Intensive care support and clinical outcomes of patients with Ebola virus disease (EVD) in West Africa

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Abstract

Purpose: We investigate the impact on outcome of different levels of supportive treatment in Ebola virus disease (EVD). The NGO EMERGENCY delivered care sequentially at two Ebola Treatment Centres (ETC) in Sierra Leone: first at Lakka (fluids, symptomatic, antibiotic, antimalaria treatment, and hospital level medical care), and thereafter in Goderich, adding organ support in the only African ETC with an equipped and staffed intensive care unit (ETC-ICU).

Methods: The primary outcome in this retrospective cohort study was in-ETC mortality. Secondarily, we used multi-variable logistic regression to investigate the independent impact of the IC on mortality by comparing patients in two ETCs, adjusting for potential confounders, including the viral load (base-10 logarithm in copies/ml) (LVL), modelled as a piecewise linear function. Mortality was plotted versus LVL. Confidence bands were constructed by a bootstrap technique. The number of hospital-free days within 28 was computed to assess the burden of EVD.

Results: Data from 229 EVD patients were analysed (123 in Lakka, 106 in Goderich). Crude analysis showed a non-statistically significant difference in mortality (57.7% in Lakka vs 50.0% in Goderich; \( p = 0.19 \)). Age and LVL were associated with mortality. Adjusted mortality was lower at the Goderich ICU-ETC (\( p = 0.055 \)). This difference was observed with 80% confidence for patients with LVL between 7.5 and 8.5 copies/ml. Hospital-free days (of 28 days) were greater (7.7 vs 5.5; \( p = 0.03 \)) for patients treated in the ICU-ETC.

Conclusions: Provision of critical care to patients with EVD is feasible in resource-limited settings and was associated with improved survival and less time in hospital.

Keywords: Ebola virus disease, Intensive care, Multiple organ failure, Health-care in resource limited countries

Introduction

The Ebola virus disease (EVD) outbreak in West Africa in 2013–2016 was the largest, longest-lasting epidemic of its kind, and for the first time also involved non-African countries. The outbreak led to a broader understanding of Ebola epidemiology and heightened recognition of the need to respond rapidly to interrupt transmission early [1]. Considerable progress has also been made on vaccine development [2–6], but there is still limited knowledge on EVD pathophysiology [7] and therapeutic yielded inconclusive findings [8–13].

Management guidelines [14] developed from previous outbreaks and available in 2013, focused on patient cohorting and healthcare worker safety, proposing treatments that could be delivered in resource-limited settings in rural areas with limited access to medical care.

In 2014, many groups operating in the field [15, 16] endorsed the need for more aggressive symptomatic treatment, treatment of dehydration and related
electrolyte imbalances and organ-supporting care. Human resources and funding, combined with experience from EVD treatment of patients transported to North America and Europe, strengthened the idea of critical care provision in resource-constrained settings.

EMERGENCY, an Italian NGO (http://www.emergency.it), was founded in 1994 with the primary mission of delivering care to civilian war victims worldwide. Since 2001 it has also been running a Surgical and Paediatric Centre on the outskirts of Freetown, Sierra Leone. At the start of the epidemic, the Ministry of Health of Sierra Leone invited EMERGENCY to contribute to the fight against Ebola. The NGO rapidly built a patient assessment centre in Lakka to provide clinical triage, assessment and Ebola diagnostic testing, which soon became a patient Ebola Treatment Centre (ETC). A second ETC, in Goderich Sierra Leone was subsequently constructed, incorporating a well-equipped intensive care unit (ICU), capable of providing 24 h nursing and medical assessment/support, mechanical ventilation, intravenous vasoactive medications, and renal replacement therapy (Supplementary information, S2). To our knowledge, this was the first ever, dedicated ICU-ETC in Africa.

Our aims for this retrospective cohort study was to describe the feasibility of providing intensive care with organ-supporting treatment to patients with Ebola in a resource-limited setting, to describe patient outcomes, and to compare outcomes of patients between two distinct treatment settings (Goderich ETC with an ICU vs Lakka ETC with no ICU), adjusting for predictors of survival, including patient age and viral load at admission [17–23].

