AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

REVIEW

Bacillus cereus Invasive Infections in Preterm Neonates: an Up-to-Date Review of the Literature

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SUMMARY *Bacillus cereus* group species are widespread, Gram-positive, spore-forming environmental bacteria. *B. cereus sensu stricto* is one of the major causes of food poisoning worldwide. In high-risk individuals, such as preterm neonates, *B. cereus* infections can cause fatal infections. It is important to note that the phenotypic identification methods commonly used in clinical microbiology laboratories make no distinction between *B. cereus sensu stricto* and the other members of the group (*Bacillus anthracis* excluded). As a result, all the invasive infections attributed to *B. cereus* are not necessarily due to *B. cereus sensu stricto* but likely to other closely related species of the *B. cereus* group. Next-generation sequencing (NGS) should be used to characterize the whole genome of the strains belonging to the *B. cereus* group. This could confirm whether the strains involved in previously reported *B. cereus* invasive infections preferentially belong to formerly known or emerging individual species. Moreover, infections related to *B. cereus* group species have probably been overlooked, since their isolation in human bacteriological samples has for a long time been regarded as an environmental contaminant of the cultures. Recent studies have questioned the emergence or reemergence of *B. cereus* invasive infections in preterm infants. This review reports our current understanding of *B. cereus* infections in neonates, including taxonomical updates, microbiological characteristics, bacterial identification, clinical features, host-pathogen interactions, environmental sources of contamination, and antimicrobial resistance.

KEYWORDS *Bacillus cereus*, preterm neonates, infection, antimicrobial agents, environmental microbiology, pediatric infectious disease

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The authors declare no conflict of interest.

Published 9 February 2022

INTRODUCTION

Bacillus cereus group species consist of large, sporulating, Gram-positive, and rod-shaped aerobic or facultative anaerobic bacteria that are widespread in the environment. These bacteria can be isolated from their environmental reservoir: soil, sea sediments and seawater, plants, and carcasses of animals that died after infection with *Bacillus anthracis* (1–3). These bacterial species are known to have a significant impact on human health, agriculture, or food industry, especially *B. anthracis*, *B. cereus sensu stricto*, and *Bacillus thuringiensis* (2, 4). *B. cereus sensu stricto* can contaminate food, especially vegetables and starchy food, and is mainly involved in gastrointestinal (GI) infections in humans. *B. cereus sensu stricto* represents one of the major causes of food poisoning outbreaks in Europe (5). Furthermore, some strains of *B. cereus sensu stricto* display a high virulence potential and are involved in various invasive and frequently fatal infections, particularly in immunocompromised patients, patients with substance use disorders, postsurgical patients, and preterm neonates. It is important to keep in mind two major points. First, it is difficult to distinguish between *B. cereus sensu stricto* and the other members of the group with the phenotypic identification methods routinely used in the clinical microbiology laboratory. Therefore, most human infections attributed to *B. cereus* in the literature should be considered *B. cereus* group species infections. Second, invasive infections related to *B. cereus* have probably been overlooked, since the isolation of *B. cereus* in human bacteriological samples, especially in blood culture bottles, has for a long time been regarded as an environmental contaminant of the cultures (6). Recent studies have suggested the emergence or reemergence of *B. cereus* invasive infections in preterm neonates, and a recent epidemiological survey found an increase of *B. cereus* bacteremia incidence in the neonatal intensive care unit (ICU) at the Assistance Publique des Hôpitaux de Paris (APHP) in France (7). In our tertiary care center in Nice, France, we reported the death of two premature neonates in 2013 despite appropriate wide-spectrum antibiotic treatment (8). The increasing number of recent data concerning *B. cereus* infections in preterm neonates is of major concern in pediatric public health.

This review reports the current knowledge on *B. cereus* infections in preterm neonates, including a taxonomical update, microbiological characteristics, clinical features, sources of contamination, and antimicrobial resistance. This review also aims to address the question of whether this environmental bacterium might be involved in lethal infections in premature infants because of the existence of hypervirulent strains or because of the immaturity of the neonatal immune system.

