Author's response to reviews

Title: Severe imported falciparum malaria among adults requiring Intensive Care: a cohort study.

Authors:

Michael Marks (michael.marks@nhs.net)
Margaret Armstrong (margaret.armstrong@uclh.nhs.uk)
Muhiddin M Suvari (muhid.suvari@uclh.nhs.uk)
Steve Batson (steve.batson@uclh.nhs.uk)
Christopher JM Whitty (Christopher.Whitty@lshtm.ac.uk)
Peter L Chiodini (Peter.Chiodini@lshtm.ac.uk)
Geoff Bellinghan (geoff.bellingan@uclh.nhs.uk)
Justin F Doherty (tom.doherty@uclh.nhs.uk)

Version: 4 Date: 11 January 2013

Author's response to reviews: see over
Dear Mr Atienza,

Thank you very much indeed for provisionally, at least, accepting our paper for publication in BMC Infectious Diseases and for including the very helpful comments of your three referees. We have addressed their comments in this letter and attach an amended version of the paper with changes highlighted in colour.

Reviewer's report:
The validation of prognostic markers and scores for the management of severe malaria is of high clinical importance. Important differences in the clinical presentation and management in endemic versus non-endemic regions are the well justified rationale for this retrospective analysis of two previously published scoring tools. The study methodology is well conceived and the data are well presented. Please find my specific comments below:

MAJOR: The title implies that this study is a cohort study. However, to my understanding this is not the case since participants were chosen based on the outcome under investigation (in this case severe malaria) and not prior to exposure. Please reconsider this classification. We have changed the title to “Severe imported falciparum malaria among adults requiring intensive care: a retrospective study at the Hospital for Tropical Diseases, London”

ABSTRACT: The statement that HIV co-infection is common (8 cases) and bacterial co-infection uncommon (7 cases) in this patient population seems not very objective. Please reconsider this statement. We have changed this to “Co-infection with HIV was relatively common but, compared to studies in children, bacteraemia was uncommon”

Besides CAM and MSA another internationally established scoring tool (Lambarene-Organ Dysfunction Score; Helbok et al. J Infect Dis.) has been proposed and the manuscript would greatly benefit from inclusion of this score in the analysis.

Both the CAM and MSA scoring systems were derived for use in adults, whereas the Lambarene Organ Dysfunction Score was specifically written to assess severity among children in an endemic area. We therefore chose to validate the CAM and MSA scores but do not think it appropriate to use a scoring system designed for children amongst an adult population.

The clinical presentation of patients is very well described and highly informative.

Thank you
MINOR:

The use of abbreviations is at some points confusing. For example "AKI" is used in the abstract without introducing this abbreviation. Personally I advise to refrain from all abbreviations if possible. **We have removed all abbreviations from the abstract.**

Given the wealth of data and the detailed clinical and laboratory description of patients, the authors could set out to identify risk factors for adverse outcome in this cohort. Several studies have shown that age is associated with malaria-related deaths in returning travelers and similar associations may be considered for pre-existing co-morbidities, initial parasitaemia, schizontaemia, etc. Such an analysis would help to identify prognostic markers for this patient populations. **We have amended the section on statistical analysis in the methods to make it clearer that we have undertaken the analysis requested by the reviewer. It now states “The relationship between the MSA and CAM scores and risk of death and severe ICU malaria were compared using chi-square. Logistic regression was used to examine variables, including in the model the presence or absence of complications, age, gender and immune status, to determine factors associated with either death or severe ICU malaria.”**

We have also amended the last two paragraphs in the results section where we report the results of our statistical analysis to make them clearer. The last sentence of the penultimate paragraph now reads: “In logistic regression adjusting for the potential confounding factors outlined in the methods, no clinical factor was significantly associated with either death or severe ICU malaria.” The last two sentences of the final paragraph now read: “A CAM score ≥2 was significantly associated with an increased risk of death (12% vs 0%, p=0.02) and of severe ICU malaria (50% vs 21%, p=0.003). An MSA score ≥5 was associated with an increased risk of death (22% vs 3%, p = 0.04) but was not associated with a statistically significant increased risk of severe ICU malaria (44% vs 33%, p = 0.49).”

