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The profile of ancillary laboratory tests in neonates with positive blood and/or cerebrospinal fluid cultures

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Background. Blood and cerebrospinal fluid (CSF) cultures are used as a gold standard to diagnose neonatal sepsis/meningitis. A challenge in their use is low yield, and limited availability, especially in low-resource settings.
Objective. To evaluate profiles of full blood count (FBC), C-reactive protein (CRP), and CSF cell count and protein in neonates with culture-proven sepsis/meningitis.
Methods. Neonates with positive blood and/or CSF cultures who had results for FBC, CRP, CSF cell count and protein performed within 24 - 48 hours of culture were enrolled. The proportion of neonates with abnormalities in these tests was calculated and comparisons among different types of pathogens was performed.
Results. A total of 942 isolates were cultured in blood and/or CSF. Organisms isolated were Gram-negative (GN) bacteria (62.0%), Gram-positive (GP) bacteria (23.4%) and *Candida* species (14.6%). Common abnormality in FBC was thrombocytopenia, which was observed in 30% of neonates with culture-proven sepsis. There was a higher proportion of neonates with thrombocytopenia among those infected with GN bacteria (39.9%) and *Candida* species (44.6%) compared with those infected with GP bacteria (15.1%; $p<0.001$). Leukopenia was relatively more common among neonates infected with GN bacteria than those infected with GP bacteria (20.8% v. 8.4%; $p<0.001$). More than two-thirds (70%) of neonates had high CRP (≥10 mg/L). Finally, less than a third of neonates (26.7%) with positive CSF cultures had abnormal CSF cell count (>20 cells/mm^3) and 61.6% had high protein (>150 mg/dL).
Conclusion. Majority of neonates with positive blood or CSF cultures have normal FBC or CSF cell count; therefore, the absence of abnormalities in these parameters cannot be used solely to exclude sepsis. CRP appears to be the most useful test for diagnosing sepsis, as it is raised in 70% of patients with culture-proven sepsis.

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Sepsis has been described as a systemic inflammatory response to pathogens such as bacteria, viruses, or fungi that is associated with haemodynamic changes and other clinical manifestations.[1,2] The definition of sepsis also includes isolation of pathogens from normally sterile body fluids such as blood and cerebrospinal fluid (CSF). Blood and/or CSF culture is the gold standard in the diagnosis of sepsis. In resource-limited settings, healthcare facilities might not have access to blood culture results for days after working up a patient with a possible serious bacterial infection (pSBI). Waiting for culture results will therefore result in delays in initiating antibiotics in neonates with pSBI. This often results in patients being treated based on clinical signs suggestive of sepsis and available laboratory ancillary tests, namely full blood count (FBC) and/or C-reactive protein (CRP), which are more easily accessible than blood cultures. Even when blood cultures are accessible, they are only available after 24 hours and the yield is low despite a patient having clinical signs suggestive of sepsis.

Delayed initiation of appropriate treatment for sepsis is associated with increased morbidity and mortality;[3,4] thus, antibiotics are started or continued based on abnormalities in FBC, white blood cell differential count (WBC-Diff) and CRP. The proportion of patients with bacterial or fungal culture-proven sepsis who have abnormal ancillary laboratory tests is not well known, especially in settings where there is a high incidence of sepsis. Knowing these proportions will assist attending physicians in estimating the likelihood of patients having sepsis due to bacterial or fungal infections in settings where culture is negative or not available. In this study we sought to determine abnormalities in FBC, WBC-Diff, and CRP in neonates with bacterial or fungal organisms considered pathogens isolated from blood, and to determine CSF cell count and protein levels in neonates with organisms isolated in CSF.

Methods

This is a retrospective study conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), a public tertiary hospital in Soweto, South Africa (SA). The study population were neonates with pSBI admitted to the neonatal unit at CHBAH and identified to have a positive blood and/or CSF culture from January to December 2017. The inclusion criteria consisted of all neonates who had positive blood and/or CSF culture due to organisms considered a possible pathogen and at least one of the laboratory ancillary test results being available from the National Health Laboratory Services (NHLS) database. *Corynebacterium*, *Bacillus*, and coagulase-negative *Staphylococcus* were considered as contaminants and thus were excluded from the analysis. Ancillary laboratory tests assessed were total white blood cell count (WBC), platelet count, WBC-Diff, CRP levels, CSF cell count, and protein levels. For multiple organisms cultured, each organism was considered as a separate episode of bloodstream infection, thus laboratory ancillary tests were captured for each separate organism. The FBCs that were assessed

were only those that were done within 24 hours of culture, and for CRPs it was only those that were done within 48 hours of culture.