TAXONOMY AND PHYLOGENY OF *B. CEREUS* GROUP

B. cereus sensu stricto belongs to the subdivision of the *Bacillus* genus. To date, 22 species have been reported in the literature as closely related to *B. cereus sensu stricto* (Table 1) (9–22). Among these species, only four new species have also been published but not yet validated by the International Committee of Systematic of Prokaryotes (16, 17, 19, 22). Historically, in the early 2000s, only six species had been described: *B. anthracis* (9), *B. cereus sensu stricto* (10), *B. thuringiensis* (12), *Bacillus mycoides* (11), *Bacillus pseudomycoides* (14), and *Bacillus weihenstephanenis* (23). But, *B. weihenstephanenis* was reclassified as a later heterotypic synonym of *B. mycoides* (20). These five species have classically been defined based on the presence of species-specific phenotypic and biochemical characteristics and on a similarity value lower than 70% using DNA/DNA hybridization methods. However, *B. cereus sensu stricto* and *B. thuringiensis* have been validated as distinct species, although these two species display a similarity value greater than 70%. Historically, the distinction between these two species was made because they display various pathogenic properties and diverse ecological lifestyles due to the presence or absence of plasmid harboring various toxin genes. Virulent strains of *B. cereus sensu stricto* can cause an emetic type of food poisoning induced by the production of cereulide, a toxin encoded by the *ces* gene that is located on a pXO1-like plasmid (24, 25). *B. thuringiensis* has insecticidal properties due to crystal proteins encoded by plasmid-borne *cry* genes. *B. anthracis* is the etiologic agent of anthrax. Pathogenic strains of *B. anthracis* harbor two virulent plasmids, i.e., pXO1 and pXO2 (26). Over the past 10 years, 17 species have been described as species closely related to *B.*

TABLE 1 Type strains phylogenetically closely related to *B. cereus sensu stricto*

Species and strain[a]	Location	Yr of isolation	Sample type[b]	Growth temp range (°C) (20–22)	Reference
Bacillus anthracis ATCC 14578^T	Germany	1872	NA	10–50	9
Bacillus cereus ATCC 14579^T	England	1887	Air	10–45	10
Bacillus mycoides DSM 11821*	Germany	1886	NA	15–40	11
Bacillus thuringiensis ATCC 10792^T	Germany	1915	Flour moth	10–45	12
Bacillus toyonensis BCT-7112^T	Japan	1966	Probiotic	10–45	13
Bacillus pseudomycoides DSM 12442^T	USA	1995	Soil isolate	10–40	14
Bacillus cytotoxicus NVH 391-98^T	France	1998	Vegetable puree	20–50	15
"*Bacillus gaemokensis*" BL3-6^T	South Korea	2010	Sediments from the Yellow Sea	15–40	16
"*Bacillus manliponensis*" BL4-6^T	South Korea	2011	Sediments from the Yellow Sea	15–40	17
Bacillus wiedmannii DSM 102050^T	USA	2012	Dairy products	5–43	18
"*Bacillus bingmayongensis*" FJAT 13831^T	China	2014	Soil isolate (Emperor Qin's terra-cotta warriors)	15–45	19
Bacillus luti KCTC 33716^T	China	2017	Sediments and seawater (Pacific Ocean)	10–39	20
Bacillus mobilis KCTC 33717^T	China	2017	Sediments and seawater (Pacific Ocean)	10–39	20
Bacillus nitratireducens KCTC 33713^T	China	2017	Sediments and seawater (Pacific Ocean)	7–39	20
Bacillus pacificus KCTC 33858^T	China	2017	Sediments and seawater (Pacific Ocean)	15–45	20
Bacillus paramycoides KCYC 33709^T	China	2017	Sediments and seawater (Pacific Ocean)	15–39	20
Bacillus paranthracis KCTC 33714^T	China	2017	Sediments and seawater (Pacific Ocean)	15–45	20
Bacillus proteolyticus KCTC 33715^T	China	2017	Sediments and seawater (Pacific Ocean)	10–39	20
Bacillus tropicus KCTC 33711^T	China	2017	Sediments and seawater (Pacific Ocean)	15–45	20
Bacillus albus KCTC 33710^T	China	2017	Sediments and seawater (Pacific Ocean)	15–40	20
Bacillus fungorum KCTC 33949^T	China	2017	Spent mushroom substrate	10–45	21
"*Bacillus clarus*" ATCC 21929^T	Papua New Guinea	NA	Soil	15–43	22

[a]Species names in quotation marks indicates species not yet validated.
[b]NA, not available.

cereus sensu stricto, mostly since 2010 due to the expansion of whole-genome sequencing techniques (13, 15–22).

