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Brief Report

Concordance between blood and cerebrospinal fluid cultures in meningitis

Ryan J. Phillips [a,d], Kyle M. Watanabe [b], Jeffrey R. Stowell [a,b,c], Murtaza Akhter [a,b,c,*]

[a] Department of Emergency Medicine, University of Arizona College of Medicine–Phoenix, Phoenix, AZ, United States of America
[b] Department of Emergency Medicine, Maricopa Medical Center, Phoenix, AZ, United States of America
[c] Department of Emergency Medicine, Creighton University School of Medicine, Omaha, NE, United States of America
[d] University of Bath, Bath, UK

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ABSTRACT

Objective: To examine the association between cerebrospinal fluid (CSF) cultures and blood cultures in patients with suspected bacterial or fungal meningitis.
Methods: A 5-year retrospective chart review, conducted from April 2012 to January 2017 of consecutive patient encounters with bacterial or fungal organism growth in CSF culture, when a blood culture was also obtained. Patients were excluded if they received antibiotics prior to either lumbar puncture (LP) or blood culture acquisition, or if CSF cultures were positive for common bacterial skin contaminants. Descriptive statistics were used to characterize the dataset.
Results: 21 patient encounters met study inclusion criteria. 13 (61.9%; 95% CI 40.2–80.5%) had blood culture growth of the same organism as the CSF culture. 1 patient had a different organism in the blood culture compared to the CSF culture. 6 patients (33.3%, 95% CI 14.8%–56.9%) with positive CSF cultures had negative blood cultures.
Conclusions: Our results suggest an insufficient degree of agreement between CSF and blood culture results. PCR may be a prudent approach in patients requiring immediate antibiotics and delayed LP.

1. Introduction

Meningitis is a life-threatening emergency, requiring urgent investigation and treatment. It affects approximately 1.38 people per 100,000 in the United States, and even with treatment, is fatal in 14.3% of cases [1]. Definitive diagnosis requires cerebrospinal fluid (CSF) collection by lumbar puncture (LP) [2]. However, lumbar puncture (LP) can delay antibiotic treatment of meningitis owing to the time required to obtain computed tomography (CT) imaging of the head in cases where increased intracranial pressure is suspected, consent acquisition, procedural preparation, and difficulty in CSF collection.

Decreasing time to antibiotic administration in meningitis may lead to better patient outcomes [3,4]. However, administration of antibiotics before an LP can decrease the diagnostic accuracy of the CSF by sterilizing the culture [5]. Emergency Medicine as well as Infectious Disease guidelines suggests a high association between CSF and blood culture results, and thus recommend antibiotic treatment immediately after blood culture acquisition (in particular, if LP will be delayed) [2,6,7]. However, prior literature also suggests poor association between blood and CSF culture results [8]. Due to the discordance of these previous studies, we sought to examine the association between CSF and blood culture results in patients with suspected meningitis.

2. Methods

2.1. Study design

This is a 5-year retrospective chart review conducted between April 2012 to January 2017 of the electronic medical records of the adult and pediatric emergency departments at Maricopa Medical Center. The study was approved by the Institutional Review Board. The data were pulled by our head information scientist, who is trained in the Structured Query Language (SQL) language behind the data in EPIC (EPIC is our electronic health record). He was blinded to the study hypothesis. The SQL query involved searching for all patients who were registered in the emergency department within the aforementioned time period AND who

* Corresponding author at: Department of Emergency Medicine, University of Arizona College of Medicine–Phoenix, ABC-1 Bldg. Room 319, 425 N. 5th St., Phoenix, AZ 85004-2157, United States of America.
E-mail address: murtazaakhter@gmail.com (M. Akhter).

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had growth in their CSF culture. Our Epic platform flags all results from CSF culture that show any growth. The query pulled all (emergency department) patients who were flagged with positive CSF cultures. Additional information obtained included blood culture results, time (hour) when cultures were drawn, and time (hour) when first antibiotics were given. These values were added to a standard chart abstraction form provided to us by our research department, and age and gender data were also added. No other patient specific information, including race or ethnicity, was collected. Accuracy of the SQL data-pull was confirmed by pulling charts of patients who were ultimately diagnosed with "meningitis." We cross-referenced a sample of these patients with those from our information scientist's original data pull and, through individual patient chart review, confirmed that the patients diagnosed with meningitis who did not show up in the original data pull were those who were presumed by the clinicians to have had viral meningitis (none of these patients had any growth in their CSF cultures).

