Association of Bacteria Species with Positive Predictive Value of Bacteria Isolated from Cerebrospinal Fluid Cultures: A Retrospective Cohort Study

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Research

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Abstract

Background: Previous studies discuss the positive predictive value through whether the bacteria are coagulase-negative staphylococci. The view may need to be updated. The aim was to evaluate the positive predictive value of different bacteria species isolated from cerebrospinal fluid cultures and discuss the rationality to view coagulase-negative staphylococci as a group.

Methods: This retrospective cohort study recruit all adults with positive cerebrospinal fluid cultures sampled by lumbar puncture 2012-2020 in the Department of Neurosurgery. The exposure was bacteria species, and the outcome was positive predictive value. An episode was defined as a patient with one bacteria. When episodes with a bacteria species reached five, the bacteria species was analyzed specifically. The positive predictive value was defined as the incidence of isolated-bacteria-related infected episodes. The isolated-bacteria-related infected episode was defined as the patient was with clinical features of bacterial meningitis, and the improvement was related to sensitive antibacterial agents. Then the differences of the positive predictive value of different bacteria in all specific bacteria species, coagulase-negative staphylococci, and non-coagulase-negative staphylococci bacteria were calculated, respectively. The results were statistically significant when P-value <.05.

Results: 1180 episodes from 1133 patients with 79 bacteria were studied; the positive predictive value was 54.3%. The bacteria included 67 bacteria species, ten bacteria genus, viridans streptococci, and unclassified coagulase-negative staphylococci. Twenty-four specific bacteria species were analyzed. The range of positive predictive values of them was 29.4%-100.0% (P<.0001). The positive predictive value for Enterobacter aerogenes, Pseudomonas aeruginosa, Enterobacter cloacae, and Klebsiella oxytoca was the highest, while the positive predictive value for Staphylococcus cohnii was the lowest. Moreover, 767 (65.0%) were with coagulase-negative staphylococci, the positive predictive value was 46.4%, and the range was 29.4%-85.7% (P=.0020); 413 (35.0%) were with non-coagulase-negative staphylococci bacteria, the positive predictive value was 69.0%, and the range was 40.0%-100.0% (P<.0001).

Conclusions: This study suggests that the positive predictive value of different bacteria species is different. It is more reasonable to discuss the positive predictive value of bacteria isolated from cerebrospinal fluid cultures through the bacteria species rather than whether they are coagulase-negative staphylococci.

Trial registration: This is a retrospective study without interventions on participants.

Introduction

Bacterial meningitis is a common complication of neurosurgery, which causes more cost, prolonged hospitalization, and higher mortality [1–3]. The bacteria isolated from cerebrospinal fluid (CSF) is valuable, which helps etiologic diagnosis, targeted treatment, and formation of bacteria spectrum [4]. Theoretically, bacteria can prove bacterial meningitis independently. However, since the bacteria colonizing in the skin or catheter could contaminate the CSF, especially opportunistic pathogens such as
coagulase-negative staphylococci (CONS), bacteria cannot prove bacterial meningitis independently [5–8].

The contamination in CSF cultures causes embarrassment in treatment: on the one hand, bacterial meningitis is a fatal disease [9, 10], recognizing the pathogens as contaminants leads to delayed treatment, following disastrous outcomes; on the other hand, high-grade antibacterial agents were used in treatments of bacterial meningitis [11, 12], recognizing the contaminants as pathogens leads to unnecessary treatment, following underlying risks [13, 14].

The positive predictive value (PPV) of bacteria isolated from CSF cultures helps distinguish the pathogens and contaminants and make an accurate decision about treatment.

Several studies discuss the PPV of bacteria isolated from CSF cultures. For several reasons, the studies need improvements. First, the samples are small, which causes different conclusions [7, 15, 16]. Second, CONS are analyzed as a group with low PPV in most studies [15, 16], which means antibacterial agents should be avoided in most situations. However, recent studies prove Staphylococcus lugdunensis is always pathogenic in other parts [17, 18], which means antibacterial agents should be used. Maybe subgroup analysis is needed for CONS, and the PPV is different of different bacteria species. Finally, non-CONS bacteria (NCONS) are overlooked as a group with high PPV, which means antibacterial agents should be used in most situations. However, several studies have testified that contamination of Acinetobacter baumannii in CSF cultures is common [15, 19], which means the antibacterial agents need evaluation before usage. Maybe comprehensive analysis is needed for NCONS, and the PPV is different of different bacteria species.

To better and comprehensively understand the bacteria isolated from CSF cultures, we performed a study to evaluate the association of bacteria species with the PPV of the bacteria isolated from CSF cultures in bacterial meningitis in adults. Moreover, we discussed the rationality to view coagulase-negative staphylococci as a group.

