# Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial

*Katherine M B Ajdukiewicz, Katharine E Cartwright, Matthew Scarborough, James B Mwambene, Patrick Goodson, Malcolm E Molyneux, Eduard E Zijlstra, Neil French, Christopher J M Whitty, David G Lalloo*

## Summary

**Background** **Southern Africa has a high incidence of bacterial meningitis in adults, often associated with HIV co-infection. Mortality exceeds 50%, even with appropriate antibiotic therapy, and is not improved with corticosteroids. Glycerol adjuvant therapy reduces long-term morbidity in bacterial meningitis in children, and its use is being promoted. We aimed to assess the effectiveness of glycerol as an adjuvant therapy for adults with bacterial meningitis in Africa.**

**Methods** **The study was done in two phases. First, in an open-label dose-finding study, 45 adult patients with symptoms, signs, and cerebrospinal fluid findings consistent with bacterial meningitis received either 50 mL, 75 mL, or 100 mL of glycerol four times a day for 4 days. We then did a randomised, double-blind, placebo-controlled trial of oral glycerol in adults with bacterial meningitis. Patients with clinical and cerebrospinal fluid findings suggestive of bacterial meningitis were randomly assigned in blocks of 12 by use of a random number list produced by an independent statistician to receive either glycerol or an equivalent volume of sugar solution. Glycerol and placebo were indistinguishable by colour or taste. The primary outcome was mortality at 40 days, with secondary outcomes including disability and mortality restricted to pneumococcal disease. All patients were analysed for the primary outcome excluding those who were lost to follow-up. This trial is registered at controlled-trials.com, number ISRCTN70121840.**

**Findings** **75 mL glycerol four times a day was the highest tolerated dose, and was used for the main study. 265 patients were assigned treatment: 137 glycerol and 128 placebo. The trial was stopped early on the advice of the data and safety monitoring board after a planned interim analysis. By day 40, 61 (49%) of 125 patients in the placebo group and 86 (63%) of 136 in the glycerol group had died (adjusted odds ratio 2·4, 95% CI 1·3–4·2, p=0·003). There was no benefit from glycerol for death and disability by day 40, and glycerol did not improve death and disability by day 40 or death at day 40 in patients with proven bacterial disease or pneumococcal disease. Two serious adverse events occurred that were possibly due to the study drug.**

**Interpretation** **Oral glycerol therapy cannot be recommended as an adjuvant therapy in adults with bacterial meningitis in resource-poor settings with a high HIV prevalence.**

**Funding** **Meningitis Research Foundation.**

*Lancet Infect Dis* 2011; 11: 293–300

Published Online February 18, 2011 DOI:10.1016/S1473-3099(10)70317-0

See Comment page 257

**Department of Medicine, College of Medicine, Chichiri, Blantyre, Malawi** (K M B Ajdukiewicz MRCP, K E Cartwright MRCP, M Scarborough PhD, J B Mwambene Dip Med Sci, P Goodson Dip Med Sci, M E Molyneux Dip Med Sci, E E Zijlstra PhD); **Monsall Unit, Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Delaunays Road, Manchester, UK** (K M B Ajdukiewicz); **Microbiology, Leicester Royal Infirmary, Infirmary Square, Leicester, UK** (K E Cartwright); **Microbiology, John Radcliffe Hospital, Headington, Oxford, UK** (M Scarborough); **Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK** (M E Molyneux, D G Lalloo FRCP); **Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands** (E E Zijlstra); **Karonga Prevention Study, Chilumba, Malawi** (N French FRCP); **Department of Clinical Research, London School of Tropical Medicine and Hygiene, Keppel St, London, UK** (N French, C J M Whitty FRCP)

Correspondence to: Katherine Ajdukiewicz, Monsall Unit, Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Delaunays Road, Manchester M8 5RB, UK **katherineaz@doctors.org.uk**

## Introduction

Meningitis is a common cause of adult in-patient death in Malawi. The incidence of bacterial meningitis has risen substantially in Malawi, as it has in other southern African countries, since the start of the HIV epidemic.[1] Even with effective antibiotics in-patient case fatality exceeds 50%, and up to half of survivors are left with neurological sequelae and disability.[2,3] Measures to reduce mortality are urgently needed.[1]

Corticosteroids, which can be an effective adjunctive treatment in settings with a low prevalence of HIV,[4] are not effective where most meningitis is HIV-related, including Malawi.[2,5,6] Raised intracranial pressure impairs cerebral blood flow, and might be a significant contributory factor to mortality and morbidity from all forms of meningitis; therefore, early reduction of intracranial pressure might improve outcome. Glycerol, an orally administered hyperosmolar liquid widely used as a food additive, has been suggested as a promising adjuvant treatment. In children with bacterial meningitis, glycerol reduces neurological sequelae but not case fatality when given either alone or in combination with dexamethasone,[7,8] although there is some controversy surrounding the design of a Latin American study that found a benefit for glycerol.[9] Glycerol has previously been used in stroke, head injury, and glaucoma to reduce increased tissue pressure.[10–18] A meta-analysis of intravenous glycerol in ischaemic stroke suggested that glycerol conferred a short-term advantage, but no benefit in terms of long-term survival.[19]

No trials of glycerol adjuvant therapy in bacterial meningitis have been reported in adults. If the paediatric findings were replicated in adults, glycerol would represent a significant advance in the treatment of

bacterial meningitis, particularly in resource-poor settings with a high prevalence of HIV, such as southern Africa, where the burden of disease is high and adjuvant steroid therapy has no clinical advantage.