2.2. Patient inclusion and exclusion criteria

Patients were included if they had a positive CSF culture and a blood culture had been obtained. Patients were excluded if the CSF culture was positive for common bacterial skin contaminants, namely, coagulase-negative staphylococci, aerobic and anaerobic diphtheroids, Micrococcus spp., Bacillus spp., and viridans group streptococci [9]. Other exclusion criteria included antibiotic administration prior to either lumbar puncture performance or blood culture administration. Two patients had multiple CSF cultures performed during the data abstraction period, and both had one positive and one negative culture each. These cultures were separated by time, and the encounters without CSF culture growth were excluded whereas those with growth were included in the study (as the goal was to assess concordance of blood cultures in patients *positive* for CSF culture growth). Additionally, chart review was performed on each meningitis (based on CSF) patient to assess if the patient had clinical meningitis.

2.3. Data analysis

Microsoft Excel (Microsoft Corp., Redmond, WA) was used to create (de-identified) tables and perform calculations. Calculations were also performed on openepi.com. Confidence intervals around proportions are created using the mid-p exact method.

3. Results

3.1. Patient exclusion

29 patient encounters ranging in age from 1 month to 69 years with positive CSF culture results were identified. 6 patients were excluded for CSF cultures that were positive for common skin contaminants. 2 additional patients were excluded because no blood cultures were obtained. A descriptive analysis of the remaining 21 patient encounters was performed.

1.2. Pediatric Concordance Results

Of the remaining 21 patients, 6 were ≤18 years of age. Organisms identified in the CSF culture of this pediatric population included *Escherichia coli* (2), *Haemophilus influenzae* (2), Klebsiella oxytoca (1), and *Streptococcus pyogenes* (1). There was concordance in CSF and blood culture isolates for both *H. influenzae* patients, one of the *E. coli* patients and the one *S. pyogenes* patient. No growth was seen in the blood culture of the other *E. coli* patient nor in that of the patient with Klebsiella oxytoca. This represented a 67% (4/6) concordance of CSF and blood cultures. (Table 1) All six of these patients had clinical meningitis confirmed by chart review.

Table 1
CSF cultures compared to blood cultures in pediatric patients ($n = 6$). *E. coli = Escherichia coli, H. influenzae = Haemophilus influenza, K. oxytoca = Klebsiella oxytoca, S. pyogenes = Streptococcus pyogenes*

Age	Gender	CSF culture	Blood culture
2 m	f	*E. coli*	No growth 5 days
4 m	f	*E. coli*	*E. coli*
2	f	*H. influenzae*	*H. influenzae*
4	f	*K. oxytoca*	No growth 5 days
7	m	*H. influenzae*	*H. influenzae*
8	f	*S. pyogenes*	*S. pyogenes*

3.2. Adult concordance results

Amongst adult patients, CSF cultures were positive for *Cryptococcus neoformans* (6), *Escherichia coli* (2), *Staphylococcus aureus* (2), *Neisseria meningitidis* (2), *Pseudomonas aeruginosa* (1), *Haemophilus influenzae* (1), *Enterobacter cloacae* (1) and *coccidioides immitis* (1). There was a 60% (9/15) concordance between CSF cultures and blood cultures. In particular, 5 patients with positive CSF had negative blood cultures, and 1 patient had a different organism (contaminant) grow from the CSF culture as compared to the blood culture result (Table 2). All 15 patients, per chart review, were treated as clinical meningitis patients. One patient had cervical epidural abscess with bacteremia (both *Staphylococcus aureus*) but, as mentioned, was covered with antibiotics for meningitis as well. Of note, of the 6 adult patients with positive CSF cultures for *Cryptoccoccus neoformans*, 83% (5/6) were AIDS-positive, with CD4 counts well below 200. The remaining patient was HIV-negative.

3.3. Combined concordance results

Overall (combing adults and children), 13/21 (61.19%; 95% CI 40.2–80.5%) had blood culture growth of the same organism as the CSF culture. Of the remaining 8/21 blood cultures, 7 had no growth and 1 grew a contaminant.

