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Blood Culture Positive for Gram-Positive Rods: Contamination or a True Infection-A literature Review

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ABSTRACT

Today, human bloodstream infections (BSIs) are recognized as a major cause of morbidity and mortality worldwide. The bacteria, responsible for bacteremia, are usually identified in diagnostic clinical laboratories, using blood cultures. True bacteremia is defined as a positive blood culture (>15 CFU/mL), with signs and symptoms of infection (e.g., fever and chills). A wide range of bacteria can cause true bacteremia and some bacterial isolates from BSIs may be responsible for contamination. Gram-positive bacilli, such as Bacillus species, and coryneform bacteria are suspected sources of contamination in blood cultures. However, in certain patients, such as immunocompromised patients and intravenous drug users, gram-positive bacilli can act as a true pathogen. Therefore, it is important to know when gram positive bacilli act as a true pathogen and when they act as contamination. So, the rapidly diagnosis of true pathogens and appropriate treatment play a very important role in controlling infection with these bacteria. Effective measures are especially important in patients with an underlying disease or an immunocompromised status. In this article, we reviewed the literature on common Gram-positive rod-shaped bacteria, which were isolated from blood cultures and were suspected to be true pathogens or contaminants.

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Introduction

The human blood is considered to be sterile under normal and healthy conditions. Due to acute localized or systemic infections, microorganisms can enter the bloodstream through the lymphatic system (1). Bacteremia is defined as the presence of bacteria in the bloodstream. A bloodstream infection (BSI) occurs when the immune system cannot rapidly remove the microorganisms from the blood (2). BSIs are recognized as one of the main causes of mortality among hospital-admitted patients.The bacteria, responsible for bacteremia, are usually identified in diagnostic clinical laboratories, using blood cultures. True bacteremia is defined as a positive blood culture (>15 CFU/mL), with signs and symptoms of infection (e.g., fever and chills) (3). Staphylococcus aureus, Streptococcus pneumoniae, and Escherichia coli are the most commonly isolated pathogens of BSIs (4).Bacteremia and endocarditis with Gram-positive rods (GPRs), which are often considered as contaminants, are known to be uncommon (5). Blood culture contamination may be caused by a non-pathogenic microorganism, which is assumed to be present in the culture during either specimen collection or processing. Among these contaminants, different Bacillus species have the highest frequencies. Other Gram-positive bacteria, which are often considered as contaminants in blood cultures, include coagulase-negative Staphylococcus species (75-88% of contaminated cases), viridans streptococci, and Micrococcus species

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(1,6). Also, coryneform bacteria, such as Arthrobacter, Brevibacterium, Corynebacterium, and Mycobacterium species, as well as Propionibacterium and Lactobacillus species, are sources of contamination in blood cultures (7-10). Blood culture contamination may be associated with different factors, such as the skin antisepsis procedure, type of antiseptic agents for cleaning the blood collection bottles, type of blood sampling system, and antiseptic blood culture techniques.

An isolate collected from a blood culture is suspected to be a contaminant under two conditions: First, when a skin microflora isolate of coagulase-negative Staphylococcus (CoNS), Corynebacterium species, Micrococcus species, Bacillus species, or Propionibacterium species is collected from one or more blood cultures, without isolating the same organism from another potentially infected site (e.g., intravenous catheter tip); and second, when a common skin microflora is isolated from a patient with inconsistent clinical signs, no attributable risks, and recovery without specific therapy (11-13).

In this study, we reviewed the literature on common Gram-positive rod-shaped bacteria, which were isolated from blood cultures and were suspected to be true pathogens or contaminants.

Literature review

1. *Gram-positive bacilli isolated from blood cultures*

1.1. Bacillus species

Bacillus species are a group of rod-shaped, Gram-positive, aerobic or facultative, endospore-forming bacteria, with a low guanine-cytosine (GC) content. They are usually arranged in pairs or chains with round or square ends and are motile by means of peritrichous flagella (14,15).

Lysinibacillus and Paenibacillus are common Gram-positive Bacillus-shaped bacteria, initially known as Bacillus species. These environmental bacteria, if isolated in diagnostic microbiology laboratories, are assumed to be contaminants, especially in blood cultures due to their ubiquitous nature and lack of pathogenicity. These bacteria, with vegetative or sporulated forms, are widely distributed in nature, and their potential to induce human diseases has been documented (16). Bacillus species, isolated as pathogenic agents from blood cultures, include B. anthracis, B. cereus, B. pumilus, B. thuringiensis, B. licheniformis, B. subtilis, B. megaterium, L. sphaericus, L. fusiformis, and P. amylolyticus (Table 1) (17-21). Isolation of B. anthracis from blood cultures can indicate a high risk and poor prognosis in patients (21).However, bacteremia, caused by other Bacillus species, is predominantly attributed to B. cereus, especially in immunocompromised patients with hematologic malignancies (Table 1)(22,23).