Glycerol has been used as a food additive and for cosmetic purposes for many years. Toxicity data for oral glycerol indicate that it is safe. Side-effects are infrequent, usually mild, and are mostly gastrointestinal in origin.[20,21] There are rare reports of neurological side-effects, such as headache, dizziness, confusion, and amnesia (in elderly patients),[22,23] and one report of spontaneously reversible hemiparesis in a patient who ingested 500 mL of pure glycerol as a single dose.[24] Glycerol is stable in hot climates, widely available, and inexpensive, and would therefore be ideal for use in resource-poor settings.

Queen Elizabeth Central Hospital (QECH) is a large hospital in Blantyre, Malawi, and serves a catchment population in excess of 1 million people. According to UNAIDS, HIV prevalence in adults in Malawi aged 15–49 years in 2006 was 12%.[25] Admissions to QECH exceed 10000 per year, and 70% of admitted patients are infected with HIV.[26] Meningitis is one of the commonest causes of admission, with *Streptococcus pneumoniae* the most common form of bacterial meningitis.[1] Mortality from bacterial meningitis exceeds 50%, and adjunctive steroid therapy in adults does not reduce mortality, so it is not routinely used.[2]

We designed a randomised, double-blind, controlled trial to test whether glycerol is an effective and safe adjuvant treatment for adults with bacterial meningitis in a setting with high HIV seroprevalence and high mortality from meningitis.

## Methods

### Patients

The trial started on Sept 10, 2006, and recruitment was halted on Aug 23, 2008. There were no facilities for the invasive monitoring of patients at the time of the trial.

Adult patients admitted to the QECH with signs and symptoms of meningitis were screened by clinicians on the wards. All patients had a lumbar puncture and received intravenous ceftriaxone. Patients were then referred to the trial staff for assessment of eligibility. Trial inclusion criteria were clinical suspicion of meningitis (headache, neck pain or stiffness, reduced level of consciousness, photophobia, confusion, fits, rash, or fever) plus cerebrospinal fluid evidence of bacterial meningitis (>100 white cells per µL with predominant neutrophils or Gram-stain showing bacteria), or cloudy cerebrospinal fluid if microscopy was delayed (eg, at night). Exclusion criteria were age less than 16 years, cryptococcal meningitis (India ink stain or cryptococcal antigen positive on cerebrospinal fluid), less than 100 white cells per µL or lymphocytic meningitis, pregnancy, heart failure, and known type-2 diabetes. A capillary whole blood glucose (BM glucose) greater than 12 mmol/L was added as a criterion for exclusion for phase 2 of the study on the advice of the data and safety monitoring board.

Ethics approval was granted by the College of Medicine Research Committee, Malawi, and the Liverpool School of Tropical Medicine, UK. Written informed consent was obtained from all study participants.

### Randomisation and masking

A randomisation number list in blocks of 12 was produced by an independent statistician using Stata version 9.0. Numbers and allocation were placed into sealed envelopes. Envelopes were opened sequentially by an independent person not involved in the clinical care or assessment of trial participants, who labelled pre-prepared containers of glycerol and placebo with a unique study number. Study drug packs were then placed in consecutive order within a secure room. If a patient fulfilled the study inclusion criteria, verbal and written informed consent was obtained from the patient or, if the patient was unconscious or confused, from the patient's legal guardian. Those unable to read gave witnessed consent. Allocation of the next available study number constituted entering the trial, and analysis was based on study allocation irrespective of subsequent treatment. All envelopes were accounted for. Allocation was masked from clinicians and patients. Treatment with glycerol or placebo was given by trial staff. After the addition of Orange SOBO (a locally produced orange squash) into glycerol and placebo, both liquids were a pale orange colour and were more palatable and indistinguishable in appearance and taste, as assessed by medical and clerical staff within the Department of Medicine, QECH.

### Procedures

The study was done in two phases. The first was an open-label study to assess the ease of giving glycerol and the tolerability of a range of doses by patients to find the highest tolerated dose for use in the second phase—the double-blind, randomised controlled trial.

45 adult patients with symptoms, signs, and cerebrospinal fluid findings consistent with bacterial meningitis infection who fulfilled inclusion criteria were recruited. After consent was obtained, 15 patients each received 50 mL, 75 mL, or 100 mL of glycerol four times a day for 4 days. Paediatric studies used 6 mL/kg per day:[8] this corresponded to 300–360 mL glycerol daily for the average Malawian weighing 50–60 kg. Glycerol was diluted with water at a ratio of 5:4 so that the consistency was indistinguishable from that of 50% sugar solution (the proposed placebo for phase 2). Patients therefore received diluted glycerol 90 mL, 135 mL, or 180 mL four times a day. Clinical details of all cases, including possible or probable adverse events due to glycerol, were recorded.

The second phase of the study was the main trial, in which patients were randomly assigned to receive the highest tolerated dose of glycerol or equivalent volume of

placebo. All patients with probable meningitis were treated with intravenous ceftriaxone twice a day for at least 10 days, or until treatment was changed according to the results of culture and sensitivity testing. If cryptococcal infection was diagnosed after recruitment to the study, patients were treated with oral fluconazole (in accordance with national guidelines), and the study drug was discontinued. Those not enrolled in the study received standard care in accordance with national guidelines.

