

Characteristics of Patients With Inflammatory Bowel Disease Who Develop Bloodstream Infection

Mitsuhiro Kamada^{a, d, e}, Motoyasu Miyazaki^{a, d}, Akio Nakashima^a, Yota Yamada^a, Takafumi Nakano^b, Daiki Hagiwara^b, Yukie Komiya^c, Koichi Matsuo^a, Osamu Imakyure^a

Abstract

Background: The causative microorganisms of bloodstream infections (BSIs) in patients with inflammatory bowel disease (IBD) and the clinical characteristics of these patients have not yet been fully identified. Therefore, this study investigated IBD patients who developed BSI to determine their clinical characteristics and identify the BSI-causing bacteria.

Methods: The subjects were IBD patients who developed bacteremia between 2015 and 2019 at Fukuoka University Chikushi Hospital. The patients were divided into two groups according to IBD type (Crohn's disease (CD) or ulcerative colitis (UC)). The medical records of the patients were reviewed to determine their clinical backgrounds and identify the BSI-causing bacteria.

Results: In total 95 patients, 68 CD and 27 UC patients were included in this study. The detection rates of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Klebsiella pneumoniae* (*K. pneumoniae*) were higher in the UC group than in the CD group (18.5% vs. 2.9%, $P = 0.021$; 11.1% vs. 0%, $P = 0.019$, respectively). Immunosuppressive drugs use was higher in the CD group than in the UC group (57.4% vs. 11.1%, $P = 0.00003$). Hospital stay length was longer in the UC group than in the CD group (15 vs. 9 days; $P = 0.045$).

Conclusions: The causative bacteria of BSI and clinical backgrounds differed between patients with CD and UC. This study showed that *P. aeruginosa* and *K. pneumoniae* had higher abundance in UC patients at the onset of BSI. Furthermore, long-term hospitalized patients with UC

required antimicrobial therapy against *P. aeruginosa* and *K. pneumoniae*.

Keywords: Crohn's disease; Ulcerative colitis; Bloodstream infection

Introduction

Inflammatory bowel disease (IBD) is an intractable disease that presents with symptoms such as mucous stool, diarrhea, and abdominal pain due to immune and organic abnormalities in the intestinal tract [1]. IBD is broadly divided into Crohn's disease (CD) and ulcerative colitis (UC). In CD, the entire gastrointestinal tract from the mouth to the anus is inflamed, whereas in UC, only the innermost layer of the intestinal wall in the colon is superficially inflamed [2]. Although the intestinal tract has defense mechanisms against pathogens in the intestinal flora and other bacteria [3], patients with IBD have reduced intestinal immunity with complex interactions between the intestinal flora and host immune function [4, 5]. Therefore, IBD is known to be a risk factor for developing bloodstream infection (BSI) [6].

BSI is a high mortality condition that is often seen in health-care settings. BSI can occur when bacteria enter the bloodstream (i.e., bacteremia), which can lead to sepsis and death. Both gram-positive and gram-negative bacteria are known to cause bacteremia. Understanding the causative organisms of BSI is thought to help reduce patient mortality [7], but differences between the BSI-causing bacteria in CD and UC patients have not been fully elucidated. Although IBD has been listed as a causative agent of bacteremia [8], there remain no large-scale epidemiological data specific to IBD patients. A better understanding of the cause of BSI in CD and UC patients could help determine the initial treatment needed in IBD patients with BSI. The aim of this study was to compare the causative organisms and clinical backgrounds of blood isolates from CD and UC patients from a single medical center.

Materials and Methods

Study design and survey items

The study subjects were IBD patients who developed bacteremia

Manuscript submitted April 11, 2023, accepted May 29, 2023
Published online May 31, 2023

^aDepartment of Pharmacy, Fukuoka University Chikushi Hospital, Fukuoka 818-8502, Japan

^bDepartment of Pharmacy, Fukuoka University Hospital, Fukuoka 814-0180, Japan

^cDepartment of Clinical Laboratory, Fukuoka University Chikushi Hospital, Fukuoka 818-8502, Japan

^dThese authors contributed equally to this work.