B. anthracis, as the causative pathogen of anthrax, is a tier 1 select agent. It is associated with a high risk of deliberate misuse and other adverse consequences. Pulmonary anthrax, caused by the germination of B. anthracis spores in mediastinal lymph nodes, induces hemorrhagic mediastinitis, which can lead to bacteremia and meningitis.

The pathogenic spectrum of B. cereus ranges from probiotic strains to highly toxic, lethal strains for humans (24,25). From a taxonomic perspective, B. cereus sensu lato (also known as the B. cereus group) consists of six species, including B. cereus and B. thuringiensis, with a high degree of phenotypic similarity (26). Commonly, individual species from the B. cereus group cannot be distinguished in diagnostic laboratories, with the exception of B. anthracis, which is non-motile and non-hemolytic (27).

B. cereus in the hospital setting may be attributed to the contamination of linens, fiber-optic bronchoscopy equipment, ventilator supplies, diapers, washing apparatuses, steamed tissues, intravenous fluids, dialysis equipment, and alcohol prep pads, causing outbreaks and pseudo-outbreaks in intensive care units (ICUs). Moreover, B. cereus has been isolated from umbilical cords (in neonates), the hands of ICU personnel, and endotracheal secretions. The most common characteristic of true bacteremia, caused by Bacillus species (especially B. cereus as a common species), is the ability to form a biofilm. The produced biofilm can lead to the attachment of the bacterium to the catheter (3,15,28).

The biofilm is composed of hydrated extracellular polymeric substances (EPS), proteins, lipids, and DNAs, forming a self-produced matrix. The biofilm matrix in the Bacillus life cycle exhibits the mechanical stability of biofilms, acts as an intermediary adhesive to the surface, and forms a sticky, three-dimensional lattice polymer, which interconnects and transiently immobilizes the biofilm cells (15). Generally, Bacillus species are involved in Bacillus catheter-related bloodstream infections (CRBSIs) and central line-associated bloodstream infections (CLABSIs) (29).

Farnia et al. (2020) in a cross-sectional study, showed that the prevalence of physical and psychological abuse was equal to 43.2%. Being a housewife mother increased the chance of child abuse by 0.62 times, and the occurrence of psy

chological problems in the family increased the chance of child abuse by 2.56 times. The chance of child abuse among the parents who were both addicted was 2.66 times more than among the families where the father alone was addicted (48).

1.2. Corynebacterium species

The Corynebacterium genus consists of various species and strains. Until April 2017, the Pathosystems Resource Integration Center (PATRIC) data-