Definitions of abnormalities for different parameters on laboratory ancillary tests were as follows: leukocytosis - white blood cell count >25 × 10^9/L;[5] leukopenia − white blood cell count <5 × 10^9/L; thrombocytopenia − platelet count <100 × 10^9/L;[6] neutrophilia − neutrophil count >7 × 10^9/L;[5,7] neutropenia − neutrophil count <1.75 × 10^9/L;[5] increased immature to total neutrophil ratio − ratio ≥0.2;[5,8] high CRP - CRP ≥10 mg/L;[9] abnormal CSF white cell count − cell count >20 cells/mm^3;[10] and high CSF protein - protein >150 mg/dL.[11]

The data were captured into a Microsoft Excel spreadsheet and analysed using Statistica (TIBCO Software Inc., USA). Comparisons in the proportion of patients with abnormalities in blood or CSF parameters among the different organisms were made using the Chi-squared test. The difference with a $p<0.05$ was considered statistically significant. The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (ref. no. M180289).

Results

Organisms isolated from sterile sites

There were 942 neonates with pSBI who had positive cultures due to organisms considered to be pathogens over a 12-month period. A total of 886 and 106 pathogens were isolated in blood and CSF, respectively, and 50 of these were isolated from both blood and CSF (Table 1). Gram-negatives were the most common type of organisms found in both blood and CSF (62.0%; *n*=584). The most common bacteria isolated among the Gram-negatives were *Acinetobacter baumannii* (46.4%; *n*=271) and *Klebsiella pneumoniae* (33.9%; *n*=198). Among the Gram-positives, the common bacteria were *Enterococcus* species (33.6%; *n*=74), *Staphylococcus aureus* (21.4%; *n*=47) and *Streptococcus viridans* (20.9%; *n*=46). The most common fungi were *Candida parapsilosis* (62.3%; *n*=86) and *Candida albicans* (27.5%; *n*=38).

Table 1. Pathogens isolated from blood and/or cerebrospinal fluid

	Blood and/or CSF (*N*=942)*, *n* (%)	Blood (*N*=886), *n* (%)	CSF *N*=106, *n* (%)
Gram-negatives	584 (62.0)	543 (61.3)	84 (79.2)
Acinetobacter baumannii	271 (46.4)	247 (45.5)	54 (64.3)
Klebsiella pneumoniae	198 (33.9)	191 (35.2)	20 (23.8)
Pseudomonas species	32 (5.48)	30 (5.52)	2 (2.38)
Escherichia coli	29 (4.97)	27 (4.97)	2 (2.38)
Enterobacter species	20 (3.42)	17 (3.13)	3 (3.57)
Klebsiella oxytoca	6 (1.03)	6 (1.10)	0
Achromobacter xylosoxidans	4 (0.68)	4 (0.74)	0
Providentia species	4 (0.68)	4 (0.74)	0
Neisseria species	3 (0.51)	3 (0.55)	0
Acinetobacter Iwoffi	2 (0.34)	2 (0.37)	0
Others	15 (2.57)	12 (2.21)	3 (3.57)
Gram-positives	220 (23.4)	205 (23.1)	18 (17.0)
Staphylococcus aureus	47 (21.4)	46 (22.4)	2 (11.1)
Streptococcus viridans	46 (20.9)	41 (20.0)	5 (27.8)
Enterococcus faecium	41 (18.6)	36 (17.6)	7 (38.9)
Enterococcus faecalis	33 (15.0)	31 (15.1)	2 (11.1)
Listeria monocytogenes	26 (11.8)	25 (12.2)	1 (5.56)
Streptococcus agalactiae	23 (10.5)	22 (10.7)	1 (5.56)
Others	4 (1.82)	4 (1.95)	0
Candida and other yeasts	138 (14.6)	138 (15.6)	4 (3.78)
Candida parapsilosis	86 (62.3)	86 (62.3)	1 (25.0)
Candida albicans	38 (27.5)	38 (27.5)	3 (75.0)
Other *Candida* species	14 (10.1)	14 (10.1)	0

*50 neonates had the same organisms in blood and cerebrospinal fluid and were counted once.

