Can broad-range 16S ribosomal ribonucleic acid gene polymerase chain reactions improve the diagnosis of bacterial meningitis? A systematic review and meta-analysis

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CRD summary
This review concluded that high sensitivity and specificity values supported the use of 16S ribosomal ribonucleic acid gene polymerase chain reaction test as an adjunctive tool for the diagnosis of bacterial meningitis. The review was generally well conducted and the authors’ conclusions reflect the data presented and are likely to be reliable.

Authors’ objectives
To assess the performance of broad-range 16S ribosomal ribonucleic acid (rRNA) gene polymerase chain reaction (PCR) test for the diagnosis of bacterial meningitis.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched, without language restriction; search terms, but not dates were reported. The bibliographies of review articles were screened for additional studies.

Study selection
Studies which assessed the performance of 16S PCR for the diagnosis of meningitis caused by any bacterial species were eligible for inclusion. Studies had to report adequate information to be included in the analysis.

“Proven” bacterial meningitis was defined by the growth of bacteria from cerebrospinal fluid culture. Culture-negative presumed bacterial meningitis was defined as reported in individual studies.

Studies included neonates, children and adults (age range 0 to 91 years). Studies used a variety of extraction processes and primers (details in article). PCR techniques included conventional PCR followed by agarose gel detection, and real-time PCR; half of the included studies performed bacterial identification with sequencing. Reported detection limits for PCR techniques varied between 3.25 and over 1,000 colony forming units/mL (cfu/mL).

Two reviewers assessed studies for inclusion and any disagreements were resolved by consultation with a third reviewer.

Assessment of study quality
The methodological quality of included studies was assessed by two reviewers using the 14-item QUADAS checklist. Any disagreements were resolved by consultation with a third reviewer.

Quality assessment was reported for the 14 studies included in the main review and for the four additional studies which only reported data on the performance of 16S PCR to detect bacteria in cases of culture-negative presumed bacterial meningitis.

Data extraction
Data were extracted on the numbers of true positive, false positive, false negative and true negative PCR test results, where “proven” bacterial meningitis was used as the reference standard. Sensitivity, specificity and positive and negative likelihood ratios with 95% confidence intervals were calculated. Data were also extracted on the ability of PCR to detect bacteria in cases of culture-negative presumed bacterial meningitis, where clinical suspicion of bacterial meningitis was high despite negative culture results. For studies using real-time PCR, the definition of a positive test provided by the individual studies, according to their predetermined cycle threshold limits, was used. Samples were excluded from the analyses if the sequencing or culture results identified bacteria considered contaminants by individual study authors.

Two reviewers independently extracted data.

Methods of synthesis
Pooled estimates of sensitivity and specificity, with 95% confidence intervals, were calculated for studies that used "proven" bacterial meningitis as the reference standard, using both the bivariate random-effects model and the hierarchic summary receiver operating characteristic (sROC) model. These were used to calculate summary positive and negative likelihood ratios.

The Cochran Q and $I^2$ tests were used to estimate between-study heterogeneity. Publication bias was assessed using Deeks's test for funnel plot asymmetry.

A summary of the performance of 16S rRNA PCR to detect bacteria in cases of culture-negative presumed bacterial meningitis, where the clinical suspicion of bacterial meningitis was high despite negative culture results was also provided.

**Results of the review**

Fourteen studies, with a total of 2,780 participants were included in the main review and meta-analysis. Some data were reported for four additional studies on 16S rRNA PCR for the detection of bacteria in cases of culture-negative presumed bacterial meningitis. The main areas of methodological weakness, across all 18 studies, were an inadequate description of the reference standard and a lack of clarity of whether 16S rRNA PCR results were interpreted without knowledge of the reference standard.

The pooled sensitivity and specificity estimates for 16S rRNA PCR for the detection of "proven" bacterial meninginitis were 92% (95% CI 75% to 98%; $I^2=79.2%$), and 94% (95% CI 90% to 97%; $I^2=98%$). The summary positive and negative likelihood ratios were 16.26 (95% CI 9.07 to 29.14) and 0.09 (95% CI 0.03 to 0.28).

Fifteen studies, including four studies which were not included in the main results or meta-analysis, provided estimates of the sensitivity of 16S rRNA PCR to detect bacterial pathogens in cases of culture-negative presumed bacterial meningitis; these ranged from 3% to 100%.

The Deeks's funnel plot asymmetry test indicated a low likelihood of publication bias.

**Authors' conclusions**

The high sensitivity and specificity estimates derived form this meta-analysis supported the role of 16S rRNA PCR as an adjunctive tool for the diagnosis of bacterial meningitis.

**CRD commentary**

The review reported a clear objective and defined appropriate inclusion criteria. Several sources were searched and no language restrictions were applied, which increased the likely yield of potentially relevant studies. An assessment of publication bias was included.

The review process included measures to minimise error and bias throughout and the appropriate meta-analytic methods were employed. Full details were lacking on the four studies that only reported data on the performance of 16S rRNA PCR to detect bacteria in cases of culture-negative presumed bacterial meningitis.

Overall, the authors' conclusions reflect the data presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that 16S rRNA PCR could provide early, accurate diagnosis of infection whilst decreasing antibiotic exposure and facilitating earlier discharge of non-infected patients. They further stated that the test may have been useful in patients with culture-negative presumed bacterial meningitis and those who received antibiotic therapy before lumbar puncture.

**Research:** The authors stated that further studies were needed to define the optimal methodology for 16S rRNA PCR.

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