Table 1: Strains of Bacillus spp. associated with blood-stream infections

Species (Numbers, %)	Type of culture sys-tem	Patient condition/Underlying disease	Location/Time/ Numbers of cases	Ref
B. cereus	Not mentioned in the reference	Inject drugs (PWIDs)a	California, USA / 2013 (3 episodes)	(69)
B. cereus	Manual	Nosocomial BSI (central or peripheral vascular catheter)	Japan / 2008 to 2013 (51 episodes)	(110)
B. cereus	Manual	Neutropenic(hematological compli-ca-tion) / IVDUs b, poly-traumatized (Non hematological)	Switzerland/ 1997-2013 (56 episodes)	(111)
B. cereus	Not mentioned in the reference	Haematological malignancies	Belgium/ 2018 (2 cases)	(112)
B. cereus	Automated system	Pre-term neonate	Australia/ 2019 (A neonate case)	(113)
B. cereus	Manual	Hematological diseases	Japan / 2012 (13 cases)	(114)
B.cereus(42, 80.7%), B. subtilis(4,7.7%), B. megaterium (2, 3.8%), Bacillus spp. (4,7.7%)	BacT/ALERT SA and SN bottles	All patients have been cancer.	Sapporo, Japan / 2011 to 2016 (52 cases)	(115)
B. cereus	Not mentioned in the reference	Pre-term neonates	Brazil / 2011 (2 cases)	(116)
B. cereus	BACTEC 9000 sys-tem	All patients with positive blood culture for GPRs divided two groups: with comorbidity and without.	Japan / 2003-2012 (29 cases)	(117)
B. pumilus	BacT/ALERT, PF Paediat-ric FAN	Neonatal infants, one them was health condition and one health had Prader–Willie syndrome	Greece / 2012 (2 cases)	(118)
B.pumilus	Manual	----------	Japan / 2019 (A case)	(119)
B.pumilus	BacT/ALERT, PF pediatric FAN	A seven-year-old healthy child	Italy / 2016 (A case)	(17)
B. cereus	Not mentioned in the reference	Immunocompetent patient	Amsterdam, Netherlands/ 2011 (1 case)	(18)
B. cereus	Manual	Preterm neonates	France / 2013 (2 cases)	(120)
B. cereus	Manual, NGKG agar (Nis-sui, Tokyo, Ja-pan)	23 patients with and 45 patients with-out hematologic malignancies	Japan / 2010 (68 cases)	(121)
B. cereus	Not mentioned in the reference	Myeloid leukemia / Hepatic malignant vascular tumor / Anorexia nervosa	Japan / 2019 (3 cases)	(72)
B. licheniformis & B.subtilis	Manual	oesophageal perforation	Seoul, Republic of Korea / 2012	(19)
B. cereus (9 numbers), other Bacillus spp. (18 numbers)	Not mentioned in the reference	Pediatric oncology patients with febrile neutropenia	Utah, U.S / 2016 (27 cas-es)	(122)
B. cereus	Not mentioned in the reference	Propionic academia / indwelling ve-nous catheter	Turkey / 2016(A case)	(123)
B. subtilis	Manual	Chronic lymphocytic leukemia / Usage of probiotic strains of B. subtilis	Italy/ 1998 (A case)	(124)
B. cereus	Manual	Neonates, NICUd	Germany / 2019 (2 cases)	(125)
B. cereus	Manual	----------	U.S / 2016 (A case)	(126)
B. anthracis	Not mentioned in the reference	Intravenous drug user	U.K / 2014 (A case)	(21)
B. anthracis	Gene-Xpert instru-ment	LOD of this detection method was 5 genome equivalents per reaction, and 10 CFU/ml blood for both B. anthracis Sterne and V1B strains.	U.S / 2017 (A case)	(127)

[a] Persons Who Inject Drugs (PWID), [b] Intravenous drug users, [c] Lysinibacillus sphaericus previously known as Bacillus sphaericus, d NICU: Neonatal intensive care unit, [e] L. fusi-formis: Lysinibacillus fusiformis.

base (30) identified 466 genomes from 83 Corynebacterium species (31). The most common clinical species include the C. diphtheriae group, C. xerosis, C. striatum, C. minutissimum, C. amycolatum, C. glucuronolyticum. C. argentoratense, C. matruchotii, and C. glutamicum (31,32). The pathogenicity of Corynebacterium species is significantly associated with an immunocompromised status or indwelling catheters (33).These bacteria are known as lipophilic and rapid urea-positive (reaction in approximately 60 seconds) organisms. The hippurate is hydrolyzed in these bacteria, whereas aesculin and gelatin are not hydrolyzed. Also, nitrate is not reduced, and acid is produced from glucose (34). Non-diphtheritic corynebacteria are aerobic, non-sporulating, pleomorphic, Gram-positive bacilli, which are more uniformly stained than C. diphtheriae. They lack metachromatic granules and are arranged in a palisade fashion (35). They are usually commensal organisms of the skin and mucous membranes. Diphtheroids, isolated from BSIs, are clinically significant if they show pure growth within 48 hours (Table 2) (32). Diphtheroid species, as etiological pathogens in the human blood cultures of bacteremia patients, include C. jeikeium, C. urealyticum, C. minutissimum, C. mucifaciens, C. accolens, C. afermentans subsp. afermentans, C. afermentans subsp. lipophilum, C. amycolatum (zoonotic), C. aurimucosum, C. bovis (zoonotic), C. confusum, C. coyleae, C. durum, C. falsenii (zoonotic), C. freneyi, C. glucuronolyticum (zoonotic), C. imitans, C. jeikeium (zoonotic), C. propinquum, C. tuscaniense, and C. timonense (36,37). It should be noted that Corynebacterium species have a high morphological similarity to Listeria species, and both species are positive on catalase tests. Therefore, it is necessary to differentiate Corynebacterium species from Listeria species when isolating them from blood cultures, based on esculin hydrolysis and motility tests (at 20-25°C and 35°C, respectively)(38).