Abnormalities in full blood count

Abnormalities in FBC in neonates with culture-proven sepsis overall and for different types of organisms are presented in Table 2. More than three-quarters (85%) of neonates with positive blood cultures had results of FBC available and with blood for FBC having been taken at the same time or within 24 hours as the culture. Other FBCs had clotted and were repeated at more than 24 hours after the blood culture and thus were excluded from the analysis. The common abnormality in FBC was thrombocytopenia for all pathogens, occurring in 30% of neonates with positive cultures. Thrombocytopenia was observed in a low proportion of neonates infected with GP bacteria compared with those with GN (15.1% v. 39.9%, $p<0.001$) and fungal (15.1% v. 44.6%; $p<0.001$) infections. There were no significant differences in the proportion of neonates with thrombocytopenia infected with GN bacteria and fungi (39.9% v. 44.6%; $p=0.366$). *Klebsiella* species (53.4%) were the most common GN bacteria cultured in neonates with thrombocytopenia, followed by *Pseudomonas* species (25.0%). There were no significant differences in proportions of neonates with thrombocytopenia with specific organisms that were GP or fungi. Leukocytosis and leukopenia occurred at equal rates (15%) among neonates with positive cultures. Leukopenia was observed in relatively higher proportion in neonates infected with GN bacteria than those with GP (20.8% v. 8.4%; $p<0.001$) or fungal infections (20.8% v. 2.5%; $p<0.001$); while leukocytosis was more common in neonates with fungal infections than those with GN infection (25.6% v. 13.7%; $p=0.002$).

Abnormalities in white blood cells differential counts

The common abnormality in the WBC-Diff was neutrophilia for all types of organisms, but it was seen in higher proportions in those with fungal infection compared with those with GN (75.3% v. 36.7%; $p<0.001$) and GP bacterial infections (75.3% v. 42.6%; $p<0.001$) (Table 3). Neutropenia was more common in neonates with GN than GP (20.3% v. 9.2%; $p=0.003$) or fungal (20.3% v 3.1%; $p<0.001$) infections. Overall, less than a tenth of neonates with culture-proven sepsis had abnormal immature to total neutrophil ratio (ITNR). The proportions of the above abnormalities for individual organisms were similar for most organisms within each group of organisms.

CRP levels in neonates with positive blood cultures

CRP was done within 48 hours of blood culture and the results were available for 80% of neonates who had positive cultures (Table 4). It was abnormal in 53.9%, 73.5% and 82.7% of neonates with positive cultures for GP, GN, and *Candida* species, respectively. More than two-thirds of neonates had abnormal CRP (>40 mg/L). Less than three-quarters (70%) of neonates with GN infections had abnormal CRP except for *Pseudomonas,* where only 21.7% of cases had abnormal CRP. Among those with GP bacterial infections, a higher proportion of neonates with *Streptococcus agalactiae* (58.8%) and *Listeria monocytogenes* (86.7%) had high CRP. More than three-quarters (80%) of neonates with fungal culture sepsis had abnormal CRP.

Table 2. Abnormalities in full blood count in neonates with positive blood cultures