The taxonomic history of the *B. cereus* group has been recently reviewed (27). However, in the literature, there are no real criteria to confirm that a new species belongs to the *B. cereus* group. We have studied the phylogenetic relationships between species using multilocus sequence typing (MLST), as described in Fig. 1 (28). The comparison of three phylogenetic methods (neighbor-joining, maximum likelihood, and maximum parsimony), as well as bootstrap replications (×1,000), revealed a solid group consisting of 16 *B. cereus* species. The members of this group are also distinguished from other species outside the group by a panel of phenotypic characters, as shown in Table 2. Interestingly, the members of this group have mostly been involved in human infections, while species outside this group rarely cause human infections. Furthermore, based on analyses of 2,231 genomes, these 16 species are also in the same group (29). For these four reasons (phylogenetic, phenotypic, and genomic analyses and clinical infection), we could propose to delineate the *B. cereus* group to those 16 species, as shown in Fig. 1. In the rest of the review, when we refer to "*B. cereus*," it will be to the *B. cereus* group composed by the 16 species.

Among the new species of the *B. cereus* group, it is interesting to note that *Bacillus paranthracis*, initially isolated from sediment of the Pacific Ocean, has recently been implicated in an emetic outbreak (30). In our very recent study, WGS of three strains involved in invasive infections in newborns and belonging to the *B. cereus* group showed that one of them was *B. paranthracis* (31). These two recent WGS studies question the role of one individual species, *B. paranthracis*, in human infections and notably in invasive infections in neonates. These interesting findings need to be further investigated and underline the necessity to develop new identification strategies for discrimination between species.

SPECIES IDENTIFICATION WITHIN THE *B. CEREUS* GROUP

The bacteria belonging to the *B. cereus* group are rod-shaped and sporulating Gram-positive bacilli. The members of the *B. cereus* group, excluding *B. anthracis*, display various morphological forms depending upon the milieu in which they are observed. In the environment,