Methods

Study design and setting

This retrospective cohort study includes all consecutive patients affected by EVD hospitalized in two ETCs in Sierra Leone, from 19/09/2014 to 12/12/2014 in the Lakka Holding and Treatment Centre and from 12/12/2014 to 28/05/2015 in the Goderich ETC-ICU. Both ETCs were located near Freetown, Sierra Leone. More detailed information on the staff, facility, and operational procedures are provided in the Supplementary Material, S1 and S2. The main characteristics and differences are reported in Table 1.

Laboratory

The plasma concentration of Ebola virus (EBOV) RNA (viral load) was measured using a real-time reverse transcriptase PCR (RT-PCR) assay (RealStar Filovirus Screen. RT-PCR 1.0 kit, Altona Diagnostics), with a limit of detection of $10^3$ cp/ml of EBOV RNA. Viral RNA quantification was based on a standard reference curve provided by the kit manufacturer, spanning up to $10^9$ cp/ml of EBOV RNA. For the sake of simplicity, further analyses were performed using the base 10 logarithm of the viral load (LVL) measured in cp/ml.

At the start of the epidemic, before implementing its own virology laboratory, EMERGENCY collaborated with the WHO South Africa Ebola laboratory, which used the same diagnostic test.

Admitted patients

Patients reaching the facility with suspected EVD were admitted, under observation, to the Holding and Treatment Centre, and their symptoms treated while awaiting the RT-PCR test results. Only patients with laboratory-confirmed EVD from the holding centre, or those with EVD transferred from other facilities, were admitted for treatment.

Risk factors at admission

Demographic information including age, gender, symptoms, and possible time of Ebola exposure were collected on standardised clinical case report forms. LVL was recorded from the first diagnostic blood sample at admission. Other risk factors at admission, including markers of organ damage (renal, liver, coagulation etc.), were not systematically collected in the early months and cannot therefore be included in the analysis.

Take-home message:

An Intensive Care Unit (ICU) as part of an Ebola Treatment Centre (ETC) was run by the NGO EMERGENCY and the Istituto Malattie Infettive “Spallanzani” in Goderich, Sierra Leone during the last 5 months in the 2013-16 outbreak. Building and running an ICU with western standard in an ETC was possible also in this very difficult setting. This allowed also some research activity, essential to evaluate the interventions directly on the field in real life conditions during an epidemic and with the pressure of large numbers of cases. The outcome of the 106 patients treated in the ICU-ETC was compared in a before-after study to the outcome of the previous cohort of 123 patients treated by the same NGO in Lakka without an ICU facility. Patient risk factors, mainly the viral load at admission were adjusted as potential confounders. The availability of the ICU in the ETC led to a lower mortality in Goderich (p=0.055). This difference was observed with 80% confidence for patients with an intermediate range of viral load, indicating an intermediate probability of death (50-70%). Relatively small numbers in each subgroup and other possible risk factors limit this analysis.

The already high level of care in Lakka, the first ETC, corresponding essentially to the recently published guidelines, can be improved with the availability of an Intensive Care Unit. However also the maximal supportive effort without effective antivirals seems not able to lower mortality to an acceptable level. Intensive care and effective antiviral seem both necessary in the fight against Ebola.
Definition of outcome
A survivor is defined as a patient discharged alive. Discharge of patients from the ETCs occurred after two negative RT-PCR blood tests performed at least 24 h apart.

Co-interventions: investigational antiviral treatments
Fluids and electrolytes were administered by mouth or intravenously according to symptoms, diuresis and fluid balance; all patients were treated for symptoms as nausea, anxiety, and pain. Antibiotics were administered from admission and antimalaria treatment was discontinued only if negative tests became available.

Only a few doses of compassionate use investigational antiviral treatments were available. Two patients received ZMAb and towards the end of the outbreak, Goderich ETC took part in the Prevail II trial [8], randomizing five patients to standard care plus ZMapp (two patients) versus standard care alone (three patients). Based on the available preclinical literature suggesting in vitro and in vivo efficacy [24], a randomised clinical trial protocol was developed to investigate the efficacy of treatment of EVD with amiodarone. The trial was registered at ClinicalTrials.gov (NCT02307591) (see Supplementary material S4 for details).