^eCorresponding Author: Mitsuhiro Kamada, Department of Pharmacy, Fukuoka University Chikushi Hospital, Fukuoka 818-8502, Japan.
Email: mkamada@fukuoka-u.ac.jp

doi: <https://doi.org/10.14740/jocmr4920>

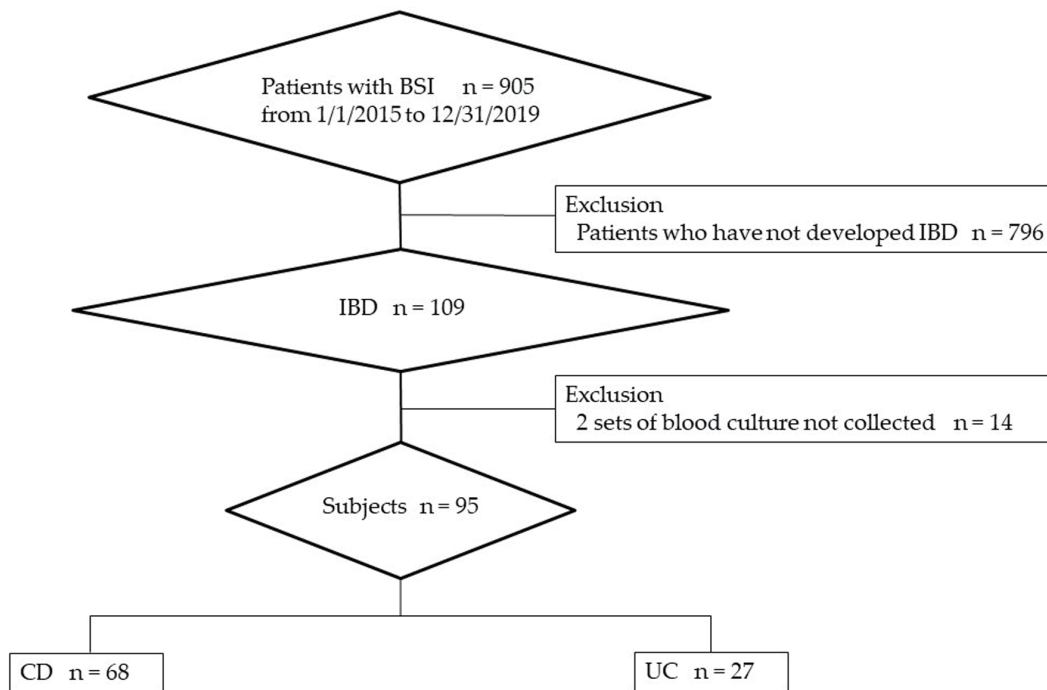


Figure 1. IBD patients with BSI during the study period. BSI: bloodstream infection; CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.

mia between 2015 and 2019 at Fukuoka University Chikushi Hospital, Fukuoka, Japan. We retrospectively evaluated the age, sex, patient background, body mass index (BMI), length of hospital stay, use of immunosuppressants and blood culture results in each case using our electronic medical records. Immunosuppressant users were defined as those who used one of the following six drugs for IBD treatment: infliximab, azathioprine, mercaptopurine, methotrexate, adalimumab, or prednisolone. Patients who did not receive two sets of blood cultures were excluded. This study was approved by the Fukuoka University-Medical Ethics Review Board (approval number C20-05-004). All methods were performed in accordance with the relevant guidelines and regulations.

Bacterial isolate

IBD patients who developed bacteremia after an interval of 3+ months were considered blood culture-positive patients for this study. For each patient, blood cultures were submitted, and the presence or absence of infectious disease-causing factors were verified under a microscope by smear examination. We also reproduced suspected infected lesions by culturing bacteria to confirm whether there was a causative bacterium. The blood culture positive patients were split into two groups based on their IBD type (CD or UC).

Statistical analysis

To compare the CD and UC patients, the Wilcoxon rank sum

test was used to compare the medians between the two groups and the Fisher's exact test was used to compare their frequency differences. The values in the text are given as the median (interquartile range). Patients with a risk rate of < 5% were considered significantly different. JMP statistical analysis software (version 10.0.2; SAS Inc., Tokyo, Japan) was used for all statistical analyses.