Since there are no Clinical and Laboratory Standards Institute (CLSI) guidelines for the disc diffusion method of diphtheroids, different studies have used the method proposed by Reddy BS et al., according to the British Society for Antimicrobial Chemotherapy (BSAC) guidelines for ciprofloxacin, penicillin, and vancomycin[39]. Other antibiotics CLSI 2014 guidelines for Staphylococcus aureus dominantly have been followed. S. aureus ATCC 25923 was used as control (32).

Table 2. The empirical antibiotic therapy and the antibiotic resistance of gram-positive rods due to true blood-stream infections episodes

Species	Empirical Therapy	Antibiotic Resistance	Comments	Ref
B. subtilis	Imipenem Combined antibiotic therapy (ceftazidime, amikacin, and vancomycin)	Strain isolated on 16 days; chloramphenicol R Strain isolated on 19 days; penicillin R, erythromycin R, rifampin R, and novobiocin R	The described recovery of two different Bacillus strains from the same probiotic preparation in distinct septicemic episodes is indicative both of the severe immunodeficiency of the patient and of a persistence of the microorganism in the intestinal tract	(124)
B. cereus	Appropriate therapy: Piperacillin-tazobactam (3 cases), vancomycin (2 cases), or ampicillin–sulbactam, cefmetazole, clindamycin, amikacin,or cefoperazone–sulbactam (1 case each) Inappropriate therapy: cefepim (6 cases), ampicillin–sulbactam, cefazolin, ceftriaxone/cefotaxim (3 cases each), ceftazidime (2 cases), cefotiam, or clindamycin (1 case each)	48.3–100 % of isolates were resistant to cephalosporins, 65.5 % were resistant to clindamycin, and 10.3 % were resistant to levofloxacin	Of 29 isolates no vancomycin, gentamicin, and imipenem-resistant isolates were found	(117)
B. cereus	Vancomycin, carbapenems	Penicillin (18/18),ceftriaxone (16/16), clindamycin (4/7)	All tested isolates were susceptible to vancomycin (20/20), fluoroquinolones (16/16), gentamicin (9/9) and cotrimoxazole (8/8)	(111)
B. cereus	Vancomycin, Meropenem, and amikacin	Not mentioned in the reference	Sensitive to meropenem, vancomycin and amikacin	(123)
B. cereus	Meropenem, vancomycin, and fosfomycin	Not mentioned in the reference	Sensitive to imipenem, meropenem, vancomycin, linezolid, and levofloxacin based on antibiogram test	(125)
B. cereus	IV vancomycin Daptomycin	Resistant to penicillin	Smoking about 1 pack of cigarettes daily	(126)

1-3 Cutibacterium species

Cutibacterium species, formerly known as Propionibacterium species, are non-sporulating, Gram-positive anaerobic bacilli and commensal bacteria of the skin. These non-pathogenic bacteria are common contaminants of the blood and body fluid cultures. These species are slow-growing and require at least six days for growth in cultures (40).

They belong to the microflora of the skin, conjunctiva, external ear canal, mouth, and upper respiratory tract, and sometimes, the intestines, urethra, and vagina (41-43). Moreover, Cutibacterium acnes is a common contaminant of blood cultures and is generally assumed to be non-pathogenic in humans (44). Cutibacterium species can cause infective endocarditis and BSI, especially in carriers of mechanical heart valves, pacemakers, or implantable cardioverter defibrillators, given their ability to adhere to foreign body surfaces and produce biofilms (Table 3) (45).

Table 3. Clinical isolates of Corynebacterium spp. associated with blood-stream infections