**Discussion**

“Previous studies particularly from France … have reported a mortality rate between 7 and 25%. It is possible that the lower mortality at this hospital could be attributed to considerable experience in the management of severe malaria acquired over many years.”

The excellence of the HTD as an institution and its individual staff members in the management of tropical diseases is beyond doubt, however other reasons than “considerable experience” – a statement implying superior clinical management – for lower mortality in this patient population than in other cohorts (including the French cohort) may also play an important role and should be discussed in more detail (differences in disease severity, differences in classification of severity or in decisions to transfer patients to ICU units between countries, etc). The mortality in this HTD cohort is comparable to what we observe at our centre in Vienna, Austria (Auer-Hackenberg et 2012 Malaria Journal). However, I would disagree to imply from this observation that the lower mortality at our institution is due to “considerable experience” compared to the highly experienced French colleagues. **We have amended the paragraph to read “Previous studies have reported a mortality rate between seven and 25%. Recent data from the Malaria Reference Laboratory have shown a marked geographical variation in mortality from imported malaria from different parts of the UK. It is possible that the lower mortality in various specialist centres may be a reflection of wider experience in the management of severe malaria”**.

**REVIEWER 2: REVIEWER: THOMAS ZOLLER**

**Reviewer’s report:**

General: this is a good retrospective review of a single-center cohort of patients with imported severe malaria. The manuscript adds relevant information to understanding the clinical presentation of this disease in a non-endemic setting, but my overall impression is that the information could be presented in a better and more systematic way, giving more valuable information to the clinician as well as making better use of the data collected.

**Thank you**

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- p1 title: …: a cohort study. A cohort study in most cases refers to prospectively defined cohorts. In order to make clear that inclusion criteria have been defined retrospectively, I suggest to classify the study as a retrospective cohort study and to amend the title accordingly.

Please see above

- Abstract line 1: …AKI occurred…The abbreviation AKI is not as common as e.g. ARDS in medical literature. I suggest to spell out AKI here.

Please see above

- Abstract: to me, one of the key messages of the manuscript (identical with personal experience) is that patients with imported severe malaria rather die from secondary intensive care and/or infectious complications than from malaria itself. This central finding mentioned in the outcome should be included in the abstract, and maybe also discussed in the conclusions section. This may lead to physicians having a low threshold for early antibacterial treatment where secondary infection cannot be ruled out clinically.

We have amended the conclusion section of the abstract to say “patients who died succumbed to complications associated with a prolonged stay on ICU rather than malaria per se”

- Complications of malaria: it would be very interesting to know if those patients developing ARDS had concurrent evidence of bacterial infection. Since ARDS due to malaria is rare and ARDS secondary to bacterial infection, sepsis or pneumonia is common in these patients, the authors may want to explore the dataset for factors discriminating between these causes of ARDS or give a clinical estimate of the likely source of ARDS, improving the clinical value of the manuscript.

ARDS was no more common among those patients who had confirmed bacterial infection and those who did not.

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

- Outcomes line 5: “All” – please make clear that the following sentence refers to those who died.

We have amended the text to make this clear.

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

- Management: there is only very little information on antimalarial treatment used. Of interest would be information on treatment duration, policy of changing to oral therapy, source of i.v.-quinine and artesunate (since these drugs are difficult to obtain), partner antimalarial drugs used. I consider this information as essential for the manuscript, as it would enhance its value for doctors with less experience in malaria treatment.

As stated in the Methods section, decisions on iv versus oral and second agents were made according to the UK Malaria Guidelines.

We have added the sentence “All patients received a second anti-malarial agent, most commonly sulfadoxine-pyrimethamine” to the “management” section in Methods

Which local criteria were applied for initiating exchange transfusion? (given in the discussion, but should be mentioned earlier).

The criteria for considering exchange transfusion are described in the “management” section of the Methods (p5).