Results

During the study period, 905 patients developed BSI. Of these, 109 had IBD. Fourteen patients who did not receive two sets of blood cultures were excluded. In total, 68 CD and 27 UC patients were included in this study (Fig. 1). *Staphylococcus epidermidis* (*S. epidermidis*) was the most frequently detected gram-positive bacteria among all included patients. *Escherichia coli* (*E. coli*) and *Enterobacter sp.* had the highest ratios, respectively, for the gram-negative bacteria (Fig. 2).

Table 1 provides a summary of the clinical backgrounds of the patients. There were no significant differences in the median age, BMI, or prevalence of diabetes between the two groups. Immunosuppressive drug use was higher in the CD group than in the UC group (57.4% vs. 11.1%, respectively; $P = 0.00003$). The hospital stay length was significantly longer in the UC group (median 15 days; 6.0 - 68.0 days) than in the CD group (median 9 days; 2 - 24.3 days) ($P = 0.045$). There was no statistical correlation between immunosuppressant use and length of hospital stay (immunosuppressant user: 9.5 days (2.3 - 30.3) vs. non-users: 15 days (1 - 30.0), $P = 0.446$).

There was no difference in the detection rates between the

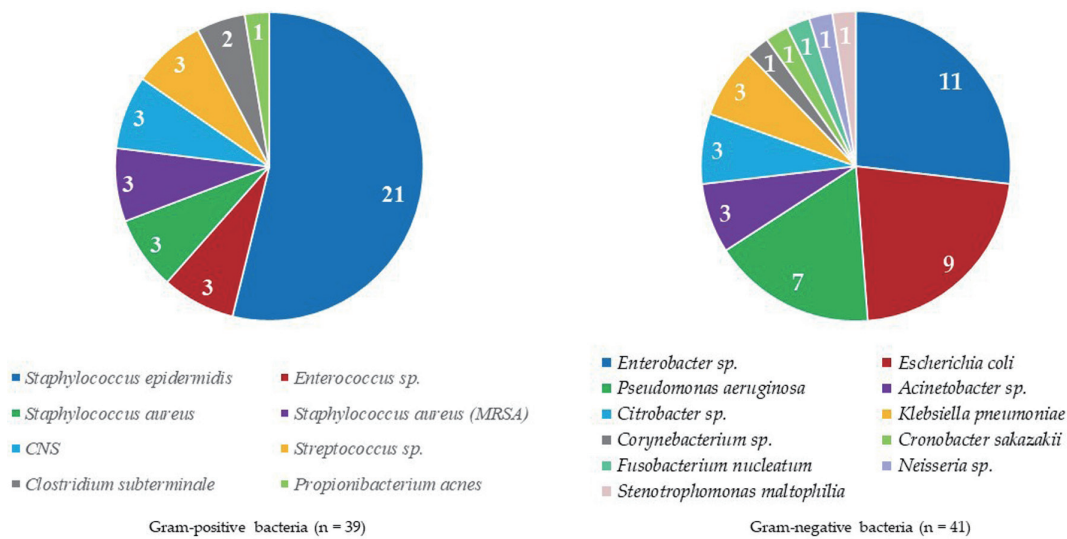


Figure 2. All detected bacteria in inflammatory bowel disease patients with bloodstream infections.

two groups for 16 bacterial species, including *Staphylococcus aureus*. The detection rate of gram-negative bacilli was significantly higher in the UC group (Table 2). The detection rates of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Klebsiella pneumoniae* (*K. pneumoniae*) were higher in the UC than the CD patients (18.5% vs. 2.9%, P = 0.021; 11.1% vs. 0%, P = 0.019, respectively).