While awaiting clinical trial initiation, and after approval by two Italian Ethics Committees, given the pre-existing high mortality rate and lack of known effective therapies, amiodarone was administered on a compassionate basis to 100 patients. Compassionate use was stopped between December 2014 and February 2015 by request of the Sierra Leonean Government, pending the opinion of the specific Ethics Committee (definitive approval granted April 23, 2015). Further information on the treatment with amiodarone is reported in the Supplementary material S4.

Statistical analysis
Descriptive analyses were presented as frequencies, proportions, means and standard deviations, medians and interquartile ranges (IQR), where appropriate to

| Table 1 Main patient management characteristics of EMERGENCY NGO’s two Ebola Treatment Centres (ETC) in Freetown, Sierra Leone; September 2014–May 2015 |
|---|---|
| **Structure** | **ETC Lakka (September 19–December 13, 2014)** | **ETC-ICU Goderich (December 14, 2014–May 28, 2015)** |
| **Number of beds** | 5 holding/17 treatment | 22 holding/24 ICU/50 ward |
| **Air conditioning** | Yes (inadequate) | Yes |
| **Oxygen** | Yes (concentrators max 5 l/person) | Yes (concentrators max 10 l/person) |
| **Virology laboratory** | External | Internal |
| **Laboratory at point-of-care** | Partial/last weeks | Yes |
| **Radiology** | No | Yes (from March 15/2015) |
| **Standard monitoring (EKG, HR pulse oximetry, non-invasive blood pressure)** | No | Yes |
| **Urinary catheter and fluid balance** | Partially | Yes |
| **Artificial nutrition** | Parenteral | Parenteral/enteral |
| **IV fluid replacement, where necessary** | Yes | Yes |
| **Blood and blood products** | Only whole O Rh neg blood | Yes |
| **Inotropes/vasoactive medication** | Dopamine | Noradrenaline, Adrenaline, Dopamine |
| **Central venous lines** | Yes, last month | Yes |
| **Arterial line and pressure monitoring** | No | Yes |
| **Advanced cardiovascular monitoring (PICCO)** | No | Yes |
| **Blood gas analyser** | No | Yes |
| **Tracheal intubation and mechanical ventilation** | No | Yes |
| **Continuous renal replacement therapy** | No | Yes |
| **Individual time limit for working inside red zone** | 60' | 120' |
| **No. doctors, mean** | 5 MDs | 14 MDs |
| **No. international nurses, mean** | 6 | 20 |
| **No. intensivists, total** | 2 intensivists | 5 intensivists |
| **Time in h/24 h any MD present in red zone** | 5 | 15 |

The staff calculation was performed by calculating the mean number of staff members per month.
characterize patients and their clinical outcomes. Pro-
portions were compared using the \( \chi^2 \) test or Fisher Test,
whereas comparisons between continuous variables were
expressed through the \( t \) test or Wilcoxon rank-sum test,
as appropriate. The number of hospital-free days within
28 days was calculated to compare the burden of EVD in
terms of hospitalization in the two ETCs, avoiding bias
due to mortality rate differences [25]. During the 28-day
follow-up period most, but not all, EVD patients either
died or recovered. The number of hospital-free days for
a patient with \( x \) days of hospitalisation was \( 28 - x \), if the
patient recovered within 28 days, and 0 if the patient
recovered after 28 days or died. Hence, the higher the
value of this indicator the lower the burden of hospital-
ization (as the patient recovered earlier), while deceased
patients were considered equivalent to alive patients with
a long recovery time.

Multivariable logistic regression models were used
to determine independent factors associated with EVD
patient mortality. ETC was forced in the model to explore
the secondary endpoint of association of intensive care
availability on mortality. To test any relationship between
the logit and the LVL, the former was modelled as a
continuous piecewise linear function of the latter. The
Akaike Information Criterion (AIC) [26] was minimised
with respect to the cut-off values of LVL where the slope
of the piecewise linear function changed. Interactions
between ETC and the other variables were only included
when they significantly reduced the AIC. The interaction
between ETC and the above-described transformation
of the viral load was also tested in this step. This allowed
different piecewise linear transformations (parametrised
by the number and values of the cut-offs) of the LVL for
the two ETCs. Missing records were excluded from the
analysis.