- Complications of malaria, last sentence: I do not understand what “in parallel” refers to; it reads better if it is omitted. I am not sure about the value of the statement made in this last sentence in this paragraph; in any way one would expect to give at least a numerical / statistical information illustrating the differences in parasitaemia at the time of occurrence of the respective complications, if this difference is considered relevant by the authors.

We have deleted the phrase “in parallel with this observation” and inserted an additional figure (Figure 2) to clarify the difference in parasitaemia that was seen in patients with cerebral malaria and / or acute kidney injury compared to those who developed ARDS.
At the end of the document we have added an appropriate legend for Figure 2

- Complications of malaria, second paragraph: in order to make it more illustrative for non-malaria experts the typical and important complication of hypoglycaemia could be better described by giving an example value or average value of glucose of patients diagnosed with hypoglycaemia.

We have defined hypoglycaemia in the text.

The same applies to “coagulopathy” and “bleeding”. Although this is a defined WHO-criterion by its own, this clinical paper should give more information on what was seen in clinical practice, e.g. DIC or bleeding due to thrombocytopenia? In addition, other than citing the WHO criterion, there is no definition of coagulopathy or bleeding given in the methods section.

We have defined coagulopathy and bleeding in the methods.

In the section on complications in results we have amended the second paragraph so it now reads: “Significant bleeding or coagulopathy was less common, occurring in 13 (11%) patients, most of whom had laboratory evidence of DIC.”

- Co-infections, second paragraph and table 3. I am not sure if table 3 is needed. The first part is entirely mentioned in the text, the second part is of limited value. I suggest to name the top three pathogens in the text and omit table 3.

We have deleted table 3

- Outcomes, line 10: has the possibility of quinine inducing cardiac arrhythmias been considered here?

Only one patient died while still receiving quinine at the time of death.

- Outcomes: I miss a table detailing the outcomes of the cohort, making the presentation of this information more systematic. Since this is the core information of the manuscript, and all numbers are written in the text, it is difficult to get an overview of the outcomes, possible underlying reasons and potential risk factors. Of particular interest are those who died; I suggest to make a separate table or section of a table detailing the complications, clinical characteristics (e.g. parasitaemia) and cause of death for this group of patients and give only summarizing descriptions in the text. A negative risk factor analysis in univariate or multivariate analysis does not argue against this.

Our original submission included a table that summarised all these data but we were asked to remove this before the paper went to peer-review. We have added the table to the re-submission (table 3) and would be happy with the decision of the editorial staff of the journal as to whether this table should be included.

- Outcomes: to improve the clinical value of the manuscript and since this is only one patient, please indicate here what the clinical presentation of the “post malaria neurological syndrome” and its outcome was.

We have included more detail in the paper to address this point.

- Outcomes: “In logistic regression...”: this output description is very short. Even if the analysis was negative, I suggest to state first that (probably) an univariate analysis was carried out, which variables were included in the logistic regression model (even if it was age and sex only) and then the final result in order to allow the reader to better understand the analysis which was carried out.

Please see above

- Given the high number of patients in the analysis, was there any variable of borderline significance? Could you briefly mention in the discussion why probably no factor was found to be significant?

We have added the sentence “No clinical factor was associated with a poor outcome but given the low case fatality rate, the study was under-powered to detect such a difference” to the third from last paragraph in the conclusions.

- Conclusions, line 11: “...this report is the first to include patients treated with parenteral artemisinins...”. This assertion is false. There are at least three publications known to me describing cohorts of patients where patients with imported severe malaria are treated with i.v.-artemisinins. I suggest to conduct a new literature search here.
We have amended this to read: “Finally, this report adds to the limited number of series reporting the efficacy and safety of parenteral artemisinins in severe malaria in a non-endemic setting (18–20).”

We have amended the reference list to reflect this.

- Conclusions, next page top: “It is possible that the lower mortality at this hospital….” I personally do not support such a conclusion statement without carrying out a thorough comparison of underlying populations in French or other studies published, local treatment plans, local healthcare circumstances and any other factor possibly influencing survival. The authors may reconsider this assertion carefully.