	Total	Blood count done same time as culture, *n* (%)	Leukocytosis (>25 × 10^9/L), *n* (%)	Leukopenia (<5 × 10^9/L), *n* (%)	Thrombocytopenia (<100 × 10^9/L), *n* (%)
All organisms	886	766 (86.5)	115 (15.0)	115 (15.0)	267 (30.1)
Gram-negatives	543	466 (85.8)	64 (13.7)	97 (20.8)	186 (39.9)
Gram-positives	205	179 (87.3)	20 (11.2)	15 (8.38)	27 (15.1)
Fungi	138	121 (87.7)	31 (25.6)	3 (2.48)	54 (44.6)
Specific Gram-negatives					
Acinetobacter species	249	200 (80.3)	24 (12.0)	54 (27.0)	69 (34.5)
Klebsiella species	197	178 (90.4)	30 (16.9)	34 (19.1)	95 (53.4)
Pseudomonas species	30	28 (93.3)	4 (14.3)	2 (7.14)	7 (25.0)
Escherichia coli	27	25 (92.6)	0	4 (16.0)	7 (28.0)
Enterobacter species	17	15 (88.2)	2 (13.3)	2 (13.3)	6 (40.0)
Achromobacter xylosoxidans	4	4 (100)	1 (25.0)	0	1 (25.0)
Providentia species	4	2 (50.0)	1 (50.0)	0	0
Neisseria species	3	2 (66.7)	1 (50.0)	0	0
Others	12	12 (100)	1 (8.33)	1 (8.33)	1 (8.33)
Specific Gram-positives					
Staphylococcus aureus	46	40 (87.0)	6 (15.0)	6 (15.0)	9 (22.5)
Streptococcus viridans	41	34 (82.9)	5 (14.7)	1 (2.94)	6 (17.6)
Enterococcus faecium	36	27 (75.0)	2 (7.41)	1 (3.70)	3 (11.1)
Enterococcus faecalis	31	29 (93.5)	3 (10.3)	2 (6.90)	4 (13.8)
Listeria monocytogenes	25	25 (100)	3 (12.0)	5 (20.0)	2 (8.00)
Streptococcus agalactiae	22	21 (95.5)	1 (4.76)	0	3 (14.3)
Others	4	3 (75.0)	0	0	0
Specific fungi					
Candida parapsilosis	86	75 (87.2)	18 (24.0)	2 (2.67)	34 (45.3)
Candida albicans	38	33 (86.8)	8 (24.2)	0	14 (42.4)
Other *Candida* species	14	13 (92.9)	5 (38.5)	1 (7.69)	6 (46.2)

Abnormalities in CSF cells counts and protein levels among those with positive CSF cultures

The total number of pathogens isolated from the CSF was 106 (Table 5). Cell counts were missing in 4.7% (*n*=5/106) of patients and protein levels were missing in 18.9% (*n*=20/106) of patients. More than a third (45.5%; *n*=46) of CSF cultures were considered to be a bloody tap (defined as red blood cell count ≥500 × 10^9/L).[12] Jus over a quarter of neonates (26.7%) had high CSF WCC defined as count >20 cells/mm^3, while under two-thirds (61.6%) of neonates had protein levels >150 mg/dL. The proportion of neonates with high CSF WCC was similar for the different types of organisms, while those with GN- (65.2%) and *Candida* species-positive (100%) cultures had high protein levels than those with GP cultures (41.2%; $p<0.001$). There was a higher proportion of neonates who had bloody tap CSF with a high WCC (32.6% v. 21.8%, $p=0.01$) and higher protein (73.5% v. 52.9%, $p<0.001$) than those without a bloody tap.

Discussion

In this study, we found that all neonates who had cultures done had FBCs done as part of a workup for sepsis, though only 86% of FBC were available for analysis. The main reason for unavailability was that the FBC done at the time of culture had clotted. The use of CRP and WBC-Diff was relatively lower than that of FBC, at 80% and 70%, respectively. In an analysis of FBCs, the common abnormality in neonates with positive cultures was thrombocytopenia, occurring in about 30% of cases and was observed at relatively higher frequencies in neonates with positive cultures for GN and fungal isolates. The proportion of neonates with thrombocytopenia was similar between those infected with GN bacteria and *Candida* species. Abnormalities in total WBC occurred in only 15% of cases, with leukocytosis being more common in those with fungal sepsis and leukopenia being common in those with GN cultures. Among those with WBC-Diff available, the common abnormality was neutrophilia followed by neutropenia, with neutrophilia being observed more commonly in those with fungal isolates and neutropenia being more common in those with GN isolates. Abnormalities in ITNR were observed in only less than 10% of cases. Overall, the ancillary test that was abnormal in most cases with positive cultures was CRP, as it was observed to be abnormal (≥10 mg/L) in over 70% of neonates. High CSF protein was observed in a much higher proportion than high CSF cell count, occurring in about two-thirds, compared with high CSF cell count that was observed in only a quarter of neonates with positive CSF cultures.

