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# What's new in bacterial meningitis

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Primary prevention of bacterial meningitis—predominantly through vaccination programs—is of paramount importance, since mortality and long-term disabling sequelae remain substantial [1]. Routine vaccination also offers herd immunity for the unvaccinated population [2]. The most illustrative example of such a major impact is the introduction of meningococcal conjugate vaccines [3]. Vaccination against serogroup A in Africa and serogroup C in Europe have decreased its incidence by 95 % or more [3]. A novel, four-component, recombinant, meningococcal serogroup B vaccine was shown to be immunogenic and safe in two randomized controlled trials testing infants and children [4]. Implementation of this vaccine may further decrease invasive meningococcal disease, but decreasing rates of penicillin susceptibility and the possible resurgence of the disease remain a public health threat [5]. Of concern is a recent international outbreak of MenC:cc11 disease among gay men, and the demonstrated expansion of MenW:cc11 disease in England and Wales, South Africa, and South America, which were associated with high case fatality rates [6]. Overall, the implementation of vaccines has resulted in a clear decrease in bacterial meningitis incidence in the past 20 years [7].

The recognition of urgency in acute bacterial meningitis remains problematic despite the certitude of the diagnosis and even in the setting of clinical trials delays in antibiotic initiation have been documented [8]. The maxim "time is brain" also applies to potentially ravaging bacterial central nervous system infections. Neuroimaging before lumbar puncture—perhaps ordered in more vexing presentations—is an important delay in administration of IV antibiotics and corticosteroids. A recent analysis suggests improvement in early antibiotic administration is feasible using clinical judgment rather than rigid protocols [9]. If imaging is performed before lumbar puncture, empiric treatment with antibiotics and, when indicated, dexamethasone should be administered before the patient is sent for neuroimaging. Moreover, blood cultures should be drawn because they identify the causative organism in 50–80 % cases [7, 10]. Dexamethasone therapy has been shown to be beneficial on a nationwide level, but has also been associated with secondary deterioration in sporadic patients. The cause of this delayed cerebral thrombosis remains to be elucidated but prolonged immunosuppressive therapy is currently advised [11].

Randomized clinical trials (RCTs) have recently evaluated several adjunctive therapies in meningitis. Antipyretic treatments are often administered in severely ill patients, but RCTs of 723 children with bacterial meningitis in Luanda, Angola, and 360 children in Malawi, showed that paracetamol did not increase survival [12, 13] (Table 1). Case series reported favorable effects of moderate hypothermia in bacterial meningitis, but one RCT showed that moderate hypothermia did not improve outcome in patients with severe meningitis, and even suggested harm [14]. Initial RCTs suggested that glycerol could reduce hearing loss and neurologic sequelae in children with bacterial meningitis [15].

**Table 1** Recent and ongoing clinical trials in bacterial meningitis

| Study | Population | Intervention | Sample size | Trial result or if ongoing trial number |
|---|---|---|---|---|
| Mourvillier et al. [14] | Adults, France | Hypothermia vs. normothermia | 98 | Hypothermia is associated with increased mortality |
| Ajdukiewicz et al. [16] | Adults, Malawi | Glycerol vs. placebo | 265 | Glycerol is associated with increased mortality |
| Molyneux et al. [12] | Children, Malawi | Glycerol vs. placebo | 360 | No difference between glycerol and placebo |
| | | Acetaminophen | 360 | No difference between acetaminophen and placebo |
| Pelkonen et al. [13] | Children, Angola | Paracetamol vs. placebo | 723 | No difference in overall mortality or sequelae |
| Pelkonen et al. (2012) | Children, Angola | Continuous antibiotics plus paracetamol vs. bolus antibiotics plus placebo | 400 | NCT01540838 |
| Cabellos et al. (2012) | Adults, Spain | Prophylactic phenytoin vs. placebo | 122 | NCT01478035 |

However, in 2011, an RCT in Malawian adults with bacterial meningitis was stopped early because of higher mortality in the glycerol-treated patients as compared to placebo (63 vs. 49 %) [16]. A subsequent study from Malawi, including 360 children with bacterial meningitis, also showed no benefit of glycerol with comparable mortality, rates of hearing loss, and sequelae in glycerol- and placebo-treated patients [12].

Some have advocated early intracranial pressure monitoring, aggressive treatment of brain edema with high doses of corticosteroids, osmotic diuretics, decompressive craniectomy, and ventriculostomy when there is hydrocephalus, but there is no conclusive evidence of improved outcome except in anecdotal cases [17–19]. The most important variable is initial management and appropriate treatment with antibiotics within an hour of arrival in the emergency department.

Seizures occur in 17 % of adults with bacterial meningitis and are associated with poor outcome [20]. Seizures and status epilepticus (non-convulsive and convulsive) require immediate attention, but treatment must be better defined. Detection of seizures may require continuous EEG monitoring but management of periodic epileptiform discharges—once found—has not been proven to change outcome and serious concerns remain about over-aggressiveness and side effects of anesthetics.

Patients with fulminant bacterial meningitis are critically ill and can survive with neurointensive care. Septic shock accompanies acute bacterial meningitis in 20 % and may progress rapidly when antibiotic treatment is delayed [19, 21]. Early intensive care treatment of septic shock is pertinent to avoid death from multiorgan failure.

New developments in bacterial meningitis research include genetic association studies that have identified genetic variation in the complement activation to influence both susceptibility and outcome of disease [22]. This has led to new adjunctive treatment strategies such as complement inhibition, which may be tested in bacterial meningitis patients in the upcoming years [22]. Other preclinical research includes inhibitors of metalloproteinases which were shown to decrease brain damage in experimental studies [23]. Finally, evaluation of different antibiotic regimens may shed light on whether bacteriostatic antibiotics such as rifampicin have a superior efficacy compared to bacteriolytic regimens [24].

To epitomize, the incidence of bacterial meningitis has been decreasing owing to the development of effective vaccines in the past decades. Widespread introduction of conjugate vaccines, especially where disease burden is greatest, is likely to further decrease the global burden of acute bacterial meningitis. There is still an urgent need for new treatment options and refinement of emergency and neurocritical care. Delay in diagnosis and treatment remain the major concerns in the management of acute bacterial meningitis. De-escalation of care may be the most common reason for death in patients who remain

comatose after fulminant meningitis. Early withdrawal may be inappropriate because even patients who are nearly moribund may actually survive and some of them may fully recover.

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**Compliance with ethical standards**

**Conflicts of interest** All authors declared that they have no conflicts of interest.



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