Species (Numbers, %)	Type of culture system	Patient condition/Underlying disease/ Antibiotic resistance of isolate (comment)	Location/Time/ Numbers of cases	Ref
C. diphtheriae	Manual	Hypertension, mild mitral regurgitation, gout and asthma Susceptible to ciprofloxacin, ceftriaxone, gentamicin, vancomycin and meropenem. Intermediate susceptibility to penicillin	Ireland / 2019 (A case)	(128)
C. striatum (64 isolates of 51 patients)*	Not mentioned in the reference	Diabetes and solid tumors	South Korea/ 2018/ 64 isolates of 51 patients	(129)
16 (51.6%) C. jeikeium, 6 (19.4%) C. striatum, 4 (12.9%) C. amycolatum, 2 (6.5%) C.afermentans and 1 isolate (3.2%) C. propinquum	BACTEC 9120 system	Hospitalized patients (various clinical wards)	Gaziantep, Turkey /February 1999 to June 2001 /31 of 915 positive Blood culture	(9)
C. striatum	Manual	Chronic renal insufficiency & hypertensive cardiovascular disease	Japan / 2017 (A case)	(130)
Nontoxigenic- C. diphtheriae	Manual	Acute myelogenous leukemia (AML)	U.S / 2012 (A case)	(131)
Diphtheroids	Manual	Two-week history of extreme malaise and easy bruisability	Chicago/ 1986 (A case)	(132)
C.pseudotuberculosis, C. minutissimum, C. ulcerans and C. renale	BacT-Alert & BACTEC TM 9050 systems	Blood isolates were nearly sensitive to most of the antimicrobial agents (not all) A high level of resistance to Tigecycline was exhibited by the isolates	India/ 2013-2014 (A case)	(32)
Corynebacterium spp. C. striatum (n=38), C. jeikeium(n=6), C. argentoratense (n=2), other spp (n=19)	BACTEC 9240 & 9120; BD Diagnostic Systems	Central venous catheter in place (n=39) Peripheral venous catheter in place (n=5) Not have a venous catheter (n=19)Diabetes mellitus, Malignancy, ESRD on dialysis therapy, liver cirrhosis	Tokyo, Japan / 2017 (63 cases) Bacteremia (n = 28) Contamination (n = 35)	(133)
C. striatum	Not mentioned in the reference	Malignancy (n = 7), heart disease (n = 4) severe burns (n=3), pemphigoid (n=2), encephalitis/encephalopathy (n = 2), cerebral contusion/ hemorrhage (n = 2), collagen disease (n = 1), previous organ transplantation (n =1), postoperative cholangiocarcinoma (n =1) and acute hepatorenal failure (n =1) The majority of the strains were multidrug resistant (MDR) Susceptible to only vancomycin	Chiba, Japan / 2010-2014 (24 cases)	(134)

C. minutissimum	BacT-alert (Organon-Teknika)	Atrial fibrillation, pneumonia, urinary tract infection, and an episode of lower-extremity cellulitis the year before admission to the hospital.	New Hampshire, US/ 2002 (A case)	(135)
C. ureicelerivorans sp. nov.	Manual	Fever & exhibiting signs of septicemia The patient's antibiotic regimen: vancomycin, azithromycin.	Bonn, Germany/ 2007 (A case)	(34)
C. striatum	Manual	Cirrhosis Resistance of isolate was to penicillin, clindamycin, Cefotaxime, erythromycin, and ciprofloxacin Treatment was done by Daptomycin.	Brooklyn, NY, USA/ 2019 (A case)	(136)

1-4 Propionimicrobium species

Propionimicrobium is a non-spore-forming, anaerobic, non-motile,Gram-positive genus from the family Propionibacteriaceae, with one familiar species (P.lymphophilum)(46).

This bacterial species exists in the human skin and the genitourinary system; however, its pathogenicity is not well-established. Only two cases of urinary tract infection have been described recently [47]. In this regard, Cobo F. et al. recently reported a case of bacteremia, caused by this microorganism, in an elderly patient (2020, Granada, Spain) (Table 3)(48).

1.5. Lactobacillus species

Lactobacillus is the largest genus within the group of lactic acid bacteria (49). Lactobacillus species are commensal colonizers of the mouth, gastrointestinal tract, and occasionally, the female genitourinary system (50). However, its significance as a pathogen is frequently overlooked. Most patients with Lactobacillus bacteremia are immunosuppressed (Table 3)(51,52). Lactobacilli are phylogenetically divided into seven groups: L. buchneri group (bu), L. casei group (ca), L. delbrueckii group (de), L. plantarum group (pl), L. reuteri group (re), L. sakei group (sa), and L. salivarius group (sl)(53). L. fermentum, L. plantarum, L. casei, and L. rhamnosus have been isolated from the gut, whereas L. antri, L. gastricus, L. kalixensis, L. reuteri, and L. ultunensis have been isolated from the stomach mucosa. Moreover, L. crispatus, L. gasseri, L. jensenii, L. vaginalis, and L. inersare are known as common vaginal isolates. Also, L. acidophilus can be naturally found in the human and animal gastrointestinal tract and mouth. In general, the most common clinical isolates in humans include L. rhamnosus and L. casei (54-56). The clinical outcomes of Lactobacillus bacteremia range from asymptomatic to severe septicemia. Lactobacillus bacteremia may be also associated with pneumonia, deep abdominal abscesses, or endocarditis. Lactobacillus bacteremia may be underdiagnosed, as lactobacilli are difficult to culture and identify, and, in many cases, they are regarded as contaminants (50,57-59).