Methods

Study design and setting

A retrospective cohort study was performed. We recruited all patients with positive CSF cultures sampled by lumbar puncture from 2012 Jan to 2020 Dec in the Department of Neurosurgery in Beijing Tiantan Hospital, Capital Medical University (Beijing, China), a tertiary teaching hospital with one of the largest neurosurgical centers in China. Demographic, clinical, laboratory, imaging, treatment, and outcome data of the patients were from the medical records. Exclusion criteria for the patients were younger than 18 years, operated within one month in other hospitals, in the acute stage of open craniocerebral injury, with pre-hospital central nervous system infection, without surgery, and with incomplete data.
Cultures

CSF was collected from all patients with suspected bacterial meningitis. At the bedside, CSF was obtained by neurosurgical doctors using 70% isopropyl alcohol followed by 10% povidone-iodine as antiseptics. All CSF specimens were transferred to the clinical laboratory and were incubated until flagged as positive or for five days in BACTEC 9240 for 2012 Jan-2018 Sep or BacT/ALERT 3D for 2018 Oct-2020 Dec. Antimicrobial drugs were tested for activity against the bacteria using disk diffusion and broth micro-dilution methods according to the Clinical and Laboratory Standards Institute. Susceptibility testing of the bacteria was performed according to the guidelines established by the National Committee on Clinical Laboratory Standards. Clinical and Laboratory Standards Institute breakpoint values were employed. Exclusion criteria for cultures were reported fungi and sampled by methods other than lumbar puncture.

Variables

The exposure was the bacteria species, and the outcome was the PPV.

An episode was defined as a patient with one bacteria. Therefore, a patient with two and more bacteria was with two and more episodes. Episodes were categorized according to the bacteria. When episodes with a bacteria species reached five, the bacteria species was analyzed specifically.

The positive predictive value was defined as the incidence of isolated-bacteria-related infected episodes. The isolated-bacteria-related infected episode was defined as the patient was with clinical features related to bacterial meningitis [11, 12], and the improvement was related to the antibacterial agents aimed at the bacteria. However, the therapeutic effect of the medicine alone could be deficient in patients with special situations, including subcutaneous fluid, implants, CSF leak, abscess, and ventriculitis.

The contaminated episode was defined as not isolated-bacteria-related infected episodes and suited one of the following criteria.  
1. the patient had no clinical features.  
2. the patient had clinical features, but bacteria were not the pathogen; including  
   a. the improvement occurred without the antibacterial agents;  
   b. the duration of the antibacterial agent was less than 72 hours out of medical reasons, and no re-ignition occurred [20]  
   c. the antibacterial agent was not effective in patients without special situations, and the course was self-limiting without adjustment of the antibacterial agent [21].  
3. the patient had clinical features, bacteria other than bacteria isolated from CSF cultures were the pathogen, including  
   a. the improvement occurred with other antibacterial agents, and sensitive antibacterial agents were not used;  
   b. the duration of the sensitive antibacterial agent was less than 72 hours out of medical reasons while of other antibacterial agent was longer, and no re-ignition occurred [22];  
   c. the sensitive antibacterial agent was ineffective in patients without special situations, and the improvement occurred after adjustment of antibacterial agents.

Statistical analysis
Statistical analyses were performed using the R Programming Language version 4.0.2. The Wilcoxon rank-sum test was used in age, and the contingency table analysis was used in other data. The results were statistically significant when P-value < .05.

**Results**

**Participants**

In total, 2342 patients with positive CSF cultures were identified in the nine years; after the exclusion, 1180 episodes from 1133 patients were studied (Fig. 1).

Considering every patient with one episode, they had a mean age of 44.2 ± 13.3 years (18 years to 80 years). 552 (44.2%) were female. The most common main diagnosis was solid tumor, with a proportion of 79.3%. The episodes with solid tumors were more likely to be diagnosed as isolated-bacteria-related infected episodes (P = .0299), and the episodes with functional disease were more likely to be diagnosed as contaminated episodes (P = .0371) (Table 1).

