Author's response to reviews

Title: A new approach to treatment of resistant gram-positive infections: Potential impact of targeted IV to oral antibiotic switch on length of stay.

Authors:

Mohammed Desai (mdesai@hhnt.nhs.uk)
Kathleen B Bamford (K.Bamford@imperial.ac.uk)
Sarah Trust (Sarah.Trust@bsuh.nhs.uk)
Bryony D Franklin (bdean@hhnt.nhs.uk)
Mike Richards (Mrichards@hhnt.nhs.uk)
Ann Jacklin (ajacklin@hhnt.nhs.uk)
Alison Holmes (Alison.holmes@imperial.ac.uk)

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Author's response to reviews: see over
We would like to thank the reviewers for all their suggestions, which are all very helpful and constructive. These have been addressed below and have substantially helped to improve the manuscript.

Referee 2: Comments to authors

Major compulsory revisions

“The title of this manuscript does not accurately reflect the study. It is not about “emerging resistant gram positive infections, but about early switch from iv to oral antibiotic therapy. This should be changed”

>> This is a very good point and we agree. We have now changed the title to read “A new approach to treatment of resistant gram-positive infections: Potential impact of targeted IV to oral antibiotic switch on length of stay”. We believe this now more accurately reflects the study content.

Minor essential revisions

It would be helpful to expand on the discussion as to why selected specialist services were found to be “prolonged users”

>> This was not one of the objectives of our study. However, there are a number of possibilities. One is that patients in our trust undergoing treatment in cardiothoracic, orthopaedic, general medical, plastics and vascular specialities tend to be at a higher risk of infections due to the potentially complex nature of the surgery and other risk factors, and therefore might require prolonged treatment with glycopeptides. Another is that the antibiotic therapy could be inappropriate. This study was intended to reflect ‘real life’. It did not specifically set out to assess the appropriateness of either the choice of or length of therapy but did compare antibiotic selection with bacteriological cultures and found that there was positive microbiology in 80% of situations where glycopeptides were used for five or more days. In some cases discharge may not be arranged for social or other clinical reasons such as the need for further investigations or treatment, and if some other events occurred. For example, in at least one case, there was a subsequent hospital acquired infection that prevented discharge. A prospective study of the implementation of this approach would provide the opportunity to identify and highlight these issues more systematically.

The discussion has been expanded as follows, to reflect this (p 10):

“It is interesting that in a number of cases there was a very prolonged stay after patients fulfilled IV to oral switch criteria. Possible contributors to a delay in discharge include occasional inappropriate antimicrobial use, subsequent development of other hospital acquired infection or new pathology, and logistic community or social issues.”
Referee 2: Comments to authors

Discretionary revisions:

It would be helpful to include in discussion; a statement that a further prospective randomised controlled study would be desirable to confirm the observations made in the paper.

>> The following statement already occurs in the discussion section; “However, we suggest that prospective studies should now be carried out to find out if our predictions are borne out in practice, and…”

We have modified this statement to reflect the desirability of a randomised controlled study and discussed the feasibility of this, as follows (p11)

“However, we suggest that prospective studies should now be carried out to find out if our predictions are borne out in practice. Ideally this would be a randomised controlled trial to compare outcomes for inpatient and outpatient treatment. Unfortunately it is likely that recruitment to this type of study would present problems and patient choice may dictate a significant preference for home treatment. Again, this is an area that needs to be explored systematically. We also suggest that a comparison be made with other options such as an ambulatory IV service. While ambulatory IV therapy retains the disadvantages of IV line use, it may be a cost-effective approach in some settings [19]."
Referee 1: Comments to authors

Major compulsory revisions

Please add information regarding the reasons patients were not felt to be eligible for oral switch. We routinely switch even critically ill patients to oral therapy in the presence of nasogastric suction, ileus, or bowel obstruction.

Patients were not felt to be eligible for IV to oral antibiotic switch if they did not meet the “IV to oral switch criteria” (table 1, as presented in the paper). This was adapted from previously published guidelines and is currently in use in our trust. We accept that in some cases a clinical decision may be made to switch to oral therapy even in the presence of ileus etc, in which case more patients could potentially be switched. The more flexible approach suggested is not routine practice amongst all our specialties and for uniformity it was decided that any medical problem leading to potential for reduced oral absorption should be an exclusion to an oral antibiotic for the purpose of this study. We also feel that these represent patients who are not likely to be suitable for discharge home and were therefore not among our target population.

We have clarified this by expanding the text and have produced an additional table (1b), with the specific exclusion criteria to IV to oral switch.

Table 1a - IV to oral switch inclusion criteria used

| 1. Clinical status | • Temperature less than 38°C for 24 hours                  |
|                   | • White cell count normalising                           |
|                   | • No unexplained tachycardia (Heart rate less than 100 beats per minute) |
|                   | • Sensitivity received (if microbiology positive)         |
| 2. Oral absorption | • Patient tolerates oral fluids                         |
|                   | • No medical problems leading to reduced oral absorption (e.g. vomiting, diarrhoea, and gastrointestinal surgery) |
|                   | • No surgical operation scheduled within next 36 hours    |
Table 1b - IV to oral switch specific exclusion criteria used

| 1. Continuing sepsis | • Temperature less than 36°C or more than 38°C  
|                      | • White cell count less than 4 X10⁹/L or more than 12 x 10⁹/L  
|                      | • Unexplained tachycardia (Heart rate greater than 100 beats per minute in last 12 hours)  
| 2. Oral route compromised | • Vomiting or severe diarrhoea  
|                          | • Other ongoing or potential absorption problem |

In addition we have modified the discussion to clarify this, as follows (p10):

‘Patients were not felt to be eligible for IV to oral antibiotic switch if they did not meet the predetermined IV to oral switch criteria (tables 1(a) and 1(b)). In some settings, a clinical decision may be made to switch to oral therapy even in the presence of nasogastric suction, ileus or bowel obstruction; in which case more patients could potentially be switched. However for the purposes of this study our criteria reflected current guidelines and practice in our hospital.’

Discretionary revisions

It would be good to give some general estimates of the cost savings that could be realised with oral switch.

>> Accurate financial accounting was not possible as part of this study but we generally use the number of inpatient days saved as a good marker of potential estimated savings. The cost of a single bed day saved varies between hospitals and specialities, and so for simplicity, we have chosen to report just the number of in-patient days saved. A rough estimate of a bed day saved is £200. Against this, one would need to consider the cost of the oral antibiotic and additional clinic visits and follow up. However this still suggests considerable savings could be gained.

We have modified the discussion accordingly by adding the following statement on p9;

‘While accurate financial accounting was not possible as part of this study we have reported the number of bed days saved as a marker of potential cost savings. The savings realised from a bed day saved needs to be balanced against the cost of outpatient oral antibiotic treatment and clinic follow up. However we still envisage substantial savings with this approach.’