Few studies have looked at the relationship between the presence of thrombocytopenia and positive culture results. One study that used a platelet cut-off of 100 × 10^9/L to define thrombocytopenia, reported a much higher prevalence of thrombocytopenia of 67% among those with culture-proven sepsis, compared with our findings where the prevalence was only 30%.[13] A prospective study of 230 positive blood cultures done in India[13] between the years 2000 and 2005 found that the proportion of patients with fungal, GN, and GP organisms who had thrombocytopenia was 50.0%, 45%, and 19.6%, respectively. Another cohort study of very-low-birthweight neonates with 154 positive blood cultures reported that neonates with GN and fungal isolates were more likely to have

Table 3. Abnormalities in white blood cell differential count in neonates with positive blood cultures

	Total	Differential count done *n* (%)	Neutrophilia (>7.0 × 10^9/L), *n* (%)	Neutropenia (<1.750 × 10^9/L), *n* (%)	ITNR ≥0.2, *n* (%)
All organisms	886	617 (69.6)	272 (44.1)	93 (15.1)	46 (7.5)
Gram-negatives	543	379 (69.8)	139 (36.7)	77 (20.3)	27 (7.12)
Gram-positives	205	141 (68.8)	60 (42.6)	13 (9.22)	10 (7.09)
Fungi	138	97 (70.3)	73 (75.3)	3 (3.09)	9 (9.28)
Specific Gram-negatives					
Acinetobacter species	249	165 (66.3)	61 (37.0)	41 (24.8)	15 (9.09)
Klebsiella species	197	145 (73.6)	56 (38.6)	24 (16.6)	10 (6.90)
Pseudomonas species	30	24 (80.0)	7 (29.2)	5 (20.8)	1 (4.17)
Escherichiae coli	27	18 (66.7)	2 (11.1)	4 (22.2)	1 (5.56)
Enterobacter species	17	10 (58.9)	5 (50.0)	2 (20.0)	0
Achromobacter xylosoxidans	4	4 (100)	2 (50.0)	0	0
Providentia species	4	1 (25.0)	1 (100)	0	0
Neisseria species	3	0	0	0	0
Others	12	12 (100)	5 (41.7)	1 (8.33)	0
Specific Gram-positives					
Staphylococcus aureus	46	31 (67.4)	13 (41.9)	5 (16.1)	1 (3.23)
Streptococcus viridans	41	28 (68.3)	12 (42.9)	3 (10.7)	2 (7.14)
Enterococcus faecium	36	18 (50.0)	7 (38.9)	0	2 (11.1)
Enterococcus faecalis	31	24 (77.4)	13 (54.2)	1 (4.17)	2 (8.33)
Listeria monocytogenes	25	21 (84.0)	9 (42.9)	3 (14.3)	3 (14.3)
Streptococcus agalactiae	22	18 (81.8)	6 (33.3)	1 (5.56)	0
Others	4	1 (25.0)	0	0	0
Specific fungi					
Candida parapsilosis	86	62 (72.1)	42 (67.7)	3 (4.84)	4 (6.45)
Candida albicans	38	23 (60.5)	21 (91.3)	0	3 (13.0)
Other *Candida* species	14	12 (85.7)	10 (81.3)	0	2 (16.7)

ITNR = immature to total neutrophil ratio.

low platelet counts than those with GP cultures.[14] A multivariate analysis reported that GN sepsis as opposed to GP sepsis was independently associated with thrombocytopenia in neonatal sepsis.[6] There are suggestions that the endotoxin produced by GN organisms causes platelet destruction; thus, the high prevalence of sepsis in GN-infected patients. Thrombocytopenia could also indicate the severity of illness caused by GN organisms, or be due to disseminated intravascular coagulation.[15-17] Based on our findings in this study, the absence of thrombocytopenia cannot be used to exclude sepsis, as only about a third of neonates with culture-proven sepsis have thrombocytopenia and its presence cannot be used to differentiate between patients infected with fungi and those with bacteria, as it occurs at similar rates in those infected with GN and those with fungal culture-confirmed sepsis.

