# Cerebrospinal fluid indices and culture concordance with blood in neonates with culture-proven meningitis

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**Background.** Diagnosing meningitis in sick neonates is challenging because they are often unstable for lumbar puncture (LP). In this scenario, antibiotic selections are based on positive blood culture (BC), assuming concordance between blood and cerebrospinal fluid (CSF) cultures. The value of CSF cultures is diminished when LP is performed after initiating antibiotics. Therefore, CSF white cell count (CSF-WCC) and chemistry serve as proxies for diagnosing meningitis.
**Objective.** To assess concordance between blood and CSF cultures and identify differences in CSF-WCC and protein levels between positive and negative CSF cultures.
**Methods.** We enrolled neonates who had both CSF and BCs taken for sepsis workup. Comparisons between blood and CSF cultures were performed to assess concordance. CSF-WCC and protein level discrepancies were compared between positive and negative CSF cultures.
**Results.** Ultimately, 448 neonates over 12 months met the criteria. Among those with positive BC results, 16.7% had positive CSF cultures, whereas for those with culture-positive CSF, 59.2% had positive BC. The concordance of organisms was 82.8% among those with positive blood and CSF cultures. Among neonates with culture-positive CSF, 24.5% and 59.3% had abnormal CSF-WCC and protein levels, respectively. Neonates with a positive CSF culture, compared with a negative culture, had higher CSF-WCC (24.5% v. 10.4%; $p<0.001$) and protein levels (59.3% v. 37.5%; $p<0.001$).
**Conclusion.** High proportion of neonates with positive CSF cultures had negative BCs. Therefore, meningitis cannot be excluded based on negative BC without LP, for normal CSF-WCC and protein levels without CSF culture results do not exclude meningitis.

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Diagnosing meningitis during the neonatal period is critical due to its elevated risk and the potential for significant morbidity and mortality, especially when not appropriately treated.[1,2] Diagnosing meningitis in neonates poses a major challenge owing to the subtle and non-specific nature of its signs in this population. Additionally, neonates may present severely ill and unstable, making it difficult to tolerate lumbar puncture (LP), often resulting in delays in performing LP. In most instances, when the neonate is stable enough for LP, antibiotics have already been administered, rendering culture results less helpful as they are most likely to be negative. The difficulties in performing LP in neonates involve determining the correct positioning during the procedure (sitting v. prone) and addressing the potential trauma caused by the size of the spinal needle. CSF result interpretation also varies according to gestational age, days of life as the blood-brain barrier matures, an overlap of values between uninfected and infected neonates and a wide range of CSF parameters. Since it is difficult to perform an LP in neonates, some clinicians assume concordance between blood and cerebrospinal fluid (CSF) culture results, therefore, they may wait for BC results before performing an LP.

Reportedly, 38% of neonates with culture-proven meningitis have negative BCs, therefore relying on BC results before performing a lumbar puncture might be inappropriate.[3,4] In cases where both sites have positive cultures, the discordance in the type of organism ranges from 3.5 – 49%.[3,5]

In cases where CSF culture results are negative, the diagnosis of meningitis is based on abnormalities in CSF indices, specifically elevated white cell count (WCC) and protein levels. The CSF protein and CSF- WCC are reported to have a sensitivity of 76% and 79%, respectively.[3] Most studies reporting on meningitis are from high-income countries where the burden of sepsis is relatively low compared with low-and middle-income countries. The causes of culture-proven meningitis, and the proportion of culture-proven meningitis with abnormalities in CSF indices are not well described in sub-Saharan Africa countries. The knowledge of meningitis-causing pathogens will assist attending clinicians in choosing appropriate empiric antimicrobials when meningitis is suspected, and where LP cannot be conducted. In addition, understanding the abnormalities in CSF indices among patients with positive CSF culture will aid clinicians in assessing the likelihood of meningitis in situations where a patient is suspected to have meningitis, and CSF culture is either falsely negative or unavailable. Our study objectives were to describe the organisms causing meningitis in our neonatal population, assess concordance between CSF and BC results and determine the proportion of neonates with high CSF-WCC and protein levels among neonates with positive CSF cultures.