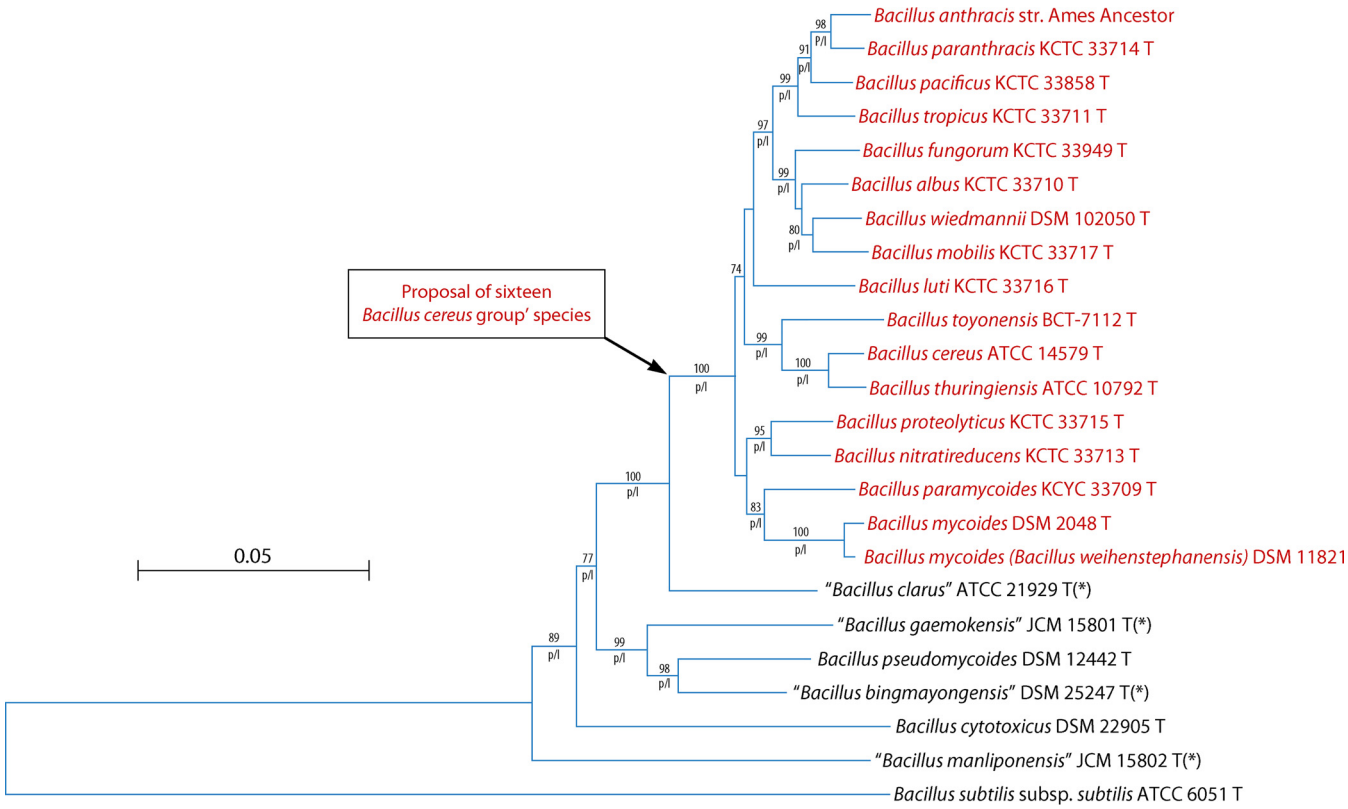

FIG 1 Phylogenetic relationships between the species of the *Bacillus cereus* group with *Bacillus subtilis* subsp. *subtilis* used as the outgroup. The tree was obtained by the neighbor-joining method based on a comparison of the concatenated sequences of seven housekeeping genes (*glpF*, *gmk*, *ilvD*, *pta*, *pur*, *pyc*A, *tpi*). The Kimura two-parameter distance measure was used as implemented in MEGA X (28). Values above the lines indicate how the tree's branches are supported by the results of bootstrap analysis (×100 replicates) (only values greater than 70% are shown). The letters "p" and "l" under the lines indicate branches that were also found by the maximum parsimony method and maximum likelihood method, respectively (28). Scale bar, accumulated changes per nucleotide. Asterisks indicate species published but not yet validated.

these bacteria persist as a sporulated and very resistant form. Spores can germinate once in contact with an insect or human host and produce vegetative cells (2, 32). Gram stains of blood culture typically yield straight to slightly curved bacilli with square ends either singly or arranged in pairs or short chains. *B. cereus* group species are aerobic or facultative anaerobic bacteria and can grow over a broad temperature range (Table 1) (2, 33–35). Colonies are usually dull gray and opaque with a rough surface. When grown at 37°C on enriched blood agar medium under an aerobic atmosphere, strains display various levels of hemolysis, from nonhemolytic to high ß-hemolytic activity (1, 36). Selective culture media for *B. cereus* group species can also be used in routine microbiology, such as MYPA (mannitol yolk polymyxin B agar), PEMBA (pyruvate egg yolk mannitol blue agar), or the chromogenic medium Brilliance *Bacillus cereus* agar (BBC) (all ThermoFisher) (37). Several biochemical and phenotypic characteristics of the different species can differentiate the species of the *B. cereus* group (20). The

TABLE 2 Main positive biochemical characteristics of type strains for proposed species in *B. cereus* group and species outside of *B. cereus* group (20–22)

	% of species positive for:						
Species group	**Acetoin production**	**Arbutin**	**Citrate utilization**	**Oxidase**	**Starch hydrolysis**	**Trehalose**	**Urease**
B. cereus group ($n = 16$)[a]	94	82	82	94	78	94	0
Species outside of *B. cereus* group ($n = 6$)[b]	60	50	33	50	33	50	33

[a]Includes *Bacillus paramycoides* KCYC 33709^T; *Bacillus albus* KCTC 33710^T; *Bacillus proteolyticus* KCTC 33715^T; *Bacillus cereus* ATCC 14579^T; *Bacillus anthracis* ATCC 14578^T; *Bacillus paranthracis* KCTC 33714^T; *Bacillus pacificus* KCTC 33858^T; *Bacillus tropicus* KCTC 33711^T; *Bacillus fungorum* KCTC 33949^T; *Bacillus wiedmannii* DSM 102050^T; *Bacillus mobilis* KCTC 33717^T; *Bacillus luti* KCTC 33716v; *Bacillus thuringiensis* ATCC 10792^T; *Bacillus toyonensis* BCT-7112^T; *Bacillus mycoides* DSM 2048^T; *Bacillus mycoides* (*weihenstephanensis*) DSM 11821; *Bacillus nitratireducens* KCTC 33713^T.