In this study, leukocytosis and leukopenia were found to be occurring at a similar rate (15%), with leukocytosis observed to occur commonly among the fungal infected cases while leukopenia was observed more commonly in neonates with GN cultures. A study that used a definition of leukocytosis (WBC >25 000) similar to ours, reported that 50% of positive blood culture cases had leukocytosis,[18] much higher than that observed in this study. Neutropenia has previously been reported to occur in 8.6% of infants with culture-proven sepsis, much lower than 15% reported in this study, but reported a higher prevalence of 26.6% among neonates with GN sepsis.[19,20] A study from Pakistan[18] reported that the immature to total neutrophil ratio (ITNR) had a sensitivity of 76.5%, much higher than the 7.5% observed in this study. In a retrospective review of 49 positive cultures in neonates, the ITNR was significantly higher among neonates with GN cultures,[20] which is different from our findings, where the rates of ITNR >0.2 occurred at similar frequencies among the different types of organisms. A study conducted in Japan[21] reported similar findings to this study, where the ITNR was similar among neonates with GP and GN bacterial growth in blood cultures.

High CRP was the most common abnormality in neonates, with positives cultures for all types of organisms. It appears that CRP is a relatively more reliable test in establishing the diagnosis of sepsis in neonates.[22] In a cross-sectional validation study of CRP done in Pakistan[18] in 2012 consisting of 147 neonates with 104 having positive blood cultures, CRP was done at 72 hours after admission, had a sensitivity of 76.9%, which is similar to findings in this study. The overall diagnostic accuracy of CRP in diagnosing neonatal sepsis has been reported to be 70%.[23,24] Some have reported that CRP was significantly higher among neonates with septicaemia due to GN sepsis than in those with GP septicaemia (75.0% v. 55.3%).[25] A retrospective cross-sectional study of 303 neonates and 88 positive blood cultures found no significant difference in CRP positivity between neonates with GN- and GP-positive cultures, similar to our findings.[26]

The common abnormality among all positive CSF cultures was high protein, and this abnormality was high among neonates, with cultures positive for fungi and GN bacteria. One study reported that CSF protein >90 mg/dL was found in 96% of neonates and levels >170 mg/dL were observed in 61% of neonates with

meningitis, making this parameter a useful indicator to rule out meningitis.[27] Only 27% of neonates with positive CSF culture had high CSF-WCC and the difference was not statistically significantly different among the different types of organisms. In a large retrospective study from 150 neonatal intensive care units by Paediatrix Medical Group consisting of 14 017 lumbar punctures, GN meningitis was associated with high WCC compared with GP meningitis (median of 1217/mm³ v. 187/mm³; p=0.043).[28] A traumatic tap was observed in 46% of patients with positive CSF cultures. This is similar to the prevalence of 39.5 - 46.0% reported in other studies.[12,29,30] The proportion of neonates with high CSF WCC and CSF protein was higher in those with a bloody tap. These findings are similar to those reported by Lyons *et al.*,[31] who reported that the sensitivity of the CSF-WCC count was 87.9% among those with traumatic lumbar puncture and 58.6% among those with non-traumatic lumbar puncture.[31]

Table 4. Abnormalities in C-reactive protein in neonates with positive blood cultures

			Number with CRP ≥ 10mg/L (*N*=500)	
	Total	CRP done, *n* %	CRP 21 - 40, *n* (%)	CRP >40, *n* (%)
All organisms	886	708 (79.9)	88 (17.6)	335 (67.0)
Gram-negatives	543	452 (83.2)	59 (17.8)	221 (66.6)
Gram-positives	205	152 (74.1)	18 (22.0)	52 (63.4)
Fungi	138	104 (75.4)	11 (12.8)	62 (72.1)
Specific Gram-negatives				
Acinetobacter species	249	205 (82.3)	35 (23.8)	80 (54.4)
Klebsiella species	197	172 (87.3)	20 (13.9)	111 (77.1)
Pseudomonas species	30	23 (76.7)	1 (20.0)	2 (40.0)
Escherichiae coli	27	21 (77.8)	1 (6.25)	13 (81.2)
Enterobacter species	17	14 (82.4)	0	9 (75.0)
Achromobacter xylosoxidans	4	3 (75.0)	1 (50.0)	1 (50.0)
Providentia species	4	3 (75.0)	1 (100)	0 (0)
Neisseria species	3	2 (66.7)	0	1 (100)
Others	12	9 (75.0)	0	4 (100)
Specific Gram-positives				
Staphylococcus aureus	46	35 (76.1)	2 (10.5)	16 (84.2)
Streptococcus viridans	41	31 (75.6)	8 (61.5)	5 (38.5)
Enterococcus faecium	36	27 (75.0)	1 (6.67)	11 (73.3)
Enterococcus faecalis	31	24 (77.4)	3 (30.0)	5 (50.0)
Listeria monocytogenes	25	15 (60.0)	2 (15.4)	9 (69.2)
Streptococcus agalactiae	22	17 (77.3)	2 (20.0)	4 (40.0)
Others	4	3 (75.0)	0 (0)	2 (100)
Specific fungi				
Candida parapsilosis	86	67 (77.9)	9 (16.1)	36 (64.3)
Candida albicans	38	26 (68.4)	0 (0)	20 (90.9)
Other *Candida* species	14	11 (78.6)	2 (25.0)	6 (75.0)

