Author's response to reviews

Title: Development of Quality Indicators for Antimicrobial Treatment in Adults with Sepsis

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Author's response to reviews: see over
To the Editor of *BMC Infectious Diseases*

Amsterdam, March 11th 2014

Re: MS: 1988538098114534

Dear Dr. David Wareham,

Thank you for considering a revision of our manuscript "Development of quality indicators for antimicrobial treatment in adults with sepsis" for publication in *BMC Infectious Diseases*.

We have carefully reviewed the comments. Please find below our responses, including a point-by-point list of changes made to the paper.

We are looking forward to receive the Journal’s review of the revised manuscript.

Yours sincerely, on behalf of all authors,

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Referee 1

There is nothing unusual or surprising about the proposals for QI indicators apart from the fact that the authors seem to have given little explicit consideration to local factors such as outbreaks or local resistance patterns. Perhaps these considerations are included in the Dutch National Guidelines, but it is hard to see how failing to take account of an outbreak of carbapenem resistant bacteria in prescribing practice indicates quality prescribing. The quality indicators (in the opinion of this referee) should say something about the account taken of local factors. National guidelines may reflect local experience across Holland, but it is far from clear that that applies in the UK context or more widely. Perhaps the authors could be asked to comment on this last point with respect to the generalizability of the recommendations?

Answer:
The referee raises an important point regarding local factors and the generalizability of the quality indicators (QIs). The issue of local resistance patterns and national versus local guideline recommendations for empirical treatment choices was extensively discussed during the Delphi consensus meeting. The national sepsis guideline underlines that hospitals can and should deviate from the recommendations based on local resistance patterns. We therefore favored to follow the national guidelines, but to guarantee the generalizability of the QIs another QI was added: local guidelines should correspond to the national guideline, but should deviate based on local resistance patterns (QI number 42). This was added to the Discussion (page 9, lines 284-290).

See also reviewer 2, point 7d.

Referee 2

1. The title of the paper states that the Quality Indicators developed for antimicrobial treatment are for adults with sepsis. However, the second Quality Indicator in the final set is for adult patients with severe sepsis and septic shock. These are not the same patient population and there needs to be clarity around this.

Answer:
The referee is correct, the QI regarding time to first dose of empirical treatment is a QI that only applies to patients with severe sepsis or septic shock. We tried to create clarity by explicitly stating “Antimicrobial therapy should be started as soon as possible, preferably within the first hour in adult patients with severe sepsis and septic shock”. We added this issue to our Discussion section (see page 9, lines 283).

2. The definition of appropriateness in measuring the impact of antimicrobial therapy on key outcomes is fundamental to this analysis. I do not accept that the authors have undertaken a full systematic review to understand how clinicians or investigators have defined appropriate antibiotic therapy. I would refer the authors to an excellent paper by McGregor JC et al in Clinical Infectious Diseases 2007; 45:329-337.

Answer:
We thank the reviewer for this excellent paper. These authors defined “inappropriate” empirical or definitive therapy on the basis of in vitro susceptibility data. We derived our key recommendations for “appropriate” antibiotic therapy from the national, evidence-based guideline for antimicrobial use in hospitalized patients with sepsis. This, according to the national and international experts, implies more than correct (empirical or definitive) antibiotic therapy alone: it defines correct antimicrobial use at the patient level along the entire antibiotic pathway, from start (including appropriate diagnostics) to streamlining and discontinuing of antimicrobial therapy. We added this to our discussion (page 9, line 291-298).

3. I cannot find in the manuscript the strength and quality of evidence to support the included and excluded indicators that were considered. As the authors will be aware that for clinical guidelines recommendations to be included as quality indicators the strength and the quality of the evidence base needs to be strong. This is particularly true when we are looking for an association of a process.
indicator on key outcomes. Therefore, I would wish to know whether compliance with each of the indicators suggested has an impact on clinical outcome, length of stay, antibiotic resistance or cost. These were the indicators that the authors have included in their analysis.