[b]Includes *Bacillus pseudomycoides* DSM 12442^T; *Bacillus cytotoxicus* NVH 391-98^T, "*Bacillus bingmayongensis* FJAT 13831^T," "*Bacillus manliponensis* BL4-6^T," "*Bacillus gaemokensis* JCM 15801^T," and "*Bacillus clarus* ATCC 21929^T."

main differences between positive biochemical characteristics of the type strains for the different proposed species in the *B. cereus* group and species outside of the *B. cereus* group are detailed in Table 2 (20–22).

In a routine clinical microbiology laboratory, bacterial identification is now based on the analyses of protein spectra obtained by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), which is a reliable tool for pathogen identification. However, this method still has limitations in identifying closely related microbial species such as the *B. cereus* group species. To date, the commercial version of the Biotyper database (Bruker Daltonics, Bremen, Germany), which is widely used in routine clinical microbiology laboratories, contains only microbial reference spectra for three species of the *B. cereus* group, as previously described (see Taxonomy and Phylogeny of *B. cereus* Group): *B. cereus sensu stricto* (4 spectra), *B. mycoides* (3 spectra), and *B. thuringiensis* (1 spectrum). Some of the newly described species of the *B. cereus* group are still missing from this database. With respect to the last version of the Vitek MS 3.2 database (bioMérieux, France), it contains reference spectra for *B. cereus sensu stricto*, *B. mycoides*, *B. thuringiensis*, and *B. weihenstephanensis*. When a bacterial spectrum matches one of these four spectra, the bacterium is identified as "*B. cereus* group." Moreover, MALDI-TOF MS could misidentify strains belonging to the *B. cereus* group. For example, the foodborne human pathogen *B. cereus sensu stricto* can be misidentified as *B. thuringiensis*, an insect pathogen widely used as a biopesticide and very closely phylogenetically related to *B. cereus sensu stricto*. Indeed, these two species differ only by the presence or absence of the Cry toxin-encoding plasmids. *B. cereus sensu stricto* can also be misidentified as *B. anthracis*. If these two species are phylogenetically related, *B. anthracis* can be implicated in anthrax, a life-threatening disease caused by the production of anthrax toxin. To overcome this important limitation in discerning *B. cereus* group species, some researchers have tried to optimize MALDI-TOF identification methods provided by the manufacturers by enrichment of available spectra and by using specific algorithms allowing discrimination between the different species of the *B. cereus* group (38–40).

Molecular approaches such as 16S rRNA gene sequencing are widely used for routine bacterial identification (41). However, as suggested by previous studies, 16S rRNA gene sequencing has failed to discriminate between *B. cereus*, *B. thuringiensis*, and *B. anthracis* because of the high similarity in 16S rRNA gene sequences between these three species.

To conclude, we recommend the use of MLST (as described in Taxonomy and Phylogeny of *B. cereus* Group) and determination of a panel of phenotypic characters (Table 2) in order to classify a species as belonging to the *B. cereus* group as defined above. Furthermore, promising tools such as WGS using core genome MLST or new MALDI-TOF approaches as described above (38–40) should be performed to reach identification to the species level.

HABITAT AND EPIDEMIOLOGY

B. cereus is widespread in nature. The natural environmental reservoir for *B. cereus* consists of soil, decomposing organic matter, fresh and marine water, plants, and the intestinal tracts of invertebrates (2, 42). From this natural habitat, the microorganism is able to contaminate a wide variety of food products, and this can lead to the transient colonization of the human gut (43). Moreover, *B. cereus* is capable of growing quickly under a wide variety of conditions, which explains its ubiquitous worldwide distribution regardless of the environment. *B. cereus* also produces endospores that enable it to withstand desiccation, temperature and pH variations, and anaerobic conditions (34). Interestingly, the spores of certain *B. cereus* strains are inactivated by a heat shock treatment of 10 to 20 min at 90°C and 2 min at 95°C. According to Stadhouders et al., a heat shock treatment of 10 to 20 s at 125°C is necessary to inactivate *B. cereus* spores in milk (44). This ability to survive under unfavorable conditions makes it difficult to eliminate in areas such as food production or hospital-based care services because the spores can adhere to surfaces and are resistant to pasteurization. Some *B. cereus* strains are also able to form diverse biofilms that allow them to resist biocleaning procedures (45). Biofilm formation and sporulation are therefore responsible for the persistence of *B. cereus* in the environment. In general, human *B. cereus* infections occur via ingestion of contaminated food, inhalation of spores, or direct inoculation into the skin.