4. Discussion

Meningitis is a life-threatening infection. The traditional gold standard for diagnosis is CSF analysis with culture. However, it is

Table 2
CSF cultures compared to blood cultures in adult patients ($n = 15$). *C. immitis = Coccidioides immitis, C. neoformans = Cryptococcus neoformans E. cloacae = Enterobacter cloacae, E. coli = Escherichia coli, H. influenzae = Haemophilus influenza, N. meningitidis = Neisseria meningitides, P. aeruginosa = Pseudomonas aeruginosa, S. aureus = Staphyloccocus aureus, S. epidermidis = Staphylococcus epidermidis*

Age	Gender	CSF culture	Blood culture
26	m	*P. aeruginosa*	No growth 5 days
29	m	*C. neoformans*	*C. neoformans*
30	m	*C. neoformans*	*C. neoformans*
34	f	*N. meningitidis*	No growth 5 days
36	m	*E. cloacae*	*S. epidermidis*
36	m	*S. aureus*	No growth 5 days
37	m	*C. neoformans*	*C. neoformans*
40	f	*E. coli*	*E. coli*
42	f	*N. meningitidis*	*N. meningitidis*
42	m	*S. aureus*	*S. aureus*
44	m	*C. immitis*	No growth 5 days
46	m	*C. neoformans*	*C. neoformans*
46	m	*C. neoformans*	*C. neoformans*
61	f	*H. influenzae*	*H. influenzae*
69	m	*C. neoformans*	No growth 5 days

generally accepted that in cases of suspected bacterial or fungal meningitis, an LP should not delay the administration of empiric antibiotics [3,4,7]. However, antibiotic administration prior to LP can yield false negative cultures, thereby limiting the ability not only to isolate the organism but to also assess for antibiotic sensitivity and resistance. Previous literature suggests that blood cultures – which can more easily be obtained and therefore be performed without delaying antibiotics – are sufficiently sensitive to identify the culprit organism [2,6]. However, others have suggested that there is little correspondence between blood and CSF culture results [8].

This retrospective study sought to explore whether there is reliable agreement between CSF and blood culture results in patients with suspected bacterial or fungal meningitis. Our results suggest an insufficient degree of agreement between CSF cultures and blood cultures. Using CSF as the standard, blood cultures in our study showed only 61.2% sensitivity.

Our study has multiple limitations. The generalizability of the study findings is restricted as this is a relatively uncommon disease process evaluated at a single center. Additionally, a significant portion of CSF results contained likely skin flora contamination (9/29, 31.0%), which reduced the sample size. Furthermore, we are not reporting measures such as specificity, predictive value, etc., as the goal of this paper is not to assess the accuracy of the blood culture as a standard for meningitis but rather to evaluate its concurrence with CSF results. For example, it is possible that there were patients diagnosed with bacterial or fungal meningitis even with negative CSF cultures (for example, based on clinical symptoms or based on only blood cultures), and our study would not have included these patients because our study analyzed only patients with positive CSF cultures by definition. As mentioned in our methods, we did analyze a sample of patients who were diagnosed with meningitis despite negative CSF results and all these patients were deemed to have viral meningitis. However, there may be patients missed, and furthermore, patients *without* a diagnosis of meningitis who had negative CSF cultures would not have been picked up in our data pull. Therefore, we are unable to provide full diagnostic test characteristics of blood cultures, but are rather reporting their concurrence with CSF results.

Our findings perpetuate the meningitis diagnostic conundrum – on one hand, early antibiotics improve outcomes [3,4,7]; however, unreliable CSF culture results limit the provider's ability to narrow the antibiotic regimen and therefore can cause unnecessary personal and population-wide antibiotic side effects [10].

One emerging alternative technique to the current gold standard of CSF cultures is molecular diagnostics – in particular, Polymerase Chain Reaction (PCR). PCR is a DNA amplification technique that demonstrates high potential for rapid detection and species identification in meningitis. Current literature suggests high sensitivity and specificity [5,10]. Moreover, PCR is *significantly* more sensitive than CSF culture for identifying the causative organism in meningitis patients who receive antibiotics prior to LP. For example, when LP is performed after antibiotics but within the same day, CSF cultures have only 27% sensitivity whereas PCR still has 100% sensitivity [5]. In patient presentations that are highly concerning for meningitis, a prudent approach may be to initiate early antibiotics and perform PCR of CSF fluid obtained from delayed LP. This approach could improve outcomes via early antibiotic administration while still allowing for the ability to detect the causative organism.

Future approaches may involve metagenomic next generation sequencing (NGS), which can catch organisms that traditional tests are unable to [11]. However, NGS is a very recent advancement and more validation is needed.

In conclusion, blood cultures are insufficiently sensitive to diagnose bacterial or fungal meningitis. Further research should investigate whether NGS or PCR of CSF – particularly in patients who need pre-LP antibiotics – are reliably predictive tests for meningitis.

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Declarations of Competing Interest

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