Despite the low yield in ancillary blood tests and culture results, these tests should still form part of the workup for sepsis in those neonates with suspected sepsis. These results can help guide the clinicians in determining the likelihood of the offending organism and guide the choice of antibiotics, especially in resource-limited settings where cultures are often not done, and if done, the results are often delayed or reported as negative despite a neonate having signs strongly suggestive of sepsis. These blood results should be interpreted in the context of signs and symptoms of sepsis. Normal ancillary test results cannot be relied upon to exclude sepsis.

Study strengths and limitations

The strength of the present study is that there was a large number of patients with positive cultures enrolled. Secondly, there was a high proportion of neonates with positive cultures who had ancillary laboratory tests performed at about the same time as positive cultures, and their results were available.

The limitations of the study are that it is a retrospective study; thus, not all ancillary test results could be analysed as some were missing. These results are from a single tertiary centre and therefore the results should be carefully considered before they are generalised to other centres as laboratory normal ranges might vary from laboratory to laboratory. Another limitation is that the demographics could not be captured, so we could not determine whether there is a difference in these abnormalities between premature and term infants and also classify organisms into early and late-onset sepsis. The lack of the group with negative cultures was another limitation in this study; therefore, parameters like sensitivity or specificity could not be determined for the different ancillary laboratory tests. More studies need to be performed in similar settings and these should include those with both negative and positive cultures.

Table 5. White cell count and protein levels in CSF in neonates with positive CSF cultures.

	All with culture-positive CSF (*N*=106)*		Culture-positive CSF that were bloody taps (*N*=46)		Culture-positive CSF that were not bloody taps (*N*=60)	
	WCC >20/mm³, *n* (%)	Protein >150mg/dL, *n* (%)	WCC >20/mm³, *n* (%)	Protein >150mg/dL, *n* (%)	WCC>20/mm³, *n* (%)	Protein >150mg/dL, *n* (%)
All organisms (*n*=101)	27/101 (26.7)	53/86 (61.6)	15/46 (32.6)	25/34 (73.5)	12/55 (21.8)	27/51 (52.9)
Gram-negatives (*n*=79)	21/79 (26.6)	43/66 (65.2)	11/38 (28.9)	22/28 (78.6)	10/41 (24.4)	20/37 (54.1)
Gram-positives (*n*=18)	5/18 (27.8)	7/17 (41.2)	3/5 (60.0)	1/4 (25.0)	2/13 (15.3)	6/13 (46.2)
Candida species (*n*=4)	1/4 (25.0)	3/3 (100)	1/3 (33.3)	2/2 (100)	0/1	1/1 (100)

CSF = cerebrospinal fluid; WCC = white cell count.
* 5 cerebrospinal fluids were missing cell counts and 15 were missing protein count.

Conclusion

In conclusion, CRP appears to be the most useful test for diagnosing sepsis as it is abnormal in more than two-thirds of patients with positive cultures. The absence of abnormalities in FBC, WBC-Diff cannot be used to exclude culture-confirmed sepsis, as less than 50% of patients with positive cultures have abnormalities in blood counts. Similarly, for CSF-WCC, normal CSF-WCC cannot be used to exclude positive CSF culture results, as only 27% of patients with meningitis have abnormal CSF count. Thus, a decision to stop empiric antibiotics must not be based on FBC or CSF cell counts alone but also on getting negative culture results. This highlights the importance of ensuring that cultures or other tests that can identify the organisms are performed and made available timeously and not to rely on ancillary laboratory tests only.

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