EXTRADIGESTIVE AND INVASIVE *B. CEREUS* INFECTIONS

B. cereus is an opportunistic pathogen responsible for extradigestive, localized or systemic, nosocomial infections, frequently occurring in immunocompromised patients and in newborns (premature or full-term). In these populations, *B. cereus* causes various types of infections, including sepsis, septic shock, central nervous system (CNS) infections, and even eye infections (2). Recently, Messelhäußer and Ehling-Schulz have summarized the main cases of extradigestive infections described in the literature between 2012 and 2017. In this review, they report bacteremia or sepsis for 42% of cases, CNS infections with cerebral damage (abscess, meningoencephalitis) for 21% of cases, endocarditis and eye infections for 17% of cases, two cases of necrotizing fasciitis, and one case of peritonitis and hepatic abscess (34). In immunocompromised subjects, the main risk factors for infection are malignant hemopathies, intravascular devices, intravenous drug injections, and traumatic or surgical lesions (46, 47). In immunocompetent patients, systemic infections such as anthrax-like disease type and catheter-related bloodstream infections (CRBSI) have also been reported (48, 49). In immunocompetent adults, systemic *B. cereus* infections are rarely fatal, unlike infections that occur in at-risk populations such as preterm neonates, where the fatality rate can reach up to 30%, as shown by Fournier and colleagues (7).

Overall, there is a wide clinical spectrum of human *B. cereus* infections. Indeed, as already mentioned, extradigestive infections are probably overlooked, because *B. cereus* has, for a long time, been regarded as an environmental contaminant when isolated in bacteriological samples, especially in blood cultures, due to its wide distribution in the environment. However, the increasing volume of recent data concerning *B. cereus* invasive and frequently fatal infections in preterm neonates is of major concern in pediatric public health and is discussed hereafter.

EMERGENCE OF *B. CEREUS* INFECTIONS IN PRETERM NEONATES

B. cereus has an emerging role in opportunistic infections in at-risk populations such as the elderly, immunocompromised patients, and preterm neonates. In this review, we focus on *B. cereus* invasive infections in infants, which are being increasingly reported in the literature (Fig. 2). A newborn is considered premature when birth occurs before the start of the 37th week of pregnancy (50). Invasive infections in these patients occur sporadically or in outbreaks. A very recent description of nosocomial outbreaks in France, Germany, and Israel led to a reconsideration of the global risk of this potentially serious burden (7, 51–53). Therefore, improving the current knowledge regarding *B. cereus* pathogenesis, transmission risks, and treatment is of major concern in pediatric public health. We performed a survey of the literature between January 1977 and January 2021 for data on *B. cereus* infections in neonates by using Medline and Scopus. The search terms *B. cereus*, *Bacillus cereus*, newborn, neonate, infant, premature, preterm, and neonatal were used.

To date, 145 cases have been reported in 106 patients, including 69 cases of bacteremia (48%) (7, 8, 51–77), 36 CNS infections (25%) (8, 51, 53, 55–57, 61–64, 67, 68, 70, 71, 73–82), 18 respiratory tract infections (12%) (8, 52, 53, 56, 74, 76, 83), 13 cases of skin infections (9%) (53, 84), six cases of GI infections (4%) (53, 85, 86), two cases of osteoarticular infections (1%) (71, 72), and a single case of urinary tract infection (UTI) (1%) (53) (Table 3). *B. cereus* infection was fatal in 33 of 106 patients (31%). Regarding treatment, the implementation of antibiotic treatment, based on vancomycin for *B. cereus* invasive infection (87), did not prevent patient death in 11 of 33 cases (33%) when considering only patients for whom antibiotic therapy information was available (51, 52, 60, 70, 72, 75, 79, 88).

Collectively, two groups of infections stand out from the data found in the literature regarding *B. cereus* infections in newborns: systemic involvement with bacteremia and other serious infections without bacteremia.