## Methods

### Study design and population

This was a retrospective analytical study conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa. The study population comprised neonates with suspected sepsis admitted to the neonatal unit at CHBAH who underwent LP between 1 January 2017 and 31 December 2017, and had positive blood and/or CSF cultures. The inclusion criteria were all neonates who had both CSF and BC results recorded in the National Health Laboratory Services (NHLS) database. Among positive cultures, *Corynebacterium* spp, *Bacillus* spp and coagulase-negative *Staphylococcus* were considered contaminants, thus, those with positive cultures for these bacteria were excluded from the analysis. Only cultures from neonates who were aged ≤30 days were included.

#### Study setting

CHBAH is a public, tertiary, referral hospital for community health centres in Soweto and surrounding areas and also a referral centre for surgical services for neonates from the local district and regional hospitals. The hospital performs ~20 000 of the 33 000 annual births in Soweto. The neonatal unit at CHBAH has 185 beds. Neonates born at CHBAH requiring admission are admitted from the delivery room. Neonates born at other facilities, who have never left that facility, are referred to the neonatal unit at CHBAH for tertiary care. These admitted neonates remain in the neonatal unit until discharged home or, unfortunately, in the event of death. For neonates with suspected sepsis on admission, only full blood count and BC are performed. LP is only performed if the BC is positive, or the neonate has abnormal neurological signs indicative of meningitis. LP is performed at the time of the work-up for sepsis in neonates with suspected hospital-acquired infection, but it is deferred if the neonate is critically ill. LP is not recommended for neonates with suspected infection soon after birth unless their BC results come back positive. The collection of blood and CSF samples is done following an aseptic technique. The recommendation is that at least 1 mL of blood for BC, and at least 10 drops of CSF for biochemistry and culture are collected. The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (ref. no. M180289).

### Data sources and data collection

The study included neonates with recorded results for both CSF and BC in the NHLS database. The laboratory measurements assessed were BC results, CSF cell count, protein, and culture. The local microbiology laboratory uses an automated continuous monitoring BC system, the BacT/Alert system (BioMerieux, France).

### Data definitions

Concordance between blood and CSF cultures was assessed by comparing specimen results taken within a 7-day interval. Among neonates with positive blood and CSF cultures, concordance was assessed by comparing organisms isolated in the two specimens. High CSF-WCC was defined as total WCC >20 cells/mm$^3$[6] and high CSF protein was defined as protein levels >150 mg/dL.[7] Bloody CSF tap was defined as CSF with a red blood cell count ≥500 cells/mm$^3$.[8] Concordance was defined as the same organism being cultured in both CSF and BCs within 7 days of collection.

### Data analysis

Data were captured into an Excel spreadsheet and analysed using Statistica (StatSoft, USA). The $\chi^2$ test was employed to compare the proportion of patients with abnormalities in CSF parameters among various organisms or between culture-positive and negative CSF samples. $P<0.05$ was considered statistically significant.

## Results

### Results of cultures and identified organisms isolated from blood and/or cerebrospinal fluid samples of neonates

Initially, 448 neonates had BCs and LP performed during the 12 months, with at least one of these having a positive result. Among them, 22 had culture-positive CSF with organisms considered to be contaminants, thus, the analysis only included data from 426 neonates. Of these, 382 and 108 had positive blood and CSF cultures, respectively. Among the 382 with positive BCs, 64 (16.7%) had positive CSF cultures. Of the 108 with positive CSF cultures, 64 (59.2%) had positive BCs. In cases with concomitant positive blood and CSF cultures, 82.8% revealed the presence of the same organism in blood and CSF samples (Fig. 1).

