Reviewer's report

Title: Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: a prospective observational study

Version: 1 Date: 15 June 2006

Reviewer: Ronald Andrew Seaton

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General
This paper focuses on an important issue; the appropriateness of empiric and adjusted antibiotic therapy in hospitals. Although not entirely original the study is interesting and pertinent to prescribers and particularly to those involved in antibiotic prescribing policy. There are a number of issues requiring further explanation, modification and revision before it is suitable for publication and these are detailed below. A major omission in the paper is detail on IV to oral switch and the role and nature of the ID consultation service.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Background and Methods
The role of ID and micro needs to be detailed in the background +/- methods. What proportion of antibiotic prescriptions/patients with infection is/are ID reviewed? Which protocols do the ID team, to guide their decision-making, use? Are these the same as the guidelines used by prescribers? How are micro results communicated? How is an ID consult triggered? What is the compliance with the ID opinion?

More detail is required on the available guidelines available on the intranet. Do these include guidance on dose, duration and IV to oral switch? Is there an education/induction programme used to advertise their existence to prescribers? To what extent were the intranet guidelines and "Sandford guide" used and were other sources also used?

Why were alternating weeks studied rather than every week for a shorter period?
Clarify primary and tertiary care. In the UK this means GP/community care and specialist hospital services (not available in all hospitals) respectively. I don’t think these definitions apply here.

It is not clear who collected and analysed the data; pharmacist, nurse or doctor? How often were charts reviewed; daily, twice daily or more/less often? Were prescribers aware of the study and did this impact on prescriptions ie was there an "effect" of the study? Other interventions at the same time? Did prescriber change during the study period?

The authors have excluded a substantial proportion of patients who received antibiotic therapy prior to admission. This needs to be explained as often patients are admitted because community therapy is failing (particularly LRTI and soft tissue infection).

The authors have excluded patients who receive AB Rx 24 hrs post admission. This needs to be explained as this excludes those in whom infection has been initially missed and those who have acquired infection in hospital.

"Inadequate" prescribing must be better defined. Does this mean "inappropriate" ie over or under use or does it imply "insufficient" AB Rx. This is really open to misinterpretation and needs clarification.

The authors refer to "application modus of antibiotics" in the methods. Does this refer to IV or oral mode of administration? If it does, there does not appear to be any analysis of the appropriateness or otherwise in the results section. This is an extremely important issue. How many received overly long IV therapy and how were such criteria defined? How many received too short duration IV therapy and how was this defined? If this data is not available it is a major omission considering it looks like the data were prospectively collected. Were SIRS criteria etc collected at the time of IV-oral switch?
Statistics. There appear to be some shortcomings in this analysis in that risk factors for (defined) inappropriate use were also themselves used to define inappropriate use. Statistical expertise is required to assess the appropriateness of the multivariate analysis.

Results

Why were patients referred to another hospital within 48 hours? Seems like a large proportion. How many of these received empiric antibiotics? Were they sicker? Could they not have been included in the empiric therapy analysis?

Pathogenic bacteria isolated; Does not seem to have been a differentiation between bacteria isolated in blood (very significant), urine (may be significant), sputum/BAL fluid (potentially dubious significance). Can the authors explain how the microbiology was interpreted in relationship to the appropriateness of the therapy? eg a patient with S. aureus in urine (potentially with no WBCs) with sepsis syndrome and treated with amoxicillin for a presumed pneumonia may be appropriate clinically but potentially not on first glance with respect to micro. I would be more interested to focus on unequivocal microbiology ie blood culture of typical community acquired organisms.

Duration of IV therapy may be better expressed as median and IQR (unless normally distributed). Please confirm data was normally distributed or change to median.

Adjusted therapy; Is this just referring to IV to oral switch or to switching IV agents or stepping up from oral to IV? What proportion in each group and which were were not appropriate?

Is it valid to state that negative cultures rule out infection and therefore render the prescription inadequate? I think cultures are often negative (particularly in sputum and blood) but clinical presentations take precedence and determine antibiotic choice. In UTI, how many had received AB Rx prior to urine culture? Clarify please.

It struck me that in the multivariate model (results) that lack of an infectious disease diagnosis was found to be associated with a risk for inadequate antibiotic therapy. This was in fact a criteria for defining inadequate AB therapy so seems not appropriate to include in the model. In the univariate model for antibiotic switch, switch due to bacteriological results was associated with adequate antibiotic treatment. Surely this is obvious as this was one of the criteria for defining “adequate” antibiotic therapy! What may be more useful to highlight is that 11% of patients who had +ve microbiology failed to be given the appropriate AB Rx! This really depends on the validity of the microbiology (see above). Does female sex as a risk for inappropriate AB imply and hence negative cultures ie are there confounding variables here? Should be examined and discussed.

I am not clear from reading the text and examining the tables what the effect of the ID consult was on the appropriateness of empiric and switch therapy. This is important and should be better presented.

Tables

Table 1. Females not required as numbers of men is stated. Age should be expressed as median and range given

I would include neurology with medicine and geriatrics and considering the very small number it is not appropriate to analyse them separately. Intensive care units should be combined consistently for purposes of analysis

Terminology of site of infection; UTI referred to variably to include kidney infection later epididimitis ie define in methods are refer to UTI in tables. Please be consistent. Does gastrointestinal infections include gastroenteritis and diverticulitis, peritonitis etc Should be defined in methods. What is the difference between and suspected systemic infections without identified focus? In how many were no data recorded on the site of infection? This may be a substantial group in itself. ENT infections seemed to have been included but ENT wards were excluded; Please explain

Table 2. Looks fine except crucially I cannot tell how many of each received IV or oral or combination.

Table 3. Major omission is inappropriate route of administration as previously discussed. How many had >1 reason for inappropriate use? I calculate 9. Is this correct? How was appropriate duration determined? Does this refer to IV or oral therapy being too short or too long or a combination. This really needs clarification!

What do the authors mean by overdosed? In UK this implies self harm.

Foot note in table 3 should be described in the methods section.

Table 4. A comparison of median age (non-parametric test) may be advisable here as age division seem to influence risk of inappropriate AB Rx. Separate analysis of neurology should be removed. It is interesting that McCabe and Charlson scores did not appear to be associated with more inappropriate AB Rx as one might expect an effect eg more aggressive Rx or under Rx in this patient population given poorer prognosis.

Do the data suggest ID consults were associated with less appropriate Rx? How is this explained? Does meaned involved at all? Not sure what the other sub analysis is referring within this block of results. Hepatic failure should be removed (n=2). Renal failure; Does this refer to those with renal failure and seen by ID compared to Renal failure not seen by ID, with the ID reviewed patients getting less
appropriate empiric therapy as a result of or prior to the consultation? Terminology in the site of infection has to match that in the earlier table. Table 5 adds nothing and should be removed. The microbiology effect is potentially spurious and already is referred to in the text. The effect of ID consult does need clarification and could simply be referred to rather than in table.

Discussion
This needs to be revised in line with all of the above and my reservation about exclusions, terminology and definitions. Inadequacy continues to confuse here. The section on the ID consultation needs to be in the background and methods section which will inform the discussion. Persistent fever leading to concerns over inadequacy of IV therapy is suggested in the discussion. There has been no data presented on this and no evidence that this was investigated. Were prescribers questioned and did this affect antibiotic prescribing? Is this a finding or a postulate? The major opportunity in this study is the evaluation of antibiotic prescribing in the context of an active ID service (without a restrictive AB policy). It is this issue in my mind which generates most interest and perhaps should be a firmer focus in the resubmission.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes

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