Please see above

Reviewer 3: Reviewer: Perry van Genderen

Reviewer's report:
This cohort study deals with severe imported falciparum malaria at an intensive care unit. The paper is well written but remains superficial in its analysis, especially in relation to detection of potentially new prognosticators. It should be considered more as a descriptive study in which the manifestations of severe malaria, its occurrence in time despite adequate treatment and outcome are described rather than an analytical study specifically designed to evaluate CAM and MSA scores. As is correctly stated by the authors: the value of CAM and MSA scores are not validated in non-immune populations but it should be made more clear that these scoring systems were primarily developed for triage purposes in resource poor settings with limited supportive care facilities. In a non-endemic malarious region with sufficient supportive care facilities, one could argue that an intensive care population of malaria patients (especially if the centre is also a referral hospital for severe malaria) is probably not the most ideal setting for evaluation of CAM and MSA scores since these patients were all already identified as having severe disease and were referred for optimal supportive care (a high or low CAM or MSA score would not have changed treatment policy). Although not clearly stated, I must assume that CAM and MSA scores were also calculated retrospectively.

A study detailing new prognosticators for ICU admission would be more appealing to infectiologist dealing with imported malaria, especially in regions where treatment of malaria is centralized and decisions on whether or not referral have to be made if CAM and MSA scores were evaluated prospectively and in a cohort of malaria patients with clinical features ranging from uncomplicated to severe disease and were truly used as tools to select patients for referral to ICU or not. In addition, with only 5 case-fatalities, a low discriminative power of CAM and MSA for death could already be envisioned.

Minor essential revisions
Methods section
* A definition of ARDS is lacking
In the section on study populations we have changed the wording to:
“ARDS [bilateral pulmonary infiltrates and PaO₂:FiO₂ ratio of <26.7, not attributed to left ventricular dysfunction in the opinion the ICU clinician],”

* Definition of CAM and MSA scoring system is lacking
These data are included in the cited references.

* Management: is it true that the severe patients were treated with either quinine or artesunate ONLY and that treatments were NOT consolidated by a following oral course of antimalarials (e.g. iv quinine combined or followed by doxycycline) or iv artesunate followed by a full oral course of antimalarial?
Please see above

* Management: how was the exchange transfusion done?
Standard six unit exchange transfusion via central access. This has been made clear in the Methods section.
Results
The majority of the patients (103/124) were transferred from another centre. Were these patients already receiving adequate treatment or not?

All the patients transferred in had received intravenous quinine.

Which findings on admission were included in the table: those from admission in the referring hospital or those from the referral hospital?
The data in the table were the earliest available, from the hospital at which the patient was first seen.

What if only the most severe malaria patients were referred to THD? These potential biases, including a referral bias, should be discussed in more detail.
In the penultimate paragraph of the conclusions, we have added the sentence: “Although the possibility of referral bias cannot be excluded, it is likely that our data are applicable to all patients with imported malaria requiring admission to ICU.”

*amount of immunity: what was entered in the logistic regression analysis?
cerebral malaria, ARDS? AKI? or immunity?

Please see above

Were the individual parameters of the CAM score and MSA score also tested in multivariate analysis or just the outcome of these scores (in chi-square analysis?)

Only the overall MSA and CAM scores were tested in chi-square analyses as only combined scores have been used for determining prognosis in previous publications.

Discussion
With regard to artesunate, I would suggest to add the reference: Malaria Journal 2012 March 31;11:102 (kreeftmeijer-vegter et al). Artesunate was given to a large group of non-immune patients with severe imported malaria.

Please see above

I don't agree with the statement that all patients with malaria should be screened for HIV. The case finding was not done in all malaria patients but in a subset of patients with severe malaria. Most HIV infections were found in patients of African origin. However, I can imagine that the authors would rephrase the statement to HIV testing should be done in African patients with severe malaria.

With respect, we disagree. UK national guidelines encourage increased testing for HIV and we feel that this is an appropriate population for targeted testing.