Gram-negative bacteria were the most predominant type of organisms isolated in the blood (66.0%) and CSF (78.7%) cultures (Table 1). The most common bacteria isolated from BCs were *Acinetobacter baumannii* (31.9%) and *Klebsiella pneumoniae* (26.4%). These two were also the most common in CSF cultures at 50.9% and 18.5%, respectively. Among Gram-positive bacteria, the common bacteria from BCs were Enterococcus species (4.71%), including *Enterococcus faecium* (2.62%) and *Enterococcus faecalis* (2.09%), and *Staphylococcus aureus* (4.19%). In the CSF cultures, the common Gram-positive bacteria were the Enterococcus species (9.26%), including *Enterococcus faecium* (6.48%) and *Enterococcus feacalis* (2.78%), and *Streptococcus viridans* (4.63%). The most common Candida species were *Candida parapsilosis* in the blood (11.8%) and *Candida albicans* in the CSF (2.78%).

### Concordance of positive culture results from blood and CSF

The overall concordance rate of organisms between positive blood and CSF cultures was 82.8% (Table 2). No differences were observed in concordance rates among specimens taken within 24 hours compared with those taken ≥24 hours of each other (85.3% v. 80%; $p$=0.575). There was a higher rate of concordance in organisms between blood and CSF culture among neonates who had a bloody tap compared with those who did not (93.1% v. 70.0%; $p$=0.023).

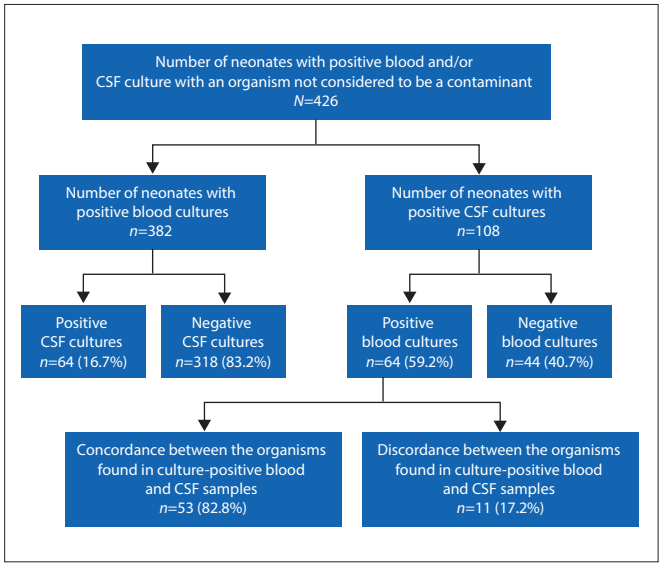


*Fig. 1. Number of neonates who had both blood and CSF taken for culture and concordance of culture results between blood and CSF.*

### Abnormalities in CSF cell count and protein levels in neonates with positive blood and/or CSF cultures

Of the 108 culture-positive CSF samples, 102 had available CSF-WCC results (Table 3). Forty-seven (46.1%) were considered bloody taps (CSF-RBC ≥500 cells/mm$^3$). Only 24.5% of the 102 culture-positive CSF samples with cell count results had CSF-WCC >20 cells/mm$^3$. Eighty-six culture-positive CSF samples had recorded protein levels, with 59.3% exhibiting >150 mg/dL levels of CSF protein. Among positive CSF cultures, no significant differences were noted in CSF-WCC (29.8% v. 20.0%, $p$=0.252) and CSF protein (71.4% v. 51.0%; $p$=0.058) between those with a bloody tap and those without. Among the 318 culture-negative CSF samples, 317 had CSF-WCC results recorded, of those, only 10.4% had a CSF-WCC >20 cells/mm$^3$. Eighty-eight of the culture-negative CSF samples (27.8%) were bloody taps. The proportion with high CSF-WCC was higher among those with bloody tap than in those with no bloody tap (15.9% v. 8.30%; $p$=0.003). Of the 307 culture-negative CSF samples, 304 had protein levels recorded and 114 (37.5%) had CSF protein levels >150 mg/dL. There was a higher proportion of neonates with high protein levels among those with a bloody tap compared with those without (55.9% v. 30.4%; $p$<0.001).