Glycerol or placebo was given orally or via nasogastric tube immediately after enrolment at a dose of 135 mL (75 mg glycerol mixed with water or 135 mL 50% sugar solution) four times a day for 4 days (16 doses). This was the highest tolerated dose in the dose-finding study. The dose was repeated after antiemetics if vomiting occurred within 30 min of administration. A nasogastric tube was routinely inserted in those with a score on the Glasgow coma scale (GCS) of less than 8, or in any patient unable to swallow for any other reason. Position of the tube was checked daily by auscultating over the epigastrium while injecting air through the nasogastric tube and by ensuring that tube aspirate was acidic (turned blue litmus paper pink).

After 48 h or at least eight doses of glycerol therapy, a second lumbar puncture was done. After 10 days of antibiotic therapy a full neurological examination including hearing assessment was done. Hearing tests were done with a Kamplex Diagnostic Audiometer AD12. All patients were treated in hospital for at least 10 days, with daily clinical assessment. Patients alive at discharge were asked to return at day 40 for follow-up assessment; those who did not attend were traced at home. At day 40, patients had a full neurological examination including hearing assessment using audiometry, and the Glasgow outcome scale was used as a measure of neurological disability.

The primary endpoint was death by day 40. Secondary endpoints were death or disability (Glasgow outcome score—disabled and partially or completely dependent) by day 40;[27] death by day 10; hearing loss in those not dead or disabled by day 40; time to death; cerebrospinal fluid opening pressure 2 days after treatment; and serious adverse events (SAEs). A-priori subgroup analyses included patients with proven or probable bacterial meningitis alone and proven pneumococcal meningitis.

Adverse events and SAEs were recorded. SAEs were classified as definitely, possibly, or probably related to study drug, as defined by the International Conference on Harmonisation Guidelines.

All patients were tested for HIV. Consent with appropriate counselling was sought at recruitment to the study, or retrospectively after recovery for those initially unconscious or confused. Patients' guardians were aware that HIV testing would be done, but they were not informed of results. Relatives and guardians were encouraged to attend for voluntary HIV testing, regardless of patients' results. Patients were counselled about their results before discharge from hospital. Those found to be HIV positive were started on cotrimoxazole prophylaxis and referred to the antiretroviral therapy clinic.

Cerebrospinal fluid and blood for culture were analysed by the Malawi–Liverpool–Wellcome Trust (MLW) laboratory. Cerebrospinal fluid was processed by use of standard laboratory techniques for cell count, differential white-cell count (when >20 cells per μL present) and Gram stain. Cerebrospinal fluid was cultured on sheep blood and chocolate agar for 48 h and subcultured for

| | 50 mL glycerol four times a day (n=15) | 75 mL glycerol four times a day (n=15) | 100 mL glycerol four times a day (n=15) |
|---|---|---|---|
| Died | 10 (67%) | 8 (53%) | 12 (80%) |
| Gastrointestinal side-effects* | 7 (47%) | 8 (53%) | 8 (53%) |
| Number with random capillary blood glucose >12·2 mmol/L† | 5 (33%) | 3 (20%) | 6 (40%) |
| Number with proven bacterial meningitis | 4 (27%) | 6 (40%) | 7 (47%) |

Data are n (%). *Nausea, vomiting, diarrhoea. †World Health organisation definition for diabetes.[29]