Discussion

In this study, we found significant differences in the types of

bacteria detected in CD and UC patients. Due to the nature of the condition, IBD patients often have a catheter inserted into their central artery and an additional intestinal fistula, such as a stoma [9]. This might explain why *S. epidermidis*, which lives in the epidermis, was detected as the most common causative bacterium among the gram-positive bacteria. Similarly, *Enterobacter spp.* and *E. coli* may have been found in greater numbers among the gram-negative bacteria because they are found in greater numbers in the intestinal flora. When both groups were considered as a single group of IBD patients, it became clear that their epidemiology was similar to that of the causative microorganisms in ordinary bacteremia patients

Table 1. Comparisons of Clinical Characteristics Between CD and UC Patients and Infection Focus in Patients With BSI

Characteristics	N (%) or median (IQR)			P value
	Total	CD (n = 68)	UC (n = 27)	
Male	55 (57.9)	40 (58.8)	15 (55.6)	0.821 ^a
Age	57 (40 - 62)	50 (39 - 62)	56 (48 - 67)	0.194 ^b
BMI	19.6 (17.3 - 21.9)	19.5 (17.4 - 21.8)	20.2 (16.9 - 21.9)	0.662 ^b
Diabetes	7 (7.4)	5 (7.4)	2 (7.4)	1 ^a
Length of hospital stay (days)	11 (1 - 32)	9 (2 - 24.3)	15 (6 - 68)	0.045 ^b
Immunosuppressants	42 (44.2)	39 (57.4)	3 (11.1)	0.00003 ^a
Catheter	28	22	6	-
Pneumonia	7	6	1	-
Pyelonephritis	20	9	11	-
Peritonitis	8	5	3	-
Bile tube	4	3	1	-
Dermatitis	1	1	0	-
Enteritis	2	2	0	-
Unknown	25	20	5	-

^aFisher’s exact test. ^bMann-Whitney U test. BMI: body mass index; BSI: bloodstream infection; CD: Crohn’s disease; IQR: interquartile range; UC: ulcerative colitis.

Table 2. Percentage of Detected Bacteria in Patients With CD and UC

Detection bacteria ^a	CD (n = 68) (%)	UC (n = 27) (%)	P-value ^b
Gram-positive bacteria	29 (42.6)	9 (33.3)	0.489
Gram-positive streptococcus	28 (41.2)	8 (29.6)	0.353
<i>Enterococcus sp.</i>	2 (2.9)	1 (3.7)	1
<i>Staphylococcus spp.</i>	23 (33.8)	7 (10.3)	0.625
<i>Staphylococcus aureus</i>	3 (4.4)	0	0.556
MRSA	1 (1.5)	2 (7.4)	0.194
<i>Staphylococcus epidermidis</i>	16 (23.5)	5 (18.52)	0.785
CNS	3 (4.4)	0	0.556
<i>Streptococcus sp.</i>	3 (4.4)	0	0.556
Gram-positive bacillus	1 (1.5)	1 (3.7)	0.490
<i>Clostridium subterminale</i>	1 (1.5)	0	1
<i>Propionibacterium acnes</i>	0	1 (3.7)	0.284
Gram-negative bacteria	24 (35.3)	17 (63.0)	0.021
<i>Acinetobacter sp.</i>	3 (4.4)	0	0.556
<i>Corynebacterium sp.</i>	0	1 (3.7)	0.284
<i>Citrobacter sp.</i>	2 (2.9)	1 (3.7)	1
<i>Cronobacter sakazakii</i>	0	1 (3.7)	0.284
<i>Enterobacter sp.</i>	8 (11.8)	3 (11.1)	1
<i>Escherichia coli</i>	7 (10.3)	2 (7.4)	1
<i>Fusobacterium nucleatum</i>	0	1 (3.7)	0.284
<i>Klebsiella pneumoniae</i>	0	3 (11.1)	0.021
<i>Neisseria sp.</i>	1 (1.5)	0	1
<i>Pseudomonas aeruginosa</i>	2 (2.9)	5 (18.5)	0.019
<i>Stenotrophomonas maltophilia</i>	1 (1.5)	0	1
Enterobacteriology bacteria	26 (38.2)	10 (37.0)	1
Anaerobic bacteria	3 (4.4)	0	0.556
Fungus	3 (4.4)	1 (3.7)	1
The strain is unknown	9 (13.2)	0	

^aMulti-fungus detection. ^bFisher's exact test. CD: Crohn's disease; CNS: coagulase-negative staphylococci; MRSA: methicillin-resistant *Staphylococcus aureus*; UC: ulcerative colitis.