Overall, a higher proportion of culture-positive CSF samples had elevated CSF-WCC (24.5% v. 10.4%; $p$<0.001) or increased protein levels (59.3% v. 37.5%; $p$<0.001) than in culture-negative CSF samples. In grouping the CSFs into bloody and non-bloody taps, similar differences were noted in CSF samples that were not bloody; CSF-WCC (20.0% v. 8.3%, $p$=0.011) and protein (51.0% v. 30.4%, $p$=0.005), but not in those that were bloody; CSF-WCC (29.8% v. 15.9%, $p$=0.058) and protein (71.4% v. 55.9%, $p$=0.116) between the culture-positive and culture-negative CSF.

## Discussion

The main findings of this study revealed that only 16.7% of neonates with positive BCs exhibited culture-proven meningitis, while 40.8% of neonates with culture-proven meningitis showed negative BCs. The common organisms causing culture-proven meningitis were Gram-negative bacteria, including *Acinetobacter baumannii* and Klebsiella species. Blood and CSF cultures were

**Table 1. Organisms isolated in neonates with positive blood and/or cerebrospinal fluid cultures**

| Organisms | Blood, *n* (%) (*N*=382) | Cerebrospinal fluid, *n* (%) (*N* = 108) |
|---|---|---|
| Gram-negative | *N*=252 (66.0) | *N*=85 (78.7) |
| *Acinetobacter baumannii* | 122 (31.9) | 55 (50.9) |
| Klebsiella species | 101 (26.4) | 20 (18.5) |
| Pseudomonas species | 5 (1.31) | 2 (1.85) |
| *Escherichia coli* | 10 (2.62) | 2 (1.85) |
| Enterobacter species | 9 (2.36) | 3 (2.78) |
| Others | 5 (1.31) | 3 (2.78) |
| Gram-positive | *N*=61 (16.0) | *N*=19 (17.6) |
| Enterococcus species | 18 (4.71) | 10 (9.26) |
| *Streptococcus viridans* | 6 (1.52) | 5 (4.63) |
| *Staphylococcus aureus* | 16 (4.19) | 2 (1.85) |
| Group B Streptococcus | 9 (2.36) | 1 (0.93) |
| *Listeria monocytogenes* | 10 (2.62) | 1 (0.93) |
| Others | 2 (0.52) | 0 (0) |
| Candida and other fungi | *N*=69 (18.1) | *N*=4 (3.70) |
| *Candida albicans* | 17 (4.25) | 3 (2.78) |
| *Candida parapsilosis* | 45 (11.8) | 1 (0.93) |
| Other fungi | 7 (1.83) | 0 |

**Table 2. Concordance in organisms among those with positive blood and cerebrospinal fluid cultures**

| | Positive blood and CSF, *n* (%) | Same organisms, *n* (%) | Different organisms, *n* (%) |
|---|---|---|---|
| Time interval between specimens* | | | |
| Within 24 hours | 34 (53.1) | 29 (85.3) | 5 (14.7) |
| 24 - 48 hours | 23 (35.9) | 18 (78.2) | 5 (21.7) |
| >48 hours | 7 (10.9) | 6 (85.7) | 1 (14.3) |
| All | 64 | 53 (82.8) | 11 (17.2) |
| Bloody tap status†‡ | | | |
| Bloody tap | 29 (49.1) | 27 (93.1) | 2 (6.90) |
| No bloody tap | 30 (50.8) | 21 (70.0) | 9 (30.0) |
| All | 59 | 48 (81.4) | 11 (18.6) |

CSF = cerebrospinal fluid.
*$p$=0.575 when comparing concordance in specimens taken within 24 v. ≥24 hours of each other.
†Five cerebrospinal fluid samples were not recorded to indicate whether they were bloody taps or not.
‡$p$=0.023 when comparing concordance in those with bloody taps and those without.