|                           | Total (n = 1180) | IIE (n = 641) | Contaminated episodes (n = 539) | P-value |
|---------------------------|-----------------|---------------|-------------------------------|---------|
| Age (y), mean ± SD        | 44.2 ± 13.3     | 43.7 ± 13.2   | 44.8 ± 13.4                   | 0.2033  |
| Female sex, n (%)         | 522 (44.2)      | 282 (44.0)    | 240 (44.5)                    | 0.9006  |
| Main diagnosis, n (%)     |                 |               |                               |         |
| Solid tumor               | 936 (79.3)      | 524 (81.7)    | 412 (76.4)                    | 0.0299  |
| Vascular malformation     | 127 (10.8)      | 68 (10.6)     | 59 (10.9)                     | 0.5056  |
| Traumatic brain injury    | 36 (3.1)        | 14 (2.2)      | 22 (4.1)                      | 0.0858  |
| Functional disease        | 49 (4.2)        | 19 (3.0)      | 30 (5.6)                      | 0.0371  |
| Other diseases            | 32 (2.7)        | 16 (2.5)      | 16 (3.0)                      | 0.7507  |

**Bacteria**

Seventy-nine bacteria were studied, including 67 bacteria species, ten bacteria genus, viridans streptococci, and unclassified CONS. Inside, Staphylococcus epidermidis was the commonest, 333 episodes were with the bacteria. Twenty-four bacteria species were analyzed specifically (Table 2). The remaining bacteria were analyzed as a rare bacteria group or two bacteria subgroups, including other
CONS and other NCONS. Thus, 111 episodes were with the rare bacteria. Insides, 25 were with other CONS, and 86 were with other NCONS (Table 3).
Table 2
No. of episodes, isolated-bacteria-related infected episodes (IIE) and positive predictive value (PPV) of different bacteria.

| Bacteria                          | No. (%) of episodes | No. of IIE | PPV, % |
|-----------------------------------|---------------------|------------|--------|
| Total                             | 1180 (100.0)        | 641        | 54.3   |
| Staphylococcus epidermidis        | 333 (28.2)          | 181        | 54.4   |
| Staphylococcus hominis            | 148 (12.5)          | 56         | 37.8   |
| Staphylococcus capitis            | 100 (8.5)           | 38         | 38.0   |
| Staphylococcus haemolyticus       | 92 (7.8)            | 42         | 45.7   |
| Klebsiella pneumoniae             | 63 (5.3)            | 53         | 84.1   |
| Staphylococcus aureus             | 47 (4.0)            | 32         | 68.1   |
| Enterococcus faecalis             | 47 (4.0)            | 34         | 72.3   |
| Enterococcus faecium              | 40 (3.4)            | 21         | 52.5   |
| Acinetobacter baumannii          | 33 (2.8)            | 22         | 66.7   |
| Staphylococcus warneri           | 23 (1.9)            | 10         | 43.5   |
| Escherichia coli                  | 20 (1.7)            | 16         | 80.0   |
| Viridans Streptococci             | 19 (1.6)            | 10         |        |
| Staphylococcus cohnii             | 17 (1.4)            | 5          | 29.4   |
| Staphylococcus saprophyticus      | 17 (1.4)            | 6          | 35.3   |
| Enterobacter aerogenes            | 15 (1.3)            | 15         | 100.0  |
| Unclassified CONS\(^1\)           | 12 (1.0)            | 4          |        |
| Pseudomonas aeruginosa            | 11 (0.9)            | 11         | 100.0  |
| Serratia marcescens               | 11 (0.9)            | 10         | 90.9   |
| Acinetobacter lwofii              | 10 (0.8)            | 4          | 40.0   |
| Enterobacter cloacae              | 8 (0.7)             | 8          | 100.0  |
| Staphylococcus lugdunensis        | 7 (0.6)             | 6          | 85.7   |
| Streptococcus pneumoniae          | 6 (0.5)             | 5          | 83.3   |
| Stenotrophomonas maltophilia      | 6 (0.5)             | 3          | 50.0   |

\(^1\) Coagulase-negative staphylococci;