The odds ratio (OR) of the two ETCs, i.e., the exponen-
tial of the difference \( d \) between the logit of the two ETCs
\( (d = \text{logit}_{\text{Lakka}} - \text{logit}_{\text{Goderich}}) \), was plotted as a function
of viral load, with the bootstrap-based confidence band.
Hence, mortality in Lakka was higher than in Goder-
ich when OR was larger than one. The OR was statisti-
cally significant for those viral load values for which the
confidence band was above the line \( \text{OR} = 1 \). To identify
the range of clinically relevant phenomena, two confi-
dence bands were constructed at the 95 and 80% levels,
respectively.

The adjusted probability of death was then plotted for
each ETC with the respective confidence bands to deter-
mine how mortality varied as a function of viral load in
the two ETCs. All variables except LVL and ETC were
chosen to be equal to their mean values. The width of the
confidence bands for Lakka and Goderich was estimated
by Payton et al. [27] approximate method. This procedure
is designed to evaluate, with a given significance level,
whether two confidence intervals overlap (Supporting
information, S5).

The role played by viral load at admission as a predic-
tor of mortality within 20 days of hospitalisation, was also
described using Kaplan–Meier curves in strata of LVL,
overall and for each ETC (Fig. 2). The cut-offs separating
the strata were determined as the LVL values at which
mortality in one ETC becomes higher or lower than in
the other ETC at the 80% confidence level (as described
in the previous paragraph). Graphically, these values cor-
respond to the points where the 80% confidence band of
the logit difference \( d \) crosses the horizontal axis \( d=0 \).
Differences between Kaplan–Meier curves in these strata
were assessed by the log-rank test.

\( p \) values lower than 0.05 were considered significant
in two-tailed tests. All analyses were performed using R
software, version 3.3.3, and SAS software, version 9.4.

More details on the statistical elaboration are reported
in Supplementary materials, S5.

Funding
Goderich ETC was built during the outbreak, in the
framework of a project to build seven Ebola treatment
centres funded by DFID (Department for International
Development—GOV.UK). In accordance with treatment
criteria and based on the previous 3 months’ experience,
the Centre was co-designed by EMERGENCY’s tech-
nical/engineering staff. Fitting it out for intensive care
delivery resulted in additional costs, borne by the NGO,
in the amount of approximately €450,000. The Istituto di
Malattie Infettive “Lazzaro Spallanzani”, which ran the
virological laboratory, was supported by a “Ricerca Cor-
rente IRCCS” grant; Ministry of Foreign Affairs, Italy (See
Supplementary material S2 for more details). The funders
had no role in study design, data collection and analysis,
decision to publish, or preparation of the manuscript.

Results
Patients and settings
Data were analysed on 229 patients with a labora-
ory-confirmed diagnosis of EVD, admitted to the two ETCs
(123 at the ETC in Lakka, 106 at the ETC-ICU in Goder-
ich). All patients with confirmed EVD received sup-
portive treatment and were followed up to the endpoint
(recovery or death). The study flow chart is shown in the
supplementary material (Fig S3.1).

The patients admitted to the ETCs did not differ in
terms of gender, while patients admitted to Goderich-
ETC were older (mean age 29.7) than those admitted to
Lakka-ETC (mean age 27.8 years) (\( p = 0.02 \)).
No major differences emerged between ETCs for admission viral load, or time from symptom onset to ETC-admission (Table 2).

The clinical manifestations and contact history of the 229 EVD patients are shown in the Supplementary material S3. None of the 13 clinical symptoms reported during the admission visit were significantly associated with mortality. The provision of interventions associated with intensive care were more common at the Goderich ETC-ICU: central venous catheter in 62 versus 12
patients (58.5 vs 9.8%, \( p < 0.0001 \)), mechanical ventilation for any duration in 33 (14.4%) and renal replacement therapy in 21 (9.2%) versus no patients in the ETC Lakka. Twenty patients had both ventilation and renal replacement therapy. Dopamine infusion was the only vasoactive medication possible in Lakka (12 patients; 1 survivor); Noradrenaline and/or Adrenaline (26 patients; 3 survivors), administered via syringe-pump and invasive monitoring of arterial pressure, central venous pressure and advanced hemodynamic assessment (Picco) in selected patients, were available in Goderich.

Clinical outcomes
The mean number of hospital-free days (of 28) days of admission was significantly higher in the Goderich ETC-ICU (7.7 vs 5.5 days; \( p = 0.03 \), Table 3).