**Table 3. Abnormalities in cell count and protein in neonates with positive blood and/or cerebrospinal fluid culture**

| | Total positive CSF culture, *n* (%) | Positive CSF culture with bloody tap, *n* (%) | Positive CSF culture without bloody tap, *n* (%) | Total Negative CSF Culture, *n* (%) | Negative CSF culture with bloody tap, *n* (%) | Negative CSF culture without bloody tap, *n* (%) |
|---|---|---|---|---|---|---|
| | *N*=108 | 47 (46.1) | 55 (53.9) | *N*=318 | 88 (27.8) | 229 (72.2) |
| Cell count >20/mm$^3$ | 25/102 (24.5)* | 14/47 (29.8) | 11/55 (20.0) | 33/317 (10.4)* | 14/88 (15.9) | 19/229 (8.30) |
| Protein >150 mg/dL | 51/86 (59.3)† | 25/35 (71.4) | 26/51 (51.0) | 114/304 (37.5)† | 47/84 (55.9) | 67/220 (30.4) |

CSF = cerebrospinal fluid.
*Six positive and one negative CSF cultures were missing cell count data.
†Twenty-two positive and 14 negative CSF cultures were missing protein measurement results.

more likely to be both positive if both specimens were taken within 24 hours. Among those with positive blood and CSF cultures, the concordance rate was 82%. A bloody tap was noted in 46% of LP cases with a positive culture, compared with 27.8% among those with negative cultures. The *Acinetobacter baumannii* and *Klebsiella pneumonia* were the most common organisms isolated among those with positive CSF cultures and a bloody tap whose BCs were also positive. Only 24.5% of neonates with positive CSF culture had a high CSF-WCC, while 59.3% had high CSF protein levels. The proportion of patients with high CSF-WCC and protein levels was higher among those with culture-positive CSF samples than those with negative ones.

The high prevalence of Gram-negative organisms in CSF mirrors that observed in BCs, suggesting that the infection's spread to the meninges is most likely hematogenous. This is supported by the observation that a relatively higher proportion of culture-positive CSF samples exhibited positive BC than vice versa. The predominance of Gram-negative bacteria as common organisms is similar to findings reported by other low and middle-income countries.[9,10] However, similar trends have also been observed in some high-income countries.[11]

More than a third of neonates (40.8%) with positive CSF cultures had negative BCs. Studies by Garges *et al.*[3] and Leazer *et al.*[12] reported similar findings, with 33% to 38% of patients exhibiting positive CSF cultures despite having negative BC results. This highlights the importance of considering the independence of culture results from these sites, indicating that a patient can have meningitis without a positive BC, and vice versa. Additionally, a high discordance of 17% was noted between organisms cultured in blood and those cultured in CSF among cases where both specimens tested positive. The discordance observed in this study is much higher than the 3.5 - 5.4% reported by the Pediatrix Medical Group.[3,5] A study conducted by Beam *et al.*[13] reported a concordance of 5%, which is much lower than that reported in our study. Similar to our findings, Beam *et al.*[13] reported that in blood-CSF culture pairs done on the same day, the concordance was higher at 11% than when the CSF was done before or after BCs at 2% and 3%, respectively. However, the percentages were much lower than those found in our study. The discordance between blood and CSF culture results could be attributed to the time interval between the collection of specimens for cultures, the volume of specimens sent for cultures and contamination during the time of collection. Furthermore, the possibility of polymicrobial infection cannot be dismissed, with one of the organisms not growing in both specimens. Delaying an LP in a neonate who has commenced antibiotic treatment can result in a sterile CSF by the time the LP is performed. However, the CSF parameters can be abnormal for up to 68 hours.[3] Another challenge arises when an insufficient amount of blood (<1 mL) is collected for BC, leading to a false negative culture result.