Invasive Infections with *B. cereus* Bacteremia

We further analyzed a total of 69 cases of *B. cereus* bacteremia in newborns (7, 8, 51–77, 88) (Table 4). The selection criterion was the presence of at least one positive blood culture for *B. cereus* in a patient. All cases have been described in neonatal or neonatal ICU departments. Eighty-one percent of patients were premature newborns, while 19% were born after the 37th week of gestation. The mean gestational age at birth was 30 weeks, and the mean

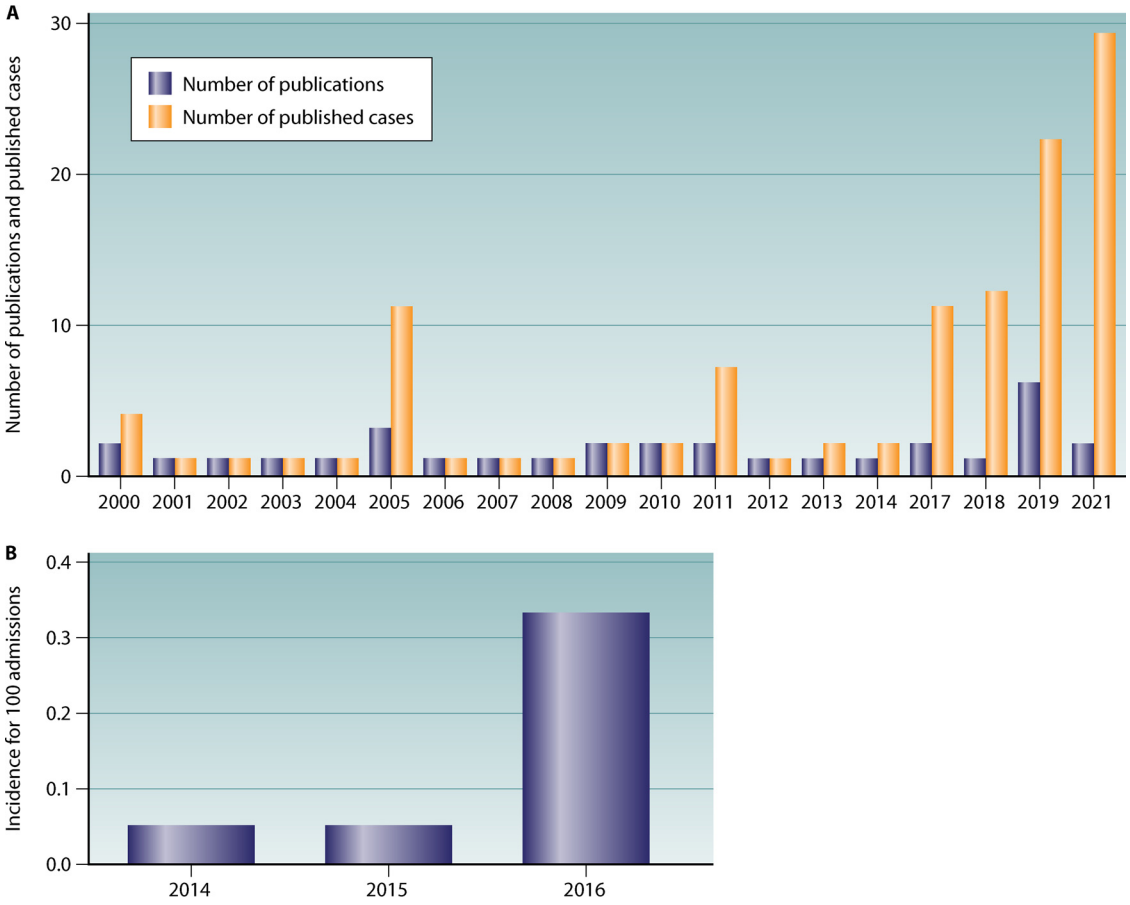

FIG 2 (A) Evolution of the number of publications and number of published cases of *Bacillus cereus* infections in preterm neonates per year for 2000 to 2021. (B) Evolution of the incidence of *Bacillus cereus* bacteremia in preterm neonates (number per 100 admissions) for 2014 to 2016 at Assistance Publique des Hôpitaux de Paris, Paris, France (7).