The overall crude case fatality rate (CFR) was 54.1% (Table 4). No statistical differences were observed between patients who survived and who died of EVD in terms of gender, age and time from symptom onset to hospital admission. CFR differed substantially according viral load at admission, ranging from approximately 30% for patients with \( 	ext{LVL} < 7.5 \) (low) to over 80% for patients with \( 	ext{LVL} \geq 8.5 \) (high) (\( p < 0.0001 \)). Crude analysis showed a non-statistically significant difference in CFR between Lakka-ETC and Goderich-ETC-ICU patient admissions (57.7 vs 50.0%; \( p = 0.19 \)) (Table 4). Multivariable logistic regression analysis showed that age and viral load were independently associated with an increase in EVD mortality. The best model (according to the lowest AIC) for predicting the probability of death included age, \( 	ext{LVL} \), ETC, and the interaction between \( 	ext{LVL} \) and ETC. As known, an interaction involving a continuous variable (like \( 	ext{LVL} \)) is difficult to represent. Hence, in Fig. 1 we plotted, as a function of \( 	ext{LVL} \), both the OR for mortality of Lakka vs Goderich (left panel) and the probability of death at each ETC (right panel). In the left panel, the 95% confidence band of the OR (light grey) never exceeds one, while the 80% confidence band (dark grey) exceeds one for medium–high viral loads (\( 	ext{LVL} \) between 7.5 and 8.5). Notably, as the confidence level varies, the band begins to exceed zero at a confidence level of 94.5%, corresponding to \( p = 0.055 \). This means that patients with a medium–high level of viremia at admission, had a

| Table 4 Case fatality rate by main patient characteristics |
|----------------------------------------------------------|
| Survivors | Non-survivors | Case fatality rate (%) | \( p \) value* |
| All patients, N | 105 | 124 | 54.1 |
| ETC | | | |
| Lakka | 52 | 71 | 57.7 | 0.19 |
| Goderich | 53 | 53 | 50.0 | |
| Sex, N (%) | | | |
| Women | 56 | 58 | 50.9 | 0.32 |
| Men | 49 | 66 | 57.4 | |
| Age (years), mean, median (IQR) | 29.7/27.0/(20.0–38.0) | 29.9/27.5/(20.0–37.0) | 0.73 |
| 0–10 | 8 | 14 | 63.6 | 0.74 |
| 11–18 | 12 | 16 | 57.1 | |
| 19–45 | 70 | 75 | 51.7 | |
| ≥ 46 | 15 | 17 | 53.1 | |
| Missing | – | 2 | – | |
| LVL at admission, mean, median (IQR) | 7.1/7.1/(6.4–7.9) | 8.1/8.2/(7.7–8.8) | < 0.0001 |
| < 7.5 | 58 | 26 | 31.0 | < 0.0001 |
| 7.5–8.4 | 32 | 46 | 59.0 | |
| ≥ 8.5 | 5 | 42 | 89.4 | |
| Missing | 10 | 10 | – | |
| Time between symptom onset and hospital admission (days), mean, median (IQR) | 5.1, 5.0 (3.0–6.0) | 4.8, 4.0 (3.0–7.0) | 4.8, 5.0 (3.0–6.0) | 0.39 |
| 0–2 | 17 | 26 | 60.5 | 0.42 |
| 3–5 | 50 | 51 | 50.5 | |
| > 5 | 33 | 43 | 56.6 | |
| Missing | 5 | 4 | – | |

LVL, base-10 logarithm of the viral load, measured in copies per millilitre
IQR, Interquartile range
* \( \chi^2 \) test or Fisher’s exact test, or Wilcoxon’s Rank-Sum Test for continuous variables.
statistically significant survival benefit (with 80% confidence level) if admitted to the treatment facility in Goderich with ICU competences and equipment.

Figure 2 shows the importance of the viral load at admission for the outcome of the overall population as Kaplan–Meier survival-curve for patients with low, intermediate and high viral loads at admission (panel a). The same analysis split in patient population of Lakka (panel b) and Goderich (panel c) shows how the intermediate line, corresponding to patients with LVL 7.5–8.5, is different in the two settings.