Performing LP in neonates is often challenging owing to the difficulty in maintaining an infant's position, which is crucial for improving access to the spinal space. This often results in CSF being bloody. Overall, 31.7% of LPs were bloody taps, with 46% occurring among those with positive CSF cultures and 27.8% among those with culture-negative results. This incidence of traumatic LP in this study is similar to that previously reported by Greenberg *et al.*[8] and Byington *et al.*[14] ranging between 10 - 39.5%.[8,14] A debate exists regarding the interpretation of CSF results in the presence of red blood cells (RBCs) (bloody tap). Lyons *et al.*[15] recommended that the CSF-WCC should not be adjusted for RBCs so as not to miss meningitis. The presence of RBCs in CSF appears to affect the CSF WCC and protein levels.[5,16,17] The RBCs increase the level of protein in the CSF owing to increased protein levels in the plasma or lysis of RBCs.[18,19] In our study, we further analysed the proportion of neonates with elevated CSF-WCC and protein levels, comparing positive and negative CSF cultures. We found that patients with culture-positive samples had higher CSF-WCC and protein levels than those with culture-negative CSF samples with or without a bloody tap. This suggests that even in the presence of bloody taps, indicating potential contamination with blood, the likelihood of observing elevated CSF-WCC and protein levels is high when meningitis is present. The relatively lower proportion of neonates with high CSF-WCC (24.5%) and a higher proportion with bloody taps (46.1%) among those with positive cultures makes it difficult to exclude the possibility that some of the positive CSF results were likely due to contamination from organisms through blood spill into the CSF. This argument is negated by the fact that we observed no significant differences in CSF-WCC between those with bloody taps and those without among the culture-positive CSF samples. However, our study sample size was too small to generalise the significance of the findings.

The sensitivity of CSF-WCC in diagnosing meningitis was 24.5%, which is much lower than the previously reported 73 - 95.1%.[3,5,20] A study done in Amsterdam reported that an elevated WBC count in CSF was associated with a proven central nervous system infection in 30.8% compared with those with a negative CSF in 12%, $p = 0.006$.[21] Rajesh *et al.*[22] reported that a delay in analysing CSF parameters alters the CSF composition, especially the CSF-WCC. In our study, we did not record the time lapse from the performance of the LP to the arrival of CSF samples at the laboratory for analysis. Therefore, the low proportion of patients with high CSF-WCC among those with positive cultures could be due to delays in getting the CSF to the laboratory. The

other possible explanation is that the inflammatory response in the meninges is inadequate in neonates. It is possible that there was an overrepresentation of preterm infants compared with term infants among those with suspected sepsis. Hence, an inadequate inflammatory response may have occurred, resulting in a relatively lower proportion of high CSF-WCC among those with culture-positive CSF samples, attributable to inadequate immune response associated with prematurity.[23] Abnormalities in CSF protein levels were noted in 59.3% of all positive CSF cultures, primarily occurring in cases involving Gram-negative bacteria, fungi and those with a bloody tap. Smith *et al.*[25] reported similar results but did not show significant differences in CSF-WCC and protein levels among Gram-negative and Gram-positive bacteria. CSF protein levels are elevated during meningitis through various mechanisms. A study by de Blauw *et al.*,[21] found that 93% of positive bacterial CSF infections had positive BC, they reported that the high CSF-WCC and protein levels were likely to be associated with a pathogen in the CSF, but were not able to differentiate between different pathogens. The Pediatrix Medical Group Inc.,[25] in a study that included only infants with *Candida* meningitis, reported a 43% prevalence of normal CSF parameters with a 37% concordance between CSF and blood samples.

The strength of our study was that many of the patients had both CSF and BCs. Moreover, a high proportion of infants had blood and CSF cultures taken within 24 - 48 hours, with most CSF parameters results available.

Our study had several limitations. First, the retrospective nature of the study prevented us from performing certain analyses due to missing data. Second, the bloody CSF were not repeated, therefore some of the CSF indices could have been falsely elevated. Third, the results are from a single tertiary centre, therefore, careful interpretation is required as they may not be generalisable to other centres since laboratory normal ranges may vary from laboratory to laboratory. Fourth, the demographics could not be captured, so we could not determine whether there were differences in these abnormalities between premature and term infants and also classify organisms into early and late-onset meningitis. Lastly, the history of antibiotic exposure before performing an LP could not be established. Future studies in similar settings are recommended to verify our findings.

## Conclusion

In our study, Gram-negative bacilli were the most common pathogens causing meningitis in neonates admitted to a unit in a low- and middle-income country. Just over a third of neonates have discordance between CSF and BC results. Traumatic LP was a common problem in neonates. Concordance between positive CSF and BC is higher if the tests are done at the same time, therefore, unless there are contraindications, LP should be performed at the same time as BC.

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**Conflicts of interest.** None.

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