Reviewer's report

Title: Risk factor for mortality in patients with Pseudomonas aeruginosa bacteremia; Impact of combination antimicrobial therapy

Version: 1 Date: 18 October 2013

Reviewer: Mical Paul

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Major Compulsory Revisions

General

In general studies examining combination vs. monotherapy in P. aeruginosa bacteremia are helpful, despite the existence of many previous, including recent studies, as they add to the accumulating knowledge. However, the contribution of studies examining “any” combination vs. “any” monotherapy is questionable. What hypothesis underlies such a comparison? Synergy exists for beta-lactam aminoglycoside combinations – and this is the analysis of interest. The comparison should be probably restricted to beta-lactams or quinolones but not any monotherapy.

The English language should be improved throughout the manuscript.

Abstract

The methods section of the abstract should be expanded to reflect more the complete methods of the study (years, location, inclusion criteria, statistical methods etc.)

Introduction

P. aeruginosa is considered the most predominant bacteremia-causing gram-negative bacillus – I don’t know what you mean by predominant, but P. aeruginosa is not the most common gram-negative bacillus causing pneumonia

Methods

14-day in-hospital mortality is the outcome examined in the study. Better to examine all deaths within 14 days if data are available.

Appropriate/ adequate empirical antibiotic treatment should be defined

In the definition of combination treatment the authors include that the combination was started with 24h of blood culture taking. Was this true also in the analysis for targeted treatment?

Survival analysis is not helpful – see below.
Results

A description of the antibiotics included in combination and monotherapy groups should be provided, preferably in a supplementary table. The hypothesis underlying the advantage of benefit for combination therapy is based on in-vitro studies showing synergy between beta-lactams and aminoglycosides. If most of the combinations in this analysis consist of colistin + aminoglycoside or most of the monotherapies of colistin or aminoglycoside alone, for example, I don’t know what the value of this analysis is. Preferably specific combination therapies should be compared to specific monotherapies, but the sample size of this study will probably not permit such an analysis. At least monotherapy regimens of aminoglycoside alone or colistin alone should be excluded in a sensitivity analysis since both have been associated with increased mortality (Leibovici et al. Antimicrob Agents Chemother. 1997 May;41(5):1127-33 and Paul et al. J Antimicrob Chemother. 2010 May;65(5):1019-27)

A factor of appropriate/ inappropriate empirical antibiotic treatment of any type (monotherapy or combination therapy) should be examined separately from the comparisons of monotherapy vs. combination therapy) and this factor, if significant should be entered into the multivariable anlaysis.

Both supplementary tables, presenting the univariate and multivariable analyses should be presented in the manuscript. The survival plots are not informative when the outcome is 14-day mortality – they add no further information and I recommend deleting.

Continuous outcomes that do not have normal distribution should be reported with medians and some dispersion measure (min/ max, percentiles) and the statistical analysis should be done with appropriate non-parametric tests. For example, length of stay before bacteremia (42.1±125.3 and 9.7±24.7 – the mean has no meaning here).

In methods, 14-day in-hospital mortality is defined as the main outcome and in results the outcome provided is 14-day infection related mortality. Which is it? 14-day all-cause mortality should be provided, since deaths within 14 days of infection and most probably attributed to infection and the direct cause of death is difficult to establish.

Absolute numbers, numerator and denominator, should be provided with all percentages.

Discretionary Revisions

The carbapenem resistance rate was very high here. It is strange that this was not associated with mortality, as carbapenem resistance probably identifies patients with extensive healthcare exposure. Perhaps the authors should valuate MDR P. aeruginosa that is resistant to carbapenems, other beta-lactams and quinolones vs. non-MDR isolates.
Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests