Updating the diagnosis of bacterial meningitis

The gold standard for the diagnosis of acute bacterial meningitis is the detection of viable bacteria from the cerebrospinal fluid (CSF) by culture. Indirect evidence of inflammation in the CSF, such as pleocytosis with predominant neutrophils, elevated protein, and hypoglycorrhachia, is often used as a surrogate of acute bacterial meningitis to guide empirical treatment where no pathogen is identified from CSF. The use of PCR for the detection of bacterial DNA from CSF is now rapidly becoming widespread. Although this approach is more sensitive than culture, it challenges the standard clinical approach to diagnosis and management of acute bacterial meningitis. All the basic clinical symptoms and signs of acute bacterial meningitis with CSF changes that are traditionally described in the literature are based on the use of culture as the gold standard. Several studies that have compared the yield from bacterial culture with PCR have found that 30–50% of culture-negative CSF specimens are positive according to PCR.[1-4] This finding has implications for the quality of patient care at locations where there are no PCR diagnostics because most of these patients will, at best, be offered only treatment regimens for presumed sepsis, which is suboptimal for treating acute bacterial meningitis both in terms of antibiotic dosage and duration of treatment.

In clinical practice, most patients with a clinical diagnosis of acute bacterial meningitis are offered prescription antibiotics or gain access to non-prescription antibiotics before obtaining CSF (a frequent occurrence in less developed countries), and this approach compromises the yield of viable bacteria from CSF; thus, the detection of bacterial DNA by PCR offers clinically relevant data. However, basic questions about the clinical relevance of bacterial DNA in CSF remain mainly unanswered. Much of the data from CSF PCR have been obtained from patients with a clinical suspicion of acute bacterial meningitis, and determining the test specificity is problematic in such settings. In particular, situations in which PCR test results are positive for a bacterial agent occur without CSF pleocytosis or presence of herpes viruses (such as human herpes virus 6 or cytomegalovirus), often creating a management dilemma for physicians.

Experimental animal models of sepsis have reported associated neuronal damage following the induction of pneumococcal bacteremia in as little as 12 hours.[5] These neuronal changes were not associated with the detection of bacteria in CSF, but these experiments did not screen CSF using PCR techniques.[5] Whether bacterial DNA can translocate asymptomatically through the blood–brain barrier, choroid plexus, or through the circumventricular organs, or how long bacterial DNA persists in the CSF after acute bacterial meningitis are unknown. Given the paucity of inflammatory modulators in the CSF, bacterial DNA will be unlikely to stimulate significant inflammatory response in the CSF. Exploring the use of PCR for the diagnosis of pneumococcal bacteremia has not been very successful due to a high rate of false positives at locations where the prevalence of asymptomatic nasopharyngeal carriage is high.[6] Perhaps the notion of meningeal inflammation as defined in acute bacterial meningitis should now be considered as continuous, with the detection of viable bacteria in the CSF by culture representing the extreme of disease severity. Exploratory studies for the detection of bacteria DNA in the CSF of people without meningeal signs will be very informative for ascertaining the clinical interpretation of this finding.

Results from the multiple studies that have evaluated PCR in the diagnosis of acute bacterial meningitis question the current dogma that diagnosis should solely depend on CSF culture, and in addition raises the question of whether patients in need of CSF evaluation for acute bacterial meningitis are being accurately identified. The decreased incidence of acute bacterial meningitis in high-income countries, due in large part to the widespread use of conjugate vaccines, has resulted in fewer opportunities for obtaining CSF, affecting the availability of CSF samples to assist in addressing this question. However, the burden of disease remains high in low-income and middle-income countries, particularly in locations where perennial outbreaks of meningitis occur on such a large scale that doing the procedure on all patients is not practical.

Future research is needed to better describe the continuum of illness from the early stages of CNS inflammation (with pathogen detection by PCR or culture) to resolution of active bacterial replication and inflammation, presumably followed by loss of PCR

positivity once all organisms are cleared, and finally a return to normal CSF biochemical parameters. Such studies might guide modifications in the approach to treatment of acute bacterial meningitis. In addition, although inflammatory responses in acute bacterial meningitis are mainly restricted to astrocytes and other glial cells, ascertainment of how much of these responses can be detected in the peripheral blood warrants examination. Identification of a surrogate marker of acute bacterial meningitis from blood (perhaps through transcriptomics) will be an invaluable diagnostic capability.

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I declare no competing interests.

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A necessary discussion after transmission of multidrug-resistant organisms through faecal microbiota transplantations

On June 13, 2019, the US Food and Drug Administration (FDA)[1] issued a safety alert concerning the risk of serious adverse reactions due to transmission of multidrug-resistant organisms through faecal microbiota transplantations (FMTs). This alert was in response to transmission of an extended-spectrum β-lactamase-producing *Escherichia coli* strain from a faeces donor to two immunocompromised recipients. One of the individuals died, but the report does not provide information on the cause of death. For reasons not specified, the donor had not been screened for multidrug-resistant organisms. The FDA now requires inclusion of multidrug-resistant organism screening into all active and future FMT-based study protocols.

The use of FMT for the treatment of patients with recurrent *Clostridioides difficile* infections is recommended by clinical guidelines worldwide.[2,3] Experts in different countries have established stool banks that provide safe and effective FMT products for the treatment of these infections and for use in trials assessing other indications. All major stool banks have implemented screening protocols to detect multidrug-resistant organisms and exclude potential donors who test positive.[4-6] No serious adverse reactions due to transmission of multidrug-resistant organisms have been observed in more than 45 000 FMT treatments supported by OpenBiome, a non-profit stool bank, founded in 2012 in Cambridge, MA, USA, and in randomised controlled trials assessing other indications.[7] Transmission of multidrug-resistant organisms was also absent in a systematic review of 50 publications reporting 78 types of adverse events of FMT and in a retrospective analysis of FMT in 99 immunocompromised patients.[8,9] Adherence to standard screening protocols used by major stool banks worldwide is most likely to have prevented these incidents, even though this speculation is uncertain due to limited information available from the FDA alert.

These incidents, however, point to another important discussion in the field of FMT. Should donors whose faeces are to be used for the treatment of immunocompromised patients undergo more extensive screening for potential pathogens than individuals donating to immunocompetent patients? In this