The Lactobacillus species are non-pathogenic organisms, used as probiotics to prevent antibiotic-associated diarrhea. Their presence in the gastrointestinal tract is related to defense against pathogens, immune system stimulation, colonic health, and host nutrition (60). They are also involved in a wide range of infections, including bacteremia, endocarditis, urinary tract infections, and intraabdominal, liver, and spleen abscesses (61). Endocarditis, caused by Lactobacillus, is associated with structural heart disease, recent history of surgery, extended antibiotic or probiotic use, reduced immunity, dental problems, and other comorbidities. Some clinical studies have reported a 30% mortality rate for endocarditis (62,63).

L. casei, L. rhamnosus, L. plantarum, L. jensenii, and L. paracasei are some Lactobacillus species, which have been reported as bacterial etiologies of human endocarditis (64-67). Also, there are sporadic cases of infection, related to Lactobacillus-containing probiotics (68).

2. Risk factors for BSIs caused by Gram-positive rods

The blood cultures of persons who inject drugs (PWIDs), as well as users of heroin and drug-injecting paraphernalia, are mostly positive for Bacillus species (69). Approximately 61% to 68% of heroin street samples in the United States are contaminated with pathogens, mainly non-anthrax Bacillus species (70).

Underlying diseases, as risk factors for BSIs caused by B. cereus, are as follows: Addiction; valvular heart disease; heparin injection; pediatric tumors (3% of cancer children with bacteremia); blood malignancies (especially in cases of bacteremia, associated with possible brain involvement, such as meningitis or abscess); peritonitis;

traumatic or surgical wounds; indwelling catheters; premature neonates; intravenous high-calorie diet or amino acid-enriched nutrition; long duration of catheter placement; use of a catheter for sick patients, with dust near the hospital beds in the healthcare setting; and needle sharing among intravenous opioid users (23,71-73).

In this regard, Jae-Hoon Ko et al. (2015) conducted a case-control study and evaluated bacteremia, caused by Bacillus species in adult cancer patients. They identified the independent risk factors for the development of Bacillus-related bacteremia in adult cancer patients. The history of extended-spectrum cephalosporin use in the past month and having a long-term central venous catheter (CVC) were the independent risk factors for Bacillus-induced bacteremia in adult cancer patients (74).

Generally, B. anthracis, as the causative agent of anthrax, is a tier 1 select agent, with a remarkable potential to cause mass casualties and other adverse consequences (75, 76). Following exposure to the spores of B. anthracis, rapid diagnosis and antibiotic therapy are necessary to prevent anthrax. Nevertheless, in the available techniques, it takes 12 hours to five days to detect B. anthracis in the blood using blood culture, as the gold standard (70,77,78).

However, this bacterium is a potential pathogen, and its presence in the blood culture must be considered as a serious threat. The most important risk factors for lactobacilli infections include diabetes mellitus, pre-existing structural heart disease (infective endocarditis), cancer (e.g., leukemia), total parenteral nutrition, broad-spectrum antibiotic use, chronic kidney disease, inflammatory bowel disease, pancreatitis, chemotherapy, neutropenia, organ transplantation (e.g., liver transplantation), HIV infection, and steroid use[68, 79]. The high-risk groups for Lactobacillus infections include the elderly, pregnant women, neonates, immunocompromised individuals, and adults with malignancies. Moreover, listeriosis can be a serious disease, with an approximate mortality rate of 20%; the case fatality rate may also increase in high-risk groups.

The risk factors for BSI were further stratified, based on the stage of liver disease. Patients with cirrhosis have a greater risk of developing Gram-positive BSI, compared to patients with chronic hepatitis [80-82]. Belmares J and etal (2007; USA) have been analyzed 129 cases of Corynebacterium endocarditis and bacteremia followed it included inclusion criteria[83]. They concluded that Corynebacterium endocarditis typically infected the left heart of adult males, and nearly one-third of patients had an underlying valvular disease. Endocarditis and BSIs, caused by C. striatum, C. jeikeium, and C. hemolyticum, are possibly nosocomial risk factors. Also, it was found that C. amycolatum infections occurred exclusively in females, while C. pseudodiphteriticum was found predominantly in men.Patients, undergoing blood and marrow transplantation, are prone to bacteremia. A study by M. Bock A et al. (2012) in Minnesota, USA, showed that among patients with allogeneic transplants, myeloablative conditioning was associated with a significantly higher risk of bacteremia, compared to reduced-intensity conditioning; a similar finding was reported regarding the development of acute graft-versus-host disease (aGVHD)[84]. Also, these patients developed infections with higher resistance to antibiotics, which are commonly used against bacterial organisms. Overall, the risk factors for Lactobacillus bacteremia include impaired host defense, severe underlying diseases, history of surgery, and prolonged ineffective antibiotic therapy for lactobacilli (63).