[10]. Thus, we concluded that the major BSI-causing organisms did not differ in IBD and non-IBD patients.

The detection rates for *K. pneumoniae* and *P. aeruginosa* were significantly higher in the UC group compared to the CD group. The high detection rate of *K. pneumoniae* in the UC group was probably because the fine structural damage in the tight junctions between mucosal epithelial cells increased the detection rate of *K. pneumoniae*. Ultrastructure disorders are attributed to tight junctions and cytokines that affect intestinal permeability [1], which allows bacterial translocation and, in severe cases, bacterial invasion to occur due to mucosal defense dysfunction [1]. In such cases, the intestinal flora (e.g., *K. pneumoniae*) permeates the intestinal tract with bacteria, which can cause bloodstream disease. Additionally, UC typically has reduced mucus barrier function due to embryonic cell miniaturization and decreased mucin production [11]. These features

are usually perceived as inflammatory changes since changes in goblet cells can also occur in infectious enteritis; however, a slight decrease in mucus barrier function is also observed in the proximal intestinal tract in patients with distal UC, suggesting that it is an early predisposition that precedes histological inflammation [12]. Thus, we concluded that the high *K. pneumoniae* detection rate in the UC group could have been due to intestinal flora invasion of the blood due to bacterial translocation.

The detection rate of *P. aeruginosa* was also significantly higher in the UC patient group. Since *P. aeruginosa* is not a common intestinal flora [13], it is unlikely that bacterial translocation occurred in the same manner as *K. pneumoniae*. The significantly longer hospital stay lengths found in the UC group compared to the CD group could have allowed for the significant increase in *P. aeruginosa* in the UC group [14]. Prolonged hospitalization and the use of immunosuppressants

are risk factors for BSI [15, 16]. Patients with *P. aeruginosa* had significantly longer median hospital stay length in comparison to those with other bacteria (40 (13.5 - 237.5) vs. 10 (0.75 - 28.0), $P = 0.0263$), but similar trend was not observed in patients with *K. pneumoniae*. In fact, the use of immunosuppressants can cause clinical problems with attenuated *P. aeruginosa* strains. In this study, the use of immunosuppressants was significantly higher in CD patients, but the hospital stay length was significantly higher in the UC patients. In addition, there was no correlation between immunosuppressant use and length of hospital stay, and no significant difference in the detection rate of bacteria between patients with and without the use of immunosuppressant (Supplementary Material 1, www.jocmr.org). These results could explain why the UC patients had significantly more *P. aeruginosa* than the CD patients. Thus, *P. aeruginosa*-derived BSI in CD and UC patients may depend on hospital stay length. Taken together, our findings indicate that IBD patients may require different treatment strategies at BSI onset depending on the type of IBD they have (CD or UC). In particular, UC patients may need therapies that target *P. aeruginosa* and *K. pneumoniae* at BSI onset.

This study had a few limitations. First, this was a pilot study retrospectively conducted in a single Japanese hospital with a relatively small study cohort; therefore, our findings may not be generalized to other hospitals or countries. Second, this study investigated only IBD patients with bacteremia and did not examine any clinical and/or microbiological factors related to bacteremia. A comparative study using a control group using statistical methods such as propensity score matching is needed to clarify the factors associated with bacteremia in IBD patients. Third, although blood culture has been the most common method for diagnosis of bloodstream pathogens, it is being supplanted with more advanced methods, such as molecular tests that can reduce the turnaround time from several days to a few hours [17]. Unfortunately, we have not yet been able to apply such technology to clinical practice, but we plan to consider it and compare these methods in terms of sensitivity and specificity for bacterial detection in the future.

This study showed that *K. pneumoniae* and *P. aeruginosa* had higher abundance in UC patients at the onset of BSI. Furthermore, long-term hospitalized patients with UC required antimicrobial therapy against *K. pneumoniae* and *P. aeruginosa*.

Supplementary Material

Suppl 1. Percentage of Detected Bacteria in the Use of Immunosuppressants.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no competing interests.

Informed Consent

Not applicable.