Answer:
The referee raises a very interesting point. For the level of supporting evidence of each potential QI we refer to table 2. Some QIs were based on available Dutch epidemiology and resistance data, which could not be graded, but none of these QIs were included in the final set of QIs.
With regard to the impact of compliance with each QI on clinical outcome and length of stay, this will be analyzed in a future paper (manuscript in prep.), when we will also report the clinimetric properties of the QIs (see page 11, lines 340-342).

4. The authors provide five final set of quality indicators as a means of monitoring antimicrobial use in hospital adult patients with sepsis. The authors do not allude to their utility as independent measures of quality process or whether they need to be applied through a bundle approach for impact on the various outcomes. I do think this needs to be clarified in more detail.

Answer:
The referee is correct, these indicators are all independent measures but they can also be applied through a bundle approach. In a recent paper by our group (Spoorenberg et al, Clin Infect Dis 2014 Jan;58(2):164-9) we found in particular that adherence to the total set of QIs showed a significant dose-response relationship with a shorter length of hospital stay in patients with urinary tract infections. This argues for application of the QIs in a bundle approach. We added this to the Discussion. See page 9, lines 299-304.

5. When one is attempting to assess the quality of care in sepsis management not only is the appropriateness of the treatment important but whether the first dose of antibiotic therapy is administered immediately. I would refer the authors to Marwick et al. JAC 2007;60:694-697. The risk assessment approach here is relevant and of interest.

Answer:
Timely administration of antibiotics turned out to be a key QI - however, only for patients with severe sepsis and septic shock the available evidence is sufficient. See also point 1 and table 2. However, the authors of the suggested paper make a valid point and this paper was added as a reference in the Discussion (page 9, line 299-301)

6. The modified Delphi procedure outlined in the development process is well validated and the authors clearly possess significant expertise in this area. I do have some concerns about the composition of the 6 panel members. Four of these are infectious disease specialists who have specialist interest in this area and are probably biased towards one specific view. Since the majority of sepsis is managed by internist or surgeons outside the ICU I would have thought inclusion of them within the expert panel would have been appropriate. Furthermore, whilst the high response rate to both questionnaires increases the validity of the results attendance of 43% by the expert panel I would not deem as satisfactory but rather disappointing. This may have an impact on the robustness of the developmental process.

Answer:
We understand the point that the referee is making, but all infectious diseases specialists primarily work outside the ICU and only three of the 14 experts were ICU specialists. We have added this to the Methods, see page 5, lines 162-164.
Forty-tree percent of the experts attended the panel meeting, which is indeed low. However the response rate of the first questionnaire was 86%, which is very high. An extensive summary with regard to the results from the consensus meeting was sent to all panel members, and they were asked to give their final remarks and approval for the added and rephrased potential QIs. Since 93% returned the second questionnaire, we believe that an incomplete attendance did not undermine the validity of the results. We added this to the Discussion. See page 10, lines 329-333.

7. My next series of comments are in relation to table 3 and the final set of quality indicators proposed.
a. Quality indicator 2 recommends that antimicrobial therapy should be started as soon as possible, preferably within the first hour. This is not clear and open to misinterpretation. Therefore I think it should have been antimicrobial therapy should be started within the first hour. This is measurable and are commonly used process indicator. The point I made in relation to severe sepsis and septic shock is applicable to this proposed indicator. Furthermore, documentation of the time of the clinical diagnosis is notoriously difficult to measure or elicit from case note review. This clearly would have an impact in defining the numerator. Have the authors considered testing these indicators in real world practice? Their ability to measure these in routine practice prospectively or retrospectively is key.