3.*Treatment and antibiotic resistance of Gram-positive rods*

Treatment of B. cereus infections is based on the antibiotic susceptibility profile. However, species-specific criteria for the in vitro assessment of antibiotic activity are yet missing [85, 86]. Also, the course of treatment is usually long, that is, 2-4 weeks for bacteremia and 4-6 weeks for endocarditis [87]. B. cereus, which is usually resistant to only β-lactams, can be assayed in clinical laboratories. This species shows resistance to penicillin, trimethoprim/sulfamethoxazole, and cephalosporins [88]. The best treatment option for B. anthracis infections includes a complex therapy, targeting both bacterial growth and toxin production. Among chemotherapy agents, ciprofloxacin, clindamycin, and penicillin are particularly effective due to the production of beta-lactamases (Table 4) (85, 86, 89, 90).

According to our literature review, Bacillus species were completely resistant to vancomycin, aminoglycosides, quinolones, gentamicin, carbapenems, tigecycline, fluoroquinolones, and newer antimicrobial drugs (linezolid, daptomycin, and telavancin) [69, 91]. They also showed intermediate susceptibility to clindamycin, tetracycline, and erythromycin. However, differences between in vitro methods have led to inconsistencies regarding the susceptibility cut-off points; also, the exact effect of minimum inhibitory concentration (MIC) on the clinical outcomes is obscure in vitro (87,92).

Table 4 presents several examples of empirical therapy, in addition to the antibiotic susceptibility patterns of clinical B. cereus isolates. In patients with intravenous lines, if the catheter is main-

tained due to the presence of a biofilm-forming Bacillus mass in the intravenous line, non-vancomycin antibiotic therapy can result in a notably shorter hospitalization. Therefore, the potential of B. anthracis to become resistant to antimicrobial drugs must be considered in the treatment of anthrax. According to previous studies, the sensitivity of B. anthracis to ciprofloxacin reduced from 0.1 to 1.6 mg/L after collecting 21 subcultures; therefore, close monitoring of anthrax treatment is essential [3, 93, 94]. Moreover, it is important to follow-up patients with bacteremia, caused by Bacillus species, to prevent poor outcomes, such as recurrence of bacteremia or endocarditis and internal abscesses. However, there is no standard methodology for susceptibility testing of coryneform bacteria. The National Committee for Clinical Laboratory Standards (NCCLS) has not defined any breakpoints for the clinical categories of antimicrobial agents against coryneform bacteria, and in Listeria species, only susceptibility to ampicillin and penicillin has been suggested (95).

C. jeikeium, C. urealyticum, and C. amycolatum are common multi-resistant organisms, and only glycopeptides remain universally active against these species (96-99). Current treatments for invasive listeriosis involve a combination of ampicillin or penicillin G with gentamicin or another aminoglycoside (100). The first multi-resistant strain of L. monocytogenes was isolated in France in 1988 [101]. Listeria species are naturally resistant to Cefotaxime (102).

It has been previously shown that ketolides show a broader spectrum of activity, compared to macrolides, as they are active against macrolide-susceptible Gram-positive cocci and Gram-positive organisms (macrolideresistance is caused by an active efflux or inducible production of methylase (103). Treatment of Propionibacterium infections, such as infective endocarditis, primarily consists of a β-lactam antibiotic, often combined with an aminoglycoside, although tibiotic, often combined with an aminoglycoside, although P. acnes is frequently resistant to the latter. Oral rifampicin is added because of its ability to penetrate into the bacterial biofilm; also, it may be combined with a quinolone antibiotic. In vitro results suggest that the combination of Daptomycin with rifampicin is highly active against P. acnes biofilms (45,104,105).

However, the antimicrobial susceptibility of Lactobacillus species is poorly defined, partly due to its taxonomic complexity, and different methods, recommended by CLSI and the International Dairy Federation (IDF), have been used for analysis[106]. The MIC of this bacterial species was interpreted, based on the NCCLS recommendations for bacterial isolates grown aerobically (107).

Lactobacillus species are generally resistant to metronidazole, aminoglycosides, and ciprofloxacin. L. acidophilus is susceptible to penicillin and vancomycin, whereas L. rhamnosus and L. casei are resistant to metronidazole and vancomycin (106). L.

Table 4. Other clinical isolates of gram-positive rods associated with blood-stream infections

Species (Numbers, %)	Type of culture system	Patient condition/Underlying disease/ Antibiotic resistance of isolate (comment)	Location/Time/ Numbers of cases	Ref
Propionimicrobium lymphophilum	BACTEC FX 40 (Becton Dickinson, Franklin Lakes, NY)	The first case of bacteremia caused by this pathogen Resistant to metronidazole Treatment with amoxicillin-clavulanic acid	Spain/ 2020 (A case)	(48)
P. lymphophilum	BacT/ALERT; SYSMEX bioMérieux, Tokyo, Japan	Colon cancer Pulmonary metastasis Diabetes mellitus neuropathy Successfully treated with ampicillin/ sulbactam	Tokyo, Japan/ 2017 (A case)	(47)
Cutibacterium acnes	Bactec 730 or Bactec 9240	Pediatric patients (16 years old) Malignancy was the most common underlying disease (13 paients, 72.2%), followed by liver cirrhosis (4 patients, 22.2%) and diabetes mellitus (3 patients, 16.7%) Incidence of clinically significant PAB was 3.5% (18/522)	Republic of Korea / 2011 / (18 cases)	(137)

C. acnes	BD Bactec "Peds Plus","Plus Anaerobic", "Lytic Anaerobic"		Netherlands / 2018	(138)
C. acnes	Manual	Treatment with ceftriaxone, levofloxacin plus rifampicin A high antibody titer to the bacterium is useful diagnostic adjunct	Switzerland / 2016 (A case)	(139)
Listeria innocua	BacT/ALERT system	The first description of a human infection caused by innocua	France/ 2003 (A case)	(102)
Listeria ivanovii	Not mentioned	Renal transplantation Intravenous amoxicillin & gentamicin	Paris, France/ 2010 (A case)	(140)
Listeria ivanovii	Manual	AIDS, lymphoma Substance abuse	Haifa, Israel/ 2006(A case) London,U.K /1994 (A case)	(141, 142)
Listeria seeligeri	Manual	L. seeligeri include strains that may cause life-threatening diseases in humans	France /1986 (A case)	(143)
Lactobacillus spp.	Manual	Liver abscess and bacteremia(simultaneously)	U.S.A / 2016 (A case)	(68)
Lactobacillus acidophilus	Not mentioned	Type 2 diabetes mellitus (DM), transient ischemic attacks (TIAs) related to drug use, current smoker, history of polysubstance abuse (including alcohol and cocaine) L. acidophilus urinary tract infection and bacteremia	U.S.A / 2019 (A case)	(144)
Lactobacillus jensenii	Not mentioned		Finland/ 2006	(145)
Lactobacillus spp.	Manual	Ischemic colitis A 14-day course of piperacillin-tazobactam and metronidazole (treatment)	U.S.A/ 2014 (A case)	(10)
Lactobacillus rhamnosus	Not mentioned	Cephalosporins would not be the ideal treatment for Lactobacillus bacteremia	France/2012 (A case) Finland/ 2006 USA, Los Angeles / 2013	(109) (145) (146)
Lactobacillus fermentum	Not mentioned	The most isolates were from blood culture.	Finland/ 2006	(145)
Lactobacillus casei	Not mentioned		Finland/ 2006	(145)
Lactobacillus salivarius	Not mentioned		Finland/ 2006	(145)
Lactobacillus gasseri	Not mentioned		Finland/ 2006	(145)
Other Lactobacillus specie	Not mentioned		Finland/ 2006	(145)

casei, L. rhamnosus, L. curvatus, and L. fermentum are inherently resistant to glycopeptides, unlike the L. acidophilus group and L. delbrueckii [108]. In a study by Salminen MK et al (2005), the results of disk diffusion method showed that imipenem, erythromycin, and clindamycin produced large inhibition zones for 85 tested isolates, which is in accordance with the low MICs on E-tests (109).

Conclusion

Every bacterium, isolated from BSIs, should be identified to evaluate a patient's clinical status. In immunocompromised people or intravenous drug users, microflora, such as Gram-positive rods and environmental bacteria (e.g., Bacillus species and coryneform bacteria), can be potential pathogens in blood cultures; therefore, we did not consider these bacteria from blood cultures to be only contaminants.

Overall, antibiotic susceptibility tests should be routinely performed to evaluate gram-positive clinical isolates, as genetic mutations have been observed at high frequencies.

Conflict of interest

The authors declare no conflicts of interest.

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