Discussion

Building an ICU in Sierra Leone dedicated to patients with EVD was founded on the hypothesis that intensive supportive care could improve the prognosis of EVD, and ethically supported by the conviction of the right of everybody to receive the best possible treatment. Based on this framework, the EMERGENCY NGO sought to optimise supportive care in a country where very few hospitals even had an ICU prior to the start of the epidemic.

After the tend-based ETC in Lakka, the Goderich ETC-ICU has been active since December 2014. It was built by the British government and run by EMERGENCY (Supplementary material, S2). The organisation recruited intensivists, infectious disease specialists, and expert nurses from various nations (Supplementary material, S1), coordinating their expertise with the experience of its own staff, specialised in intensive care medicine. Despite a long track record in hospital management in very difficult, dangerous areas and conditions, setting up a multinational ICU compliant with rigorous biosafety requirements and subject to obvious communication barriers among team members and with patients, proved to be a very challenging experience, highlighting the importance of organization, communication and cross-disciplinary and cross-cultural training.

We found that the setup of an ETC-ICU was feasible in a very short time and at relatively limited costs. Intensive supportive treatment shows shorter time to discharge in survivors (Table 3) and survival advantage in patients with intermediate-severe infection (Table 4, Fig. 1). Different factors, like delay in admission, organ failure, comorbidities, complications, factors not changed by the availability of intensive care, contribute to the mortality in patients with “low” Ebola viral load (LVL < 7.5). Patients with very high viral load (LVL > 8.5) may have a very limited benefit from intensive care support without effective antiviral treatment, because of the rapid progression of EVD to fatal multiple organ failure [28].

Only exceptionally it was possible to buy enough time for the immune system to clear the virus and reverse organ failure. Only 10% of the patients who needed mechanical ventilation, continuous renal replacement therapy and vasopressors recovered. In the supplementary material S6 we report two case histories, demonstrating how rapid both, worsening and improving, may occur according the clearance/persistence of the viral load.

Despite supportive treatment very close to the new guidelines [29] plus IC support, mortality at the
ICU-ETC was 50% overall and still 30% in patients with LVL < 7.5 (Table 4, Fig. 2). Our fatality rate is therefore much higher than the rate of 18.5% reported for patients with EVD treated outside of West Africa [30]. While it is not possible to make a direct comparison between those two groups of patients and their treatment, there remains undoubtedly an important gap which needs to be investigated. Relevant differences between the two patient populations and the treatments are: 81% of patients treated outside West Africa were Western healthcare workers (vs 1% in our population) with shorter time from symptom onset to diagnosis (3 vs 4 days), lower viral load at admission (mean values of LVL of 7.3 vs 7.8 copies/ml), and earlier treatment onset (4 vs 4.9 days). Moreover, 85% of patients treated in North America and Europe received at least one antiviral drug, and 70% received two or more such treatments. Although the various clinical trials have not demonstrated the efficacy of the investigational treatments, some have exhibited promising findings that could not be adequately investigated [8, 11].

**Limitations of the study**

Evaluating the efficacy of an intensive care approach, with a limited number of patients, in the framework of a humanitarian intervention during a major epidemic, in one of the world’s most recourse-limited regions, is clearly fraught with limitations. Outcome predictors other than age and viral load as pre-existing chronic illness and severity of organ dysfunction could not be included because of lack of complete information.

It is important to recognize that the cause of death, particularly when occurring 10–15 days after admission, may not be related solely to EVD but may also be associated with cardiovascular complications or bacterial superinfections. Finally, there is no way of assessing how far a learning curve in the treatment of EVD patients may have influenced outcomes, irrespective of the therapeutic

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**Fig. 2** Kaplan–Meier survival-curve for patients with low, intermediate and high viral loads at admission (a) and for Lakka (b) and Goderich (c), separately
setting. An important mortality reduction is reported in an earlier experience [31] but the lack of risk adjustment in the comparison limits the strength of this observation.

Conclusions

Provision of intensive care to patients within an EVD epidemic is feasible also in resource-limited settings and may be associated with improved survival and less time in hospital but the outcome with supportive care alone, without effective antiviral treatment, remains unsatisfactory.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5308-4) contains supplementary material, which is available to authorized users.

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Conflict of interest

The authors declare that no competing interests exist.

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