (19% mean improvement rate, 95% CI: 11-26, P <.001), and SBP (7% mean improvement rate, 95% CI: 2.1-12.6, P =.006). Antibiotic prophylaxis also significantly increased the mean survival rate (9.1% mean improvement rate, 95 % CI: 2.9-15.3, P =.004), without significant heterogeneity. In cirrhotic patients with gastrointestinal bleeding, short-term antibiotic prophylaxis significantly increases the mean percentage of patients free of infection and significantly increases short-term survival rate.

DISCUSSION:

Based on the results of this meta-analysis, along with consideration of additional review articles (NEJM 2010; 362: 823-32) prophylactic antibiotic therapy in acute variceal hemorrhage appears to be useful. This study demonstrates a clear survival benefit in this high mortality population and there is little additional risk.

ANALYSIS: Presented by Jack Nicolet, MD.

Synopsis: What topic did the integrative review address?

The aim of this meta-analysis is to assess the efficacy of antibiotic prophylaxis in the prevention of infections and its effect on survival rate in cirrhotic patients with gastrointestinal bleeding.
How were the potential, relevant research efforts identified?

Predetermined protocol based on recommendations of Sacks et al in NEJM (1987). MEDLINE and manual search of RCTs in English, French, German and Spanish. General reviews, references of published RCTs, letters to pharmaceutical companies, and Current Contents were used.

What determined if a research report was included in the analysis or not?

Selection criteria: RCT must have been published as an abstract or article, be randomized and prospective, include patients with cirrhosis and GI bleeding, and assess the efficacy of antibiotic prophylaxis in the prevention of bacterial infection.

Exclusion criteria: any RCT comparing two treatments, or RCTs including patient without bleeding were excluded.

How many studies were included in the analysis?

Five RCTs were included (532 patients)

What research methods were used in the studies included in the analysis?

RCT

What were the important and consistent findings?

Four end points were assessed, all of which showed an improvement in outcome measures when prophylactic antibiotics were administered as compared to controls:

- **Infection** (increased mean percentage of patients free of infection) - 32% mean improvement rate, 95% CI: 22-42, p<.001
- **Bacteremia and/or SBP** – 19% mean improvement rate, 95% CI: 11-26, p<.001
- **Incidence of SBP** – 7% mean improvement rate, 95% CI: 2.1-12.6, p<.006
- **Death** (increased survival rate) – 9.1% mean improvement rate, 95% CI: 2.9-15.3, p<.004

What were the analysts’ conclusions?

Antibiotic prophylaxis for 7 days should be systematically used in cirrhotic patients with gastrointestinal bleeding after bacteriological samples have been performed.
Credibility Profile:
Was the topic clearly defined and clinically meaningful?

The purpose of this review was clearly defined and the study groups were clearly defined. The topic is clinically important given that the mortality rate after bleeding in patients with cirrhosis is close to 30% after 3 weeks.

Was the search for potential reports broad and unbiased?

The search strategy was well-described and broad-reaching. While reasons for trial inclusion and exclusion were included in the meta-analysis, no discussion was provided on the handling of disagreement resolution by the two authors who independently reviewed and analyzed the studies. Therefore, search bias cannot be fully evaluated here. Of note, the authors state that this meta-analysis was not supported by any pharmaceutical company, government agency or other grants.

Were the characteristics of the studies displayed or discussed in sufficient detail?

Tables 1-4 and figures 1-4 present the salient details (study design, patient characteristics, results, and methodological quality) of each study included in this meta-analysis. Little discussion was provided for each individual study unless the authors concluded that unique and notable differences in methodology, inclusion/exclusion criteria or adverse events were important.

Is there truly an integration/synthesis of findings or merely a reporting of separate findings?

Study findings were integrated and synthesized. The following methods were used to assess combinability: comparison of each end-point improvement in control groups by the chi-squared test and heterogeneity tests by the Peto method and by the Der Simonian and Laird method. Quantification of the size of the difference observed between 2 groups (antibiotics vs controls) performed using the odds ratio with 95% CI and p-values reported. Sensitivity analyses using the Peto and the Der Simonian and Laird methods were used to address differences in heterogeneity (between groups within studies and between studies overall) as well as differences in antibiotics given across the range of studies.

Do the overall findings accurately reflect the findings from all the individual studies?

Overall, there is concordance between the overall findings of the meta-analysis and the individual studies. However, there were some inconsistencies worth noting, which are likely due to the way the individual trials reported their results. Following are details by outcome measure:
Percentage of patients free of infection
Percentage of patients free of SBP and/or bacteremia
Survival rate
All five RCTs provided data to address these end points. Given the range of antibiotic treatment plans and differing exclusion criteria identified across the studies, separate sensitivity meta-analyses were performed with- and without- the independent variables. The analysis showed retained statistical significance despite these differences.

Percentage of patients free of SBP
Only three of the five RCTs provided discreet data to address this end point.

What overall findings were consistently well-supported and which were less well-supported?
See above

What, if anything, could explain differences in results from study to study?
See above

ARE THE CONCLUSIONS OF THE INTEGRATION CREDIBLE?
YES

Clinical Significance:
Do the conclusions resonate with what I see in everyday practice?

While this entity is not seen everyday, it is certainly within the scope of general emergency medicine and something that most clinicians can expect to see at some point in their career.

Are the majority of findings sizable enough, consistent enough, and well enough supported that the conclusions are likely to hold up in everyday practice?

The findings are consistent and well-supported in this meta-analysis. The clinical importance of decreased infection rates - and certainly increased survival rates - is obvious. This is especially true considering the fragile health conditions of those with such debilitating chronic disease such as cirrhosis. As the authors note, “the greater the risk of infection, the greater the benefit from a decrease (in) infection.”

Applicability Profile:

Are my patients similar to any of those studied? Are they similar to those in a particular study? Was there anything of note in the results for samples or sub-samples that are most like my patients?
Given the fact that the ED is the portal of entry into the realm of definitive care for most, it is reasonable to say that our patient population includes those studies in this analysis.

**Are the outcomes achieved of value to me or my patients?**

The outcomes measured here (infection, bacteremia and/or SBP, incidence of SBP and death) are all important to patients, families and clinicians.

**What were the key features of the approach or intervention?**

Administration of prophylactic antibiotic therapy to patients with cirrhosis who present with bleeding esophageal varices.

**Am I able to safely and effectively use the approach or intervention described?**

Given the relative safety and benign side effect profile of antibiotic therapy, routine use of antibiotic therapy in cirrhotic patients with bleeding esophageal varices is reasonable and prudent, based on the results of this analysis.

**Are the findings and conclusions impressive enough to warrant trying them in any practice?**

Yes.

**Are there organizational, logistical, cost or time barriers to incorporating this approach into my practice? Could they be overcome?**

See below

**What changes, additions, training, or purchases would be needed to start using this approach?**

To create a clinical guideline for use in the ED, a more thorough evaluation of the individual studies is needed. The benefit of prophylactic antibiotics is clearly demonstrated here. However, determining the appropriate antibiotic(s) for use in the ED as well as dose, route of administration and duration of therapy is not addressed in this analysis.

**SHOULD I CONSIDER CHANGING MY PRACTICE BASED ON THESE FINDINGS?**

YES