Author Contributions

KM, MM, and OI contributed to the concept and design of the study. KM, MM, KM, and YK conducted the study. KM, AN, TN, and DH were involved with data analysis and interpretation of the results. KM and MM drafted the manuscript. KM, DH, and OI supervised the entire project and reviewed the manuscript. All the authors approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. *J Inflamm Res.* 2014;7:113-120. [doi pubmed pmc](#)
2. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A.* 2007;104(34):13780-13785. [doi pubmed pmc](#)
3. Wehkamp J, Schmid M, Fellermann K, Stange EF. Defensin deficiency, intestinal microbes, and the clinical phenotypes of Crohn's disease. *J Leukoc Biol.* 2005;77(4):460-465. [doi pubmed](#)
4. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell.* 2006;124(4):837-848. [doi pubmed](#)
5. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, et al. Diversity of the human intestinal microbial flora. *Science.* 2005;308(5728):1635-1638. [doi pubmed pmc](#)
6. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol.* 2015;37(1):47-55. [doi pubmed pmc](#)
7. Al-Hasan MN, Wilson JW, Lahr BD, Eckel-Passow JE, Baddour LM. Incidence of *Pseudomonas aeruginosa* bacteremia: a population-based study. *Am J Med.* 2008;121(8):702-708. [doi pubmed pmc](#)
8. Ministry of Health, Labour and Welfare. Japan Nosocomial Infections Surveillance. <https://janis.mhlw.go.jp/re->

- port/kensa.htm. Accessed Oct 3, 2022.
9. Shibata W, Sohara M, Wu R, Kobayashi K, Yagi S, Yaguchi K, Iizuka Y, et al. Incidence and outcomes of central venous catheter-related blood stream infection in patients with inflammatory bowel disease in routine clinical practice setting. *Inflamm Bowel Dis*. 2017;23(11):2042-2047. [doi pubmed](#)
 10. Nakada Y, Fujiwara H, Kaminada N, Takane H, Chikumi H. Blood culture-positive episodes in a tertiary university hospital in Japan. *Jpn J Environ Infect*. 2016;31:107-112.
 11. Tytgat KM, van der Wal JW, Einerhand AW, Buller HA, Dekker J. Quantitative analysis of MUC2 synthesis in ulcerative colitis. *Biochem Biophys Res Commun*. 1996;224(2):397-405. [doi pubmed](#)
 12. Wlodarska M, Thaiss CA, Nowarski R, Henao-Mejia J, Zhang JP, Brown EM, Frankel G, et al. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. *Cell*. 2014;156(5):1045-1059. [doi pubmed pmc](#)
 13. Ramphal R. Infections due to *Pseudomonas*, *Burkholderia*, and *Stenotrophomonas* species. In: Jameson JL, Fauci AS, Kasper DL, et al., editors. *Harrison's principles of internal medicine*, 20th ed. McGraw-Hill, New York, NY, USA. 2018; p. 1167-1173.
 14. Porco FV, Visconte EB. *Pseudomonas aeruginosa* as a cause of infectious diarrhea successfully treated with oral ciprofloxacin. *Ann Pharmacother*. 1995;29(11):1122-1123. [doi pubmed](#)
 15. Kollef MH, Zilberberg MD, Shorr AF, Vo L, Schein J, Micek ST, Kim M. Epidemiology, microbiology and outcomes of healthcare-associated and community-acquired bacteremia: a multicenter cohort study. *J Infect*. 2011;62(2):130-135. [doi pubmed](#)
 16. Delle Rose D, Pezzotti P, Fontana C, Altieri A, Minelli S, Mariotti B, Cerretti R, et al. An in-depth analysis of nosocomial bloodstream infections due to Gram-negative bacilli: clinical features, microbiological characteristics and predictors of mortality in a 1 year, prospective study in a large tertiary care Italian hospital. *Infect Dis (Lond)*. 2019;51(1):12-22. [doi pubmed](#)
 17. Dunbar SA, Gardner C, Das S. Diagnosis and management of bloodstream infections with rapid, multiplexed molecular assays. *Front Cell Infect Microbiol*. 2022;12:859935. [doi pubmed pmc](#)