\(^2\) For PPV of all specific bacteria species.
| Bacteria                                      | No. (%) of episodes | No. of IIE | PPV, % |
|----------------------------------------------|---------------------|------------|--------|
| Staphylococcus caprae                        | 5 (0.4)             | 3          | 60.0   |
| Klebsiella oxytoca                           | 5 (0.4)             | 5          | 100.0  |
| Sphingomonas paucimobilis                    | 5 (0.4)             | 2          | 40.0   |
| Acinetobacter spp.                           | 5 (0.4)             | 3          |        |
| Chryseobacterium indologenes                | 3 (0.3)             | 1          |        |
| Brevundimonas vesicularis                    | 3 (0.3)             | 1          |        |
| Pantoea agglomerans                          | 3 (0.3)             | 2          |        |
| Staphylococcus simulans                     | 3 (0.3)             | 2          |        |
| Moraxella osloensis                          | 3 (0.3)             | 0          |        |
| Enterococcus durans                          | 2 (0.2)             | 1          |        |
| Chryseobacterium meningosepticum            | 2 (0.2)             | 1          |        |
| Alcaligenes faecalis                         | 2 (0.2)             | 1          |        |
| Staphylococcus auricularis                  | 2 (0.2)             | 0          |        |
| Sphingobacterium multivorum                 | 2 (0.2)             | 1          |        |
| Acinetobacter johnsonii                     | 2 (0.2)             | 2          |        |
| Citrobacter freundii                         | 2 (0.2)             | 1          |        |
| Flavimonas oryzihabitans                    | 2 (0.2)             | 1          |        |
| Pseudomonas pseudoalcaligenes               | 2 (0.2)             | 1          |        |
| Staphylococcus hyicus                        | 2 (0.2)             | 1          |        |
| Staphylococcus sciuri                        | 2 (0.2)             | 1          |        |
| Moraxella spp.                               | 2 (0.2)             | 0          |        |
| Pseudomonas fluorescens                     | 2 (0.2)             | 1          |        |
| Enterobacter gergoviae                       | 1 (0.1)             | 1          |        |
| Staphylococcus equorum                      | 1 (0.1)             | 1          |        |
| Citrobacter koseri                           | 1 (0.1)             | 1          |        |
| Burkholderia cepacia                         | 1 (0.1)             | 0          |        |

1 Coagulase-negative staphylococci;

2 For PPV of all specific bacteria species.
| Bacteria                          | No. (%) of episodes | No. of IIE | PPV, % |
|----------------------------------|---------------------|------------|--------|
| Brevundimonas diminuta           | 1 (0.1)             | 1          |        |
| Shewanella alga                  | 1 (0.1)             | 1          |        |
| Staphylococcus gallinarum        | 1 (0.1)             | 0          |        |
| Staphylococcus pettenkoferi      | 1 (0.1)             | 1          |        |
| Enterobacter hormaechei          | 1 (0.1)             | 1          |        |
| Pseudomonas spp.                 | 1 (0.1)             | 0          |        |
| Serratia plymuthica              | 1 (0.1)             | 1          |        |
| Staphylococcus xylosus           | 1 (0.1)             | 0          |        |
| Streptococcus spp.               | 1 (0.1)             | 1          |        |
| Achromobacter spp.               | 1 (0.1)             | 0          |        |
| Alcaligenes spp.                 | 1 (0.1)             | 1          |        |
| Burkholderia spp.                | 1 (0.1)             | 0          |        |
| Burkholderia gladioli            | 1 (0.1)             | 0          |        |
| Citrobacter Amalonaticus         | 1 (0.1)             | 1          |        |
| Enterococcus spp.                | 1 (0.1)             | 0          |        |
| Flavobacterium spp.              | 1 (0.1)             | 0          |        |
| Morganella morganii              | 1 (0.1)             | 1          |        |
| Neisseria spp.                   | 1 (0.1)             | 1          |        |
| Providencia rettgeri             | 1 (0.1)             | 1          |        |
| Pseudomonas putida               | 1 (0.1)             | 1          |        |
| Raoultella planticola            | 1 (0.1)             | 0          |        |
| Rhodococcus equi                 | 1 (0.1)             | 0          |        |
| Salmonella choleraesuis          | 1 (0.1)             | 0          |        |
| Serratia liquefaciens            | 1 (0.1)             | 1          |        |
| Shewanella putrefaciens          | 1 (0.1)             | 1          |        |
| Staphylococcus lentus            | 1 (0.1)             | 0          |        |

1 Coagulase-negative staphylococci;

2 For PPV of all specific bacteria species.
| Bacteria                        | No. (%) of episodes | No. of IIE | PPV, % |
|--------------------------------|---------------------|------------|--------|
| Staphylococcus pasteuri        | 1 (0.1)             | 0          |        |
| Nutritionally variant streptococci | 1 (0.1)           | 0          |        |
| Streptococcus bovis            | 1 (0.1)             | 0          |        |
| Streptococcus sanguis          | 1 (0.1)             | 1          |        |
| **P-value** ^2                 |                     |            | < 0.0001 |

^1 Coagulase-negative staphylococci;

^2 For PPV of all specific bacteria species.

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Table 3

Positive predictive value (PPV) of coagulase-negative staphylococci (CONS) and non-CONS bacteria (NCONS).

| Bacteria          | No. (%) of episodes | No. of IIE | PPV, % |
|-------------------|---------------------|------------|--------|
| CONS              | 767 (65.0)          | 356        | 46.4   |
| other CONS        | 25 (2.1)            | 9          | 36.0   |
| **P-value-1** ^1  |                     |            | 0.0035 |
| **P-value-2** ^2  |                     |            | 0.0020 |
| NCONS             | 413 (35.0)          | 285        | 69.0   |
| other NCONS       | 86 (7.3)            | 44         | 51.2   |
| **P-value-3** ^3  |                     |            | 0.0010 |
| **P-value-4** ^4  |                     |            | < 0.0001 |

^1 For all specific bacteria species in CONS;

^2 For all specific bacteria species in CONS and other CONS;

^3 For all specific bacteria species in NCONS;

^4 For all specific bacteria species in NCONS and other NCONS.