***Table 1:*** **Results of the dose-finding study**

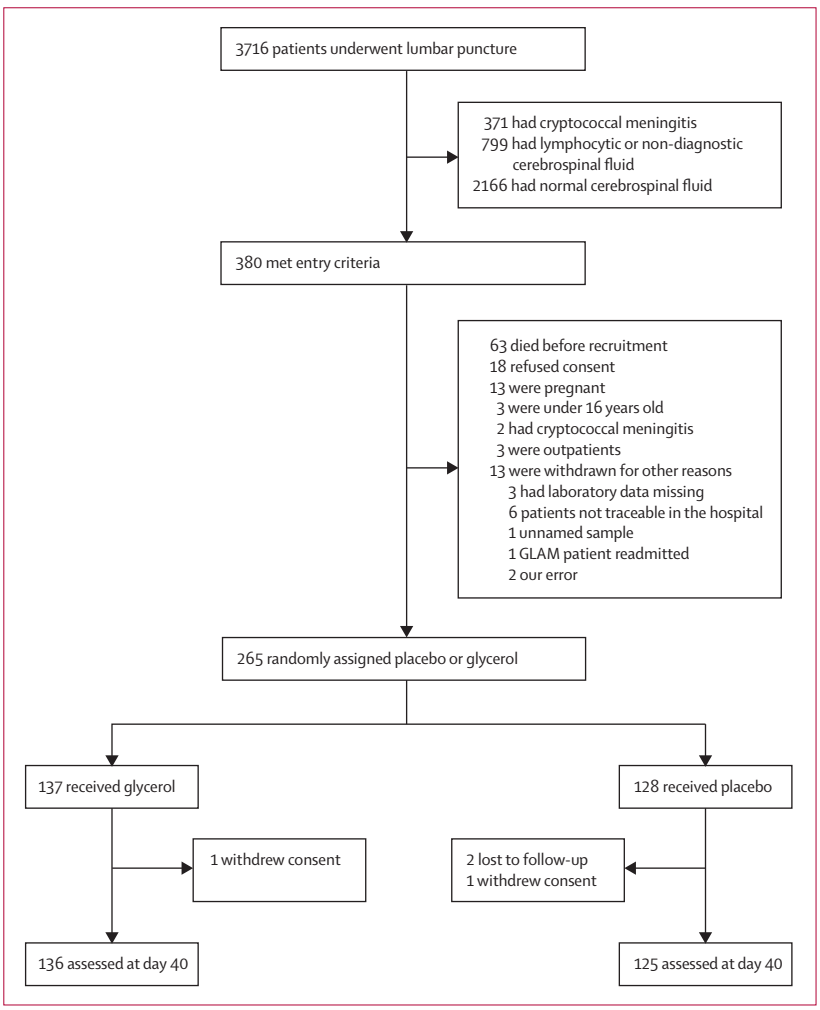


***Figure 1:*** **Trial profile**

| | Placebo | Glycerol |
|---|---|---|
| Number recruited | 128 | 137 |
| HIV seropositive* | 104/124 (84%) | 111/134 (83%) |
| Prior AIDS defining illness stage modified WHO 3 or 4 | 33/128 (26%) | 36/137 (26%) |
| Median (IQR) age (years) | 32 (27–38) | 32 (27–40) |
| Female | 67/128 (52%) | 72/137 (53%) |
| Initial Glasgow coma scale <12 | 48/128 (37·5%) | 39/137 (29·3%) |
| Initial Glasgow coma scale <8 | 14/128 (11%) | 9/137 (6·6%) |
| Median (IQR) cerebrospinal fluid white cell count (white cells per μL) | 400 (200–1040) | 395 (200–1120) |
| Proven bacterial meningitis | 54/128 (42%) | 64/137 (47%) |
| Pneumococcal disease | 52/128 (41%) | 46/137 (34%) |
| Median (IQR) cerebrospinal fluid opening pressure (cm CSF) | 28 (18–34) | 21·5 (12·5–34) |
| Fits or history of fits in last 2 weeks | 51/128 (40%) | 49/137 (36%) |
| Prior antibiotic use | 59/128 (46%) | 53/137 (39%) |
| On antiretrovirals | 16/128 (13%) | 23/137 (17%) |
| Median (IQR) duration of symptoms (days) | 6 (3–8) | 5 (3–7) |

Data are n (%) unless otherwise stated. *HIV status not known in three patients who received placebo and four patients who received glycerol.

***Table 2:*** **Baseline characteristics in the main trial**

identification as appropriate. Blood was cultured with the BacT alert system. Organisms were identified by use of conventional culture-based microbiological techniques. Cerebrospinal fluid cryptococcal antigen agglutination tests (Pastorex Crypto Plus Biorad, Marnes-la-Coquette, France) were done by the MLW laboratory on a subset of patients. Blood for malaria film, full blood count, and biochemistry was analysed by the QECH laboratory. HIV serological testing was done in duplicate for every patient by use of Uni-Gold Recombigen HIV rapid test (Trinity Biotech, Wicklow, Ireland) and Determine HIV-1/2 (Abbott, USA). BM glucose was measured with Glucostix (Bayer Diagnostics, Basingstoke, UK) at least twice a day while the patient was taking study drug.

### Statistical analysis

The sample size required to detect a reduction in mortality from 56% (previous mortality in observational studies) to 40%, with $\alpha$=0·05 and $\beta$=0·9, was 216 patients per group (calculated using Stata 8.0). Data were double entered into Microsoft Access and verified before being analysed with Stata 8.0. The analytical plan was finalised before unmasking.

All patients were analysed for the primary outcome excluding those who were lost to follow-up. A per-protocol analysis (restricted to those not withdrawn from glycerol or placebo for reasons other than death) was also planned for the mortality-defined end-points. Logistic regression was used to construct a model to estimate the primary and secondary outcomes (with the exception of hearing loss and cerebrospinal fluid opening pressure at 2 days), and odds ratios (ORs) calculated unadjusted and adjusted for the following prespecified potential confounding factors: HIV serostatus, antiretroviral use, prior AIDS-defining illness (modified WHO grades 3 or 4 ),[28] age, sex, prior antibiotic use, score on the GCS on admission, fits before admission, duration of symptoms, pretreatment with antibiotics, and organism isolated from cerebrospinal fluid or blood. The secondary analysis of time to death was analysed with Cox's proportional hazard ratios, unstratified and stratified by the same potential confounding factors. Statistical significance for the primary outcome was defined as p less than 0·05.

An unblinded interim analysis by the data safety monitoring board had been prespecified after 100 deaths. Indicative criteria for stopping included recruitment to be halted if a treatment group showed evidence of harm exceeding conventional levels of chance alone (p<0·01), and recruitment to be halted if there was clear evidence of benefit with a significance level of p less than 0·001.

The trial is registered with controlled-trials.com, number ISRCTN70121840.

### Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

The dose-finding study ran from March, 2006, to July, 2006. 45 patients were randomly assigned to receive one of three doses of glycerol (table 1). About 50% of patients in each group experienced nausea, vomiting, or diarrhoea. Vomiting did not occur in any patient receiving glycerol via nasogastric tube. No clear relation existed between the dose of glycerol and frequency of side-effects. 14 (31%) patients had transiently increased blood glucose concentrations greater than 12·2 mmol/L after taking study drug. Peak hyperglycaemia ranged from 12·2–20·4 mmol/L. One patient had a single reading of 40 mmol/L at recruitment, but died before receiving study drug. No patients needed treatment with insulin. Five patients had hyperglycaemia (12·2–20·4 mmol/L) after glycerol had been discontinued, suggesting type 2 diabetes or a stress response was the cause. Patients had difficulty swallowing the largest volume given. Eight of 15 patients in the 50 mL group, seven of 15 in the 75 mL group, and ten of 15 in the 100 mL group died in hospital. On the basis of tolerability, the 75 mL dose was used for the subsequent trial.

The trial started on Sept 10, 2006, and recruitment was halted on Aug 23, 2008. 3716 patients were screened, 380 met the inclusion criteria, and 265 were randomly assigned to placebo or glycerol (figure 1). Baseline characteristics of the two groups were similar (table 2). Follow-up of survivors to day 40 was 98% and 99% in the placebo and glycerol groups, respectively.

The study was stopped following the planned interim analysis after 100 deaths, with 7 months of the trial still to

| | Placebo | Glycerol | Odds ratio (95% CI, p) | Adjusted odds ratio (95% CI, p)* |
|---|---|---|---|---|
| Died before day 40 | 61/125 (49%) | 86/136 (63%) | 1·8 (1·1–3·0) p=0·02 | 2·4 (1·3–4·2, p=0·003) |
| Died or disability before day 40† | 75/124 (60%) | 93/135 (69%) | 1·4 (0·87–2·4) p=0·2 | 1·7 (0·97–3·1, p=0·07) |
| Died by day 10 | 53/126 (42%) | 80/136 (59%) | 2·0 (1·2–3·2) p=0·007 | 2·7 (1·5–4·8, p=0·001) |
| Per-protocol analysis death to day 40 | 57/106 (54%) | 77/118 (65%) | 1·6 (0·9–2·8) p=0·08 | 2·2 (1·2–4·1) p=0·01 |
| Died by day 40 restricted to proven bacterial disease | 21/53 (40%) | 43/63 (68%) | 3·3 (1·5–7·0) p=0·002 | 5·5 (1·9–15·4, p=0·0011) |
| Died by day 40 restricted to pneumococcal disease | 20/51 (39%) | 31/45 (69%) | 3·4 (1·5–8·0) p=0·004 | 8·2 (2·4–28·5, p=0·0006) |

Data are n (%) unless otherwise stated. *Prespecified factors: HIV status, age, organism in blood or cerebrospinal fluid, antiretroviral treatment, pre-treatment antibiotics, fits prior to admission, Glasgow coma score, duration of symptoms, sex, prior AIDS-defining events. †No day 40 data for two patients.

***Table 3:*** **Primary and secondary outcome data**

run and 61% of the predetermined recruitment completed. The data safety monitoring board advised stopping recruitment on the grounds of futility. Patients already recruited to the trial were followed up until completion of follow-up or the primary endpoint was reached.

40 days after enrolment, the proportion of patients who died was significantly larger in the glycerol group than in the placebo group; this was the same for death and disability. Overall, 61 (49%) of 125 patients in the placebo group and 86 (63%) of 136 in the glycerol group died by day 40 (odds ratio [OR] 1·8, 95% CI 1·1–3·0; p=0·02). The OR adjusted for prespecified potential confounding factors was 2·4 (95%CI 1·3–4·2, p=0·003). Glycerol did not improve death and disability by day 40, or death at day 40 in proven bacterial disease or pneumococcal disease (table 3). Among survivors tested by audiometry, 14 of 41 patients in the placebo group and four of 31 patients in the glycerol group were deaf at day 40 (p=0·02). Time to death is shown in figure 2. The unadjusted hazard ratio (HR) for death was 1·7 (95% CI 1·2–2·4), and the adjusted HR was 2·0 (95% CI 1·4–2·9), with glycerol seeming to be detrimental.

138 (52%) of 265 patients had a second lumbar puncture. The median opening pressure of cerebrospinal fluid 2 days after randomisation was 15 cm CSF (IQR 9–21) in the placebo group, and 11·5 cm CSF (IQR 6–19) in the glycerol group (Willcoxon rank sum difference p=0·08). Median BM glucose on day 2 in both groups was 6 mmol/L (range 4–11 mmol/L).

There were two deaths thought possibly to be due to study drug in view of the rapid and unexpected deterioration in the patients' clinical condition. A 70-year-old HIV-positive woman was admitted with 1 week's history of headache, fever, and confusion, and on admission had a GCS score of 13. She was assigned glycerol. Her level of consciousness improved, but on day 2 she developed seizures refractory to anticonvulsant therapy and she became hypertensive (170/90 mmHg from a baseline of 120/80 mmHg). *Salmonella typhimurium* was cultured from cerebrospinal fluid. A second lumbar puncture was not done, and the study drug was discontinued on day 3. She died on day 12. The second

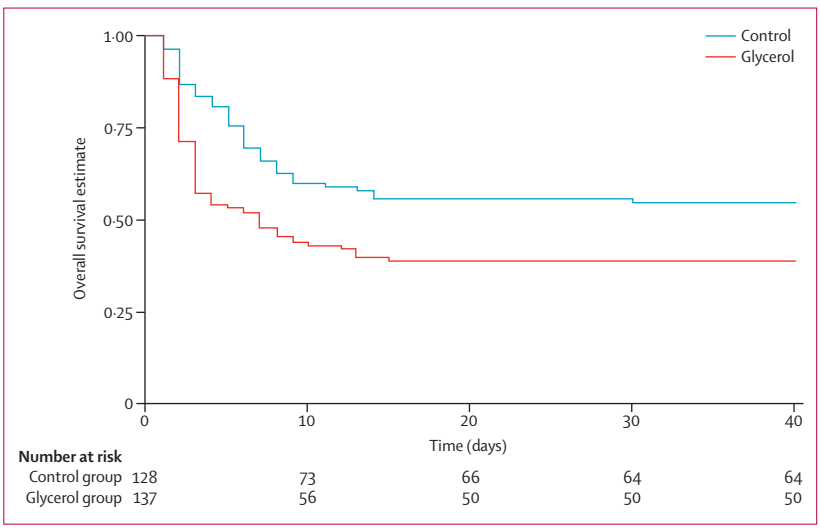


***Figure 2:*** **Kaplan-Meier survival estimates for glycerol *vs* control**

case was a 35-year-old HIV-positive woman with a 1-day history of illness and a GCS score of 12 on admission. She was assigned placebo. She improved rapidly to GCS score of 15 by day 2. *Streptococcus pneumoniae* was cultured from blood and cerebrospinal fluid. Discharge was planned on day 10 when she developed generalised weakness and vomiting without fever. She maintained a normal blood pressure and good urine output. On day 11 her level of consciousness fell (GCS 6), although no focal neurological deficit was identified. She died on day 13. The most likely diagnosis for both patients was, on clinical criteria, a major cerebrovascular event secondary to meningitis. However, a brain scan was not possible in either case in this setting.

Glycerol was well tolerated compared with placebo. 79 (65%) of 121 patients who were conscious and able to communicate had gastrointestinal adverse events (nausea, vomiting, diarrhoea) in the placebo group, compared with 85 (66%) of 129 patients who were conscious and able to communicate in the glycerol group. Seizure during the initial 10 days after randomisation occurred in 37 (31%) of 121 patients in the placebo group and 64 (50%) of 129 in the glycerol group (p=0·002);

almost half of these occurred while taking study drug. 72 (27%) of 265 patients had a seizure within the first 2 days of admission; 25 (19%) of 128 in the placebo group and 47/137 (34%) in the glycerol group (p=0·006, post-hoc analysis). No other symptoms or signs differed between the two groups after randomisation. A total of 135 (51%) patients presented with a GCS score of less than 14, 23 of whom had a GCS score of less than 8 (14 in the placebo group, and nine in the glycerol group).

## Discussion

In our study in adults, which was stopped early by the data safety monitoring board due to futility, glycerol was associated with significantly higher mortality within 40 days than was placebo. Glycerol was also associated with worse outcomes in all major secondary analyses, except deafness, at day 40. This trial therefore does not support the use of glycerol as adjunctive treatment for bacterial meningitis in adults in Malawi.

These findings from the first adult study of glycerol are markedly different from those of studies in children (panel). In a small study of infants and children in Finland, oral glycerol reduced severe or profound hearing loss.[7] A larger multicentre paediatric study in Latin America[8] suggested that glycerol prevented neurological sequelae, although several methodological concerns were subsequently raised about this study.[9] A small, randomised, double-blind study in India by Sankar and colleagues[30] comparing dexamethasone and oral glycerol adjuvant therapies in children with acute bacterial meningitis did not find any significant difference in hearing loss and neurological sequelae between the groups.[31] Animal models of pneumococcal meningitis have not shown a beneficial effect from glycerol.[32] Our findings suggest glycerol confers no benefit and might be harmful. However, there are major differences in our study population and those of other studies: our patients were adults, 84% were HIV positive, and glycerol was given for 4 days rather than 2 days. HIV serostatus was not reported in the paediatric studies, although it is highly likely that most participants were HIV negative. Additionally, access to health care is often delayed in sub-Saharan Africa compared with other settings; most of our patients had symptoms for 5 days or more, compared with over 85% presenting within 48 h of the onset of symptoms in previous studies. Despite these population differences, why glycerol seemed harmful is hard to explain. Hyperglycaemia—which adversely affects outcome compared with normoglycaemia after stroke, acute myocardial infarct, pneumonia, and in those acutely ill on intensive care[33–37]—is not a plausible explanation, because it was rarely detected in either of the treatment groups in our study. One possibility is that the sugar solution used as placebo for blinding was beneficial, but this seems unlikely; there was no evidence of hypoglycaemia in any patient before giving the study drug.

That a higher proportion of patients had convulsions in the glycerol group than in the placebo group is concerning, and might relate to the poor outcome. This could be a coincidental finding associated with the severely ill population in this study, or could be directly related to an effect of glycerol. This has not been previously documented in humans. A study in mice found that oral glycerol could produce changes in behaviour and seizures within 30 min.[38] The exact cause of these effects was not clear, but an increase in oxygen species might be the cause, and the effects were associated with increased interleukin 1β concentrations in the hippocampus. In human studies, rebound phenomena can occur with osmotherapy, particularly mannitol,[39] but evidence for its occurrence with glycerol therapy is mixed. Some studies do not show a rebound increase in intracranial pressure with either oral or intravenous glycerol (compared with mannitol),[15,39,40] others show substantial rises in intracranial pressure with continuous intravenous and intermittent oral administration.[41,42] Rebound increase of intracranial pressure might be attributable to a reversal of the concentration gradient of the osmotic agent between blood and cerebrospinal fluid (or brain interstitial fluid) as the drug is eliminated.[41] Although this increase in pressure is not generally thought to be clinically significant, its relevance is unclear in the context of bacterial meningitis. Reliable clinical interpretation of the changes in cerebrospinal fluid opening pressures is difficult, in part because of early mortality.

There are potential limitations to this study. Although this hospital is better staffed and supported than many in a similar setting, general medical care is suboptimal compared with that offered in developed countries. Additionally, there was limited intensive or high dependency care available for such critically ill patients with severe sepsis. Overall, this is a typical southern

### *Panel:* Research in context

**Systematic review**

We searched PubMed using the terms "glycerol", "adjuvant therapy", and "bacterial meningitis". There are no randomised controlled trials using glycerol adjuvant therapy in meningitis in adults. There is one trial in children in Latin America where adjuvant dexamethasone or glycerol with placebo was administered. Glycerol did not improve mortality or deafness, but did reduce severe n eurological sequelae. Hearing loss was reduced in a small study in children in Finland, but no advantage was seen from glycerol in another small paediatric study in India.

**Interpretation**

Our trial is in adults, most of whom were HIV positive, and showed evidence of increased mortality with glycerol. It therefore makes it unlikely that glycerol is beneficial in adults or in those who are HIV positive, but does not exclude the possibility of benefit in children.

African hospital, and the population of patients and trial setting is likely to be representative of other sub-Saharan African settings with a high prevalence of HIV. The results do not exclude the possibility that glycerol might be effective in a setting with low HIV prevalence in which patients present earlier and where HIV infection is less common. Residual confounding is a possibility, but the finding is highly statistically significant, no subgroup analysis suggested benefit, and adjusting for identified confounding factors only strengthened the association, making residual confounding unlikely. The mortality difference seen at interim analysis by the data safety monitoring board strengthened with follow-up of enrolled patients, and the adverse effect persisted after adjusting for confounding, thus supporting the decision to stop early.

In adults in Malawi or other resource-poor regions where bacterial meningitis presents late and commonly occurs in people who are infected with HIV, glycerol cannot be recommended as adjunctive therapy. Other ways of reducing the substantial mortality associated with this disease need to be explored. Glycerol might be harmful as adjunctive therapy in adults with bacterial meningitis in sub-Saharan African settings with a high prevalence of HIV.

#### Contributors

KMBA helped design the study, and contributed to the literature review, data collection, writing, data analysis, and interpretation. KEC contributed to data collection and writing. MS helped design and write the study. JBM and PG contributed to data collection. MEM helped do the trial, interpretation, and writing. EEZ contributed to data collection and writing. NF contributed to design, data interpretation, and writing. CJMW and DGL contributed to design, data analysis, interpretation, and writing.

#### Conflicts of interest

The authors declared no conflicts of interest.

#### Acknowledgments

We thank the trial participants and their families, and the staff of Queen Elizabeth Central hospital who helped to run this trial. We also thank Sarah White and the Malawi–Liverpool–Wellcome Trust statistics department for data entry and support; Jonny Kumwenda, Elizabeth Molyneux, and Richard Auty, members of the data and safety monitoring board; Malawi–Liverpool–Wellcome Trust laboratories for support; Ian Mackenzie for loan of an audiometer and valuable advice; and Nick Beare for valuable contributions.

#### References

1 Gordon SB, Walsh AL, Chaponda M, et al. Bacterial meningitis in Malawian adults: pneumococcal disease is common, severe, and seasonal. *Clin Infect Dis* 2000; **31:** 53–57.

2 Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-saharan Africa. *N Engl J Med* 2007; **357:** 2441–50.

3 Gordon SB, Chaponda M, Walsh AL, et al. Pneumococcal disease in HIV-infected Malawian adults: acute mortality and long-term survival. *AIDS* 2002; **16:** 1409–17.

4 de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347:** 1549–56.

5 Molyneux E, Walsh A, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi. *Lancet* 2002; **360:** 211–21.

6 van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurol* 2010; **9:** 254–63.

7 Kilpi T, Peltola H, Jauhiainen T, Kallio MJ. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J* 1995; **14:** 270–78.

8 Peltola H, Roine I, Fernández J, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2007; **45:** 1277–86.

9 Sáez-Llorens X, McCracken GH Jr. Glycerol and bacterial meningitis. *Clin Infect Dis* 2007; **45**: 1287–89.

10 Menger JS, Charney JZ, Rivera VM, Mathew NT. Treatment with glycerol of cerebral oedema due to acute cerebral infarction. *Lancet* 1971; **2:** 993–97.

11 Gilsanz V, Rebollar JL, Buencuerpo J, Chantres MT. Controlled trial of glycerol versus dexamethasone in the treatment of cerebral oedema in acute cerebral infarction. *Lancet* 1975; **1:** 1049–51.

12 Bayer AJ, Pathy MSJ, Newcombe R. Double-blind randomised trial of intravenous glycerol in acute stroke. *Lancet* 1987; **1:** 405–08.

13 Yu YL, Kumana CR, Lauder IJ, et al. Treatment of acute cortical infarct with intravenous glycerol: a double-blind, placebo-controlled randomized trial. *Stroke* 1993; **24:** 1119–24.

14 Cantore GP, Guidetti B, Virno M. Oral glycerol for the reduction of intracranial pressure. *J Neurosurg* 1964; **21:** 278–83.

15 Wald S, McLaurin RL. Oral glycerol for the treatment of traumatic intracranial hypertension. *J Neurosurg* 1982; **56:** 323.

16 Biestro A, Alberti R, Galli R, et al. Osmotherapy for increased intracranial pressure: comparison between mannitol and glycerol. *Acta Neurochir* (Wien) 1997; **139:** 725–33.

17 Casey TA, Trevor-Roper PD. Oral glycerol in glaucoma. *BMJ* 1963; **2:** 851–52.

18 Awasthi P, Srivastava SN. Role of oral glycerol in glaucoma. *Br J Ophthalmol* 1965; **49:** 660–66.

19 Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. Glycerol for acute stroke. *Cochrane Database Syst Rev* 2004; **2:** CD000096.

20 Frank MS, Nahata MC, Hilty MD. Glycerol: a review of its pharmacology, pharmacokinetics, adverse reactions, and clinical use. *Pharmacotherapy* 1981; **1:** 147–60.

21 Gilman AG, Goodman LS, Gilman A. Goodman and Gilman's the pharmacological basis of therapeutics, 6th edn. Harcourt; New York: 1980.

22 Bingel U, Andresen H, Liepert J. Acute encephalopathy due to glycerol over-consumption. *J Neurol* 2006; **253:** 125–26.

23 Thornit DN, Sander B, la Cour M, Lund-Andersen H. The effects of peroral glycerol on plasma osmolarity in diabetic patients and healthy individuals. *Basic Clin Pharmacol Toxicol* 2009; **105:** 289–93.

24 Singh R, Lehl SS, Sachdev A, Sood A, Malhotra HS. Reversible neurologic manifestation after glycerol: a short report. *Neurology India* 2001; **49:** 320–21.

25 UNAIDS 2008 Report on the global AIDS epidemic. UNAIDS 2008. http://www.unaids.org/en/dataanalysis/epidemiology/2008reportontheglobalaidsepidemic/ (accessed Jan 27, 2011).

26 Lewis DK, Callaghan M, Phiri K, et al. Prevalence and indicators of HIV and IADS among adults admitted to medical and surgical wards in Blantyre, Malawi. *Trans R Soc Trop Med Hyg* 2003; **97:** 91–96.

27 Wright J. The Glasgow outcome scale. http://www.tbims.org/combi/gos (accessed Jan 27, 2010).

28 WHO. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance, African Region. http://www.who.int/hiv/pub/guidelines/casedefinitions/en/ index.html (accessed May 5, 2010).

29 WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. http://www.wpro.who.int/wpdd/downloads/Diabetes_Book.pdf (accessed May 26, 2010).

30 Sankar J, P Singhi, A Bansal, Ray P, Singhi S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. *Indian Pediatrics* 2007; **44:** 649–56.

31 Rottenberg DA, Hurwitz BJ, Posner JB. The effect of oral glycerol on intraventricular pressure in man. *Neurology* 1977; **27:** 600–08.

32 Blaser C, Klein M, Grandgirard D, et al. Adjuvant glycerol is not beneficial in experimental pneumococcal meningitis. *BMC Infect Dis* 2010; **10:** 84.

33 Coursin D, Connery L, Ketzler J. Perioperative diabetic and hyperglycemic management issues. *Critical Care Medicine* 2004; **32:** S116–S125.

34 Capes S, Hunt D, Malmberg K, Pathak P, Gerstein H. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients. *Stroke* 2001; **32:** 2426–32.

35 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; **355:** 773–78.

36 Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycaemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87:** 978–82.

37 Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006; **61:** 284–89.

38 Donnelly S, Loscher C, Mills KH, Lynch MA. Glycerol-induced seizure: involvement of IL-1beta and glutamate. *Neuroreport* 1999; **10:** 1821–25.

39 Garcia-Sola R, Pulido P, Capilla P. The immediate and longterm effects of mannitol and glycerol. *Acta Neurochir* 1991; **109:** 114–21.

40 Nau R, Prins F, Kolenda H, Prange H. Temporary reversal of serum to cerebrospinal fluid glycerol concentration gradient after intravenous infusion of glycerol. *Eur J Clin Pharmacol* 1992; **42:** 181–85.

41 Pitlick WH, Pirikitakuhir R, Painter MJ, Wessel HB. Effects of glycerol and hyperosmolality on intracranial pressure. *Clin Pharmacol Ther* 1982; **31:** 466–71.

42 Guisado R, Tourtellotte WW, Arieff AI, Tomiyasu U, Mishra SK, Schotz MC. Rebound phenomenon complicating cerebral dehydration with glycerol. *J Neurosurg* 1975; **42:** 226–28.