Answer:
Again, the referee is making an important point. Table 3 describes a numerator and denominator description of the QIs and the numerator description of the second QI is, as suggested by the referee, to start empiric therapy within the first hour after clinical diagnosis.
We agree that measuring this indicator is difficult because of documentation of the time of clinical diagnosis, but with the gradual introduction of the electronic patient record this will become more easy over time. In addition, as mentioned in our answer to point 3, we are currently evaluating the clinimetric properties of the QIs, including the feasibility of measuring them.

b. What is the evidence base to support that at least two sets of blood cultures should be taken and their impact on the range of outcomes suggested. For pragmatic purposes one blood culture may be all that is possible and recommending this would it make a difference? Furthermore, how essential is it that culture from suspected sites of infection should be taken, particularly when there is no availability of the specimen?

Answer:
We have discussed these points during the Delphi meeting, but literature clearly shows that taking only one blood culture has a detection rate around 70-75%, in comparison with two blood cultures having a detection rate around 90%. These studies investigated the association between the number of blood cultures taken over a period of 24 hours and the detection of a bloodstream infection, [Lee, J Clin Microbiol, 2007, pp 3546-48 and Cockerill, Clin Inf Dis, 2004, pp 1724-30]. Of course we know that in daily practice it might be difficult (but not impossible) to get 2 blood cultures, as it is also not always possible to obtain a culture from the suspected site of infection (e.g. in case of cellulitis).

c. Quality indicator 4 (number 45) suggests that empiric antimicrobial therapy should be changed to pathogen directed therapy “as soon as culture results become available”. How does one in the real world measure “as soon as culture results become available”? Once more for pragmatic purposes surely it may be easier to measure a change in pathogen directed therapy within 24 hours of the culture being available?

Answer:
The referee is right that the exact time of availability of culture results might be difficult to measure. We noticed in our evaluation study we alluded to in 7a that the exact time of availability of culture results is difficult to retrieve from the patients files. Therefore, a more practical QI would be: “Empiric antimicrobial therapy should be changed to pathogen-directed therapy IF culture results become available”. We have changed this in Table 2 and 3.

d. Quality indicator 5 (numbers 42 & 43) remain confusing as they rely on a combination of measures that look at compliance with national and local guidance. Most healthcare systems who adopt national guidance allow local flexibility for adaptation and adoption of national guidance in to local practice depending on resistance patterns and so on. I think that for this indicator to be valuable in measuring real world clinical practice for managing sepsis the sole indicator should be empiric antimicrobial therapy prescribed in relation to local guidance. I think this indicator reflects very much Dutch practice and I am not sure it is entirely consistent or adaptable to practice elsewhere. Furthermore, in terms of measuring accordance to local or national guidelines does this mean that the choice of therapy is consistent with this or does it also apply to dose, proposed duration, route etc. This needs clarification.

Answer:
The referee raises an important point regarding local factors and the generalizability of the quality indicators (QIs). The issue of local resistance patterns and national versus local guideline recommendations for empirical treatment choices was extensively discussed during the Delphi consensus meeting. The national sepsis guideline underlines that hospitals can and should deviate from the recommendations based on local resistance patterns. We therefore favored to follow national guidelines, but to guarantee the generalizability of the QIs another QI was added; local guidelines should correspond to the national guideline, but should deviate based on local resistance patterns (QI number 42). This was added to the Discussion (page 9, lines 284-290).

See also reviewer 1.

Prescribing empiric therapy according to the (national) guideline means choice of the antimicrobial agent, but does also apply to dose, proposed duration, route etc. We have added this to Table 2 and 3.

e. I think the data would benefit from validity in a range of health care settings as the authors point out.

Answer:
We agree with the referee. We are currently evaluating the clinimetric properties of these QIs in a large sample of Dutch hospitals and Dutch patients (see points 3 and 7a)

f. For clinicians timely antibiotic, supportive therapy and optimising the quality of antibiotic use are all key. The utility of this bundle should be as part of the sepsis bundle. Therefore, further streamlining of indicators that have impact on outcomes and are supported by high quality evidence base only may be worth considering for inclusion in a sepsis/antibiotic bundle.

Answer:
See answer to point 4.