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**Outcome**

The PPV for all bacteria was 54.3%. The range of PPV for all specific bacteria species was 29.4–100.0% (P < .0001). The PPV for Enterobacter aerogenes, Pseudomonas aeruginosa, Enterobacter cloacae, and
Klebsiella oxytoca is the highest, while the PPV for Staphylococcus cohnii is the lowest. As the commonest bacteria species, the PPV for S. epidermidis was 54.4%. As bacteria species have been reported, the PPV for A. baumannii is 66.7%, and the PPV for S. lugdunensis was 85.7% (Table 2). The PPV for the rare bacteria was 47.7%.

**Ppv Of Cons And Ncons**

Of all episodes, 767 (65.0%) were with CONS, the PPV was 46.4%, and the range was 29.4%-85.7% (P = .0020), only considering the nine specific bacteria species, the difference of the PPV was statistically significant, too (P = .0035). On the other hand, 413 (35.0%) were with NCONS, the PPV was 69.0%, and the range was 40.0%-100.0% (P < .0001); only considering the fifteen specific bacteria species, the difference of the PPV was statistically significant, too (P = .0010) (Table 3).

**Discussion**

The PPV is different of different bacteria species isolated from CSF cultures in adults with suspected bacterial meningitis. Some bacteria species should be considered pathogens in most situations, some bacteria species lead to a dilemma, while some bacteria species should be considered contaminants in most situations. However, even for the bacteria species with the lowest PPV, S. cohnii should not be overlooked as contaminants because over a quarter were pathogens.

Although the PPV of CONS was lower than NCONS, the differences among the incidences of isolated-bacteria-related infected episodes of different bacteria species were statistically significant in CONS and NCONS, respectively. Viewing CONS as a group with low PPV may cause delayed treatment, especially for bacteria species with high PPV such as S. lugdunensis. On the other hand, viewing NCONS as a group with high PPV may cause unnecessary treatment, especially for bacteria species with low PPV such as Acinetobacter Iwoffi. Thus, the findings suggest it is unreasonable to discuss the PPV of bacteria isolated from CSF cultures by whether they are CONS.

The diagnostic criteria were different from previous studies, especially treatment effect was considered. There are several reasons for the change. First, the isolated-bacteria-related infected patients must be treated by sensitive antibacterial agents. Second, aseptic meningitis is common in neurosurgical patients, the clinical features are similar to bacterial meningitis [23], and the improvement of patients with aseptic meningitis was not related to antibacterial agents [21]. Finally, the bacteria isolated may not be the pathogen in patients with bacterial meningitis because of the high contamination rate in CFS cultures and low etiologic diagnosis rate in bacterial meningitis [2, 3].

There are several limitations of this study. First, since it is a retrospective study, only information in the medical records was collected; some patients were excluded because of incomplete data. Second, only positive cultures sampled by lumbar punctures were studied for reducing the disturbing factors; maybe the conclusions of PPV are different for other methods [24, 25]. Finally, the patients with Bacillus spp.,
Corynebacterium spp., Propionibacterium spp., and Micrococcus spp. were not collected in the database of patients with positive cultures.

Although the PPV of different bacteria species isolated from CSF cultures in bacterial meningitis in adults is different and the average was lower than other indicators [26, 27], bacteria are valuable since they lead to etiologic diagnoses and targeted treatments. Therefore, we should try to identify pathogens and contaminants to avoid delayed or unnecessary treatment.

**Conclusion**

This study suggests that the PPV of different bacteria species isolated from CSF cultures is different. It is more reasonable to discuss the PPV of bacteria isolated from CSF cultures through bacteria species rather than whether the bacteria are CONS.

**Abbreviations**

CSF: cerebrospinal fluid; CONS: coagulase-negative staphylococci; NCONS: non-CONS bacteria; PPV: positive predictive value.

**Declarations**

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors’ contributions:** GS and G Zhang designed the study. YY, G Zheng, YK, and JM analyzed and interpreted the data. YY did the statistical analysis. YY drafted the article. All authors read and approved the final manuscript.

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Figures
Figure 1

Flow chart of subject selection. CSF: cerebrospinal fluid.