Reviewer’s report

Title: Integrating sepsis management recommendations into clinical care guidelines for district hospitals in resource-limited settings: the necessity to augment new guidelines with future research

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Reviewer: Kathryn Maitland

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The article is a clarion call for developing specific sepsis bundles to address poor outcome in resource-poor settings. The focus centres around the recently published WHO IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources.

Having now read the IMAI DMC I thought it was an excellent manual – very clear, comprehensive and carefully considered. They include a step wise approach to the integrated management of the severely ill patient- appropriate for all levels of health professional with very informative ‘how to do’ sections on specific procedures (from setting up oxygen (and hierarchy of increasing its intensity) to guidance for pragmatic rates of infusion (if no weight is available).

Discretionary Revisions

I thought that the section on clinical reasoning deserves a mention- as this discusses the process by which the clinician/healthworker can weigh up possible differential diagnoses, based on prior probability and clinical data to make an informed (ideally evidence-based) decision on patient management. Even in resource-poor settings ignoring this decision making process (ie one size fits all) will result in inappropriate guideline implementation—which may neither clinically efficacious nor cost effective.

For consideration

The authors highlight the important of generating more evidence to inform future sepsis guidelines for resource poor settings but do not highlight the urgent need to also provide cost effectiveness analysis and cost utility analysis. For health providers decision-making needs to address key aspects of what is the most efficient way of spending a given budget; should a given goal (eg component of sepsis management) be pursued to a greater or less extent? I suggest these could be tailored to facility level. However, these questions can only be addressed providing there is a realistic alternative comparator (eg do nothing or maintaining usual standard of care) – rather than before and after observational studies within inherent biases.

If the evidence that bundle-based sepsis management were so overwhelming (11 supporting references were provided in the review) why are there currently three simultaneous trials being conducted to investigated efficacy? There is a general
implication that each aspect of this complex intervention (sepsis bundle) requires the existence of the other components for improving outcome – which have very important implications for cost economics- esp in resource-poor setting). However, multiple commentaries[1], reviews and even the Delinger 2008 evidence base review of the guidelines[2] call into question the evidence base of the individual components of this bundle of care. For example, the trial of activated protein C (multi-centre)[3] and tight glycaemic control (single centre)[4] were subsequently criticised for being halted too soon (well before a P<000.1 in the intervention arm)[5] and had implausibly large treatment effects- that were not borne out in subsequent trials. Once a guideline has been developed, often including aspects with low quality evidence, subsequently dropping components from the bundle are much harder than if they were never included in the first place! (See reference[5] for unwillingness to revise guidelines) For resource poor countries I suggest research first – guidelines can wait.

One final mention that the costs of setting up triage, estimated to be $1.75 per patient[6] and of 3 ½ days training course for staff in emergency care (estimated to ~ USD400 per participant; Malawi project report) are likely to result in substantial reductions in global mortality (as we witnessed in the FEAST trial) and should be highlighted as being potentially very attractive to decision makers.

Major Compulsory Revisions

I thank the authors for the reference to the FEAST trial. However, I would like to challenge their conclusions - that it has limited generalisability to other populations. Yes, 32% of patients did have severe anaemia; but 67% of patients did not have severe anaemia (data on outcome stratified Hb threshold published in NEJM correspondence[7]) – fluid boluses were harmful irrespective of baseline Hb. Yes, 57% of patient had malaria; but 43% of patients did not have malaria (that is a lot of patients!); many fulfilling the SIRS syndrome, > 30% had severe acidosis (lactate >5) and 12% had culture-proven—in all these cases fluid boluses were harmful (even more so than malaria). I contend that the study has limited external validity in Africa (which has a large proportion of the global burden of sepsis) than studies largely conducted in single centre tertiary intensive care units that have largely informed international paediatric guidelines (including WHO/ETAT guidelines).


**Quality of written English:** Acceptable

**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