weight of birth was 1,392 g. The presence of *B. cereus* in the blood culture was considered to be contamination in only four cases (4/69, 6%) (51, 59). Indeed, in these four cases, *B. cereus* was found in blood culture bottles (BCBs), and the neonate did not have any sign of infection. Therefore, the presence of *B. cereus* in the BCBs was considered a contamination of the samples from the environmental reservoir of *B. cereus*. In all other reports, *B. cereus* was responsible for sepsis (50/69, 72%) (7, 51, 53–57, 59, 60, 62, 65–68, 70–73, 76, 77, 82) or septic shock (15/69, 22%) (8, 51, 52, 56, 60, 61, 64, 69, 71, 74, 75, 88). A peculiarity of *B. cereus* sepsis in neonates is the secondary meningeal or cerebral dissemination. Indeed, meningitis or meningoencephalitis (53, 57, 61, 62, 64, 67, 70, 71, 73–75, 77) and brain abscesses or necrosis (7, 8, 51, 53, 55, 56, 62–64, 68, 75, 76) were reported in 19/65 (29%) and 12/65 (18%) of the neonates presenting with *B. cereus*-related sepsis and septic shock, respectively. Pneumonia was associated in 6 of 65 patients (9%) (52, 53, 56, 74, 76).

Other Severe Invasive Infections Caused by *B. cereus* in Neonates

Other types of severe invasive or localized infections without bacteremia in neonates have been recently reported in the literature. *B. cereus* can be responsible for severe neurological (78, 79), respiratory (83, 89), digestive (85, 90), and primary cutaneous infections (84). Recently, Viel-Thériault and colleagues have described a case of a neonate born at 26 weeks of gestational age who died of a rapidly progressive *B. cereus* necrotizing pneumonia following suspected nosocomial acquisition (89). Interestingly, *B. cereus* could also be associated with devastating intestinal infections, such as necrotizing enterocolitis (NEC). NEC is primarily a disease process of the GI tract of premature neonates that results in inflammation and bacterial invasion of the bowel wall. Despite advances in the care of premature infants, NEC remains one of the leading causes of morbidity and mortality in this population, with an incidence rate

TABLE 3 Type of infection due to *B. cereus* in neonates

Type of infection	No. (%) of cases (n = 145)	Source(s) of positive clinical specimens[a]	Reference(s) (no. of cases)
Bacteremia	**69 (48)**	Blood culture	54 (1), 88 (2), 51 (3), 52 (1), 55 (1), 53 (6), 7, (9), 8 (1), 56 (2), 57 (1), 58 (3), 59 (8), 60 (2), 61 (1), 62 (1), 63 (1), 64 (1), 65 (1), 66 (8), 67 (3), 68 (1), 69 (1), 70 (1), 71 (3), 72 (1), 73 (1), 74 (2), 75 (1), 77 (1), 76 (1)
CNS infection	**36 (25)**		
Meningitis, meningoencephalitis	23 (16)	CSF, meninges, brain tissue	53 (1), 57 (1), 61 (1), 62 (1), 64 (1), 67 (3), 68 (1), 70 (1), 71 (2), 73 (2), 74 (1), 75 (1), 77 (1), 78 (1), 79 (1), 80 (2), 81 (1), 82 (1)
Brain abscesses, empyema, or necrosis	13 (9)	Brain tissue, necrosis	51 (1), 55 (1), 53 (1, 1), 8 (1), 56 (1), 62 (1), 63 (1), 64 (1), 68 (1), 70 (1), 75 (1), 74 (1), 76 (1)
Respiratory infection	**18 (12)**		
Pneumonia	11 (8)	Tracheal aspiration, pleural fluid, lung tissue	52 (2), 53 (1), 74 (2), 89 (1), 8 (1), 83 (4)
Pulmonary abscesses or necrosis	6 (4)	Lung tissue, pleural fluid	52 (1), 56 (1), 74 (2), 76 (1), 89 (1)
Tracheobronchitis	1 (0.7)	NA	52 (1)
Cutaneous infection	**13 (9)**	Skin, armpit, umbilical cord stump swab	84 (12), 53 (1)
Gastrointestinal infection	**6 (4)**		
Digestive tract	5 (3.5)	Gastric fluid, stomach tube feeding, sample from abdominal cavity	53 (2), 85 (2), 86 (1)
Liver	1 (0.7)	NA	53 (1)
Osteoarticular infection	**2 (1)**		
Arthritis	1 (0.7)	Synovial fluid	71 (1)
Osteitis	1 (0.7)	Bone, bone marrow	72 (1)
Kidney and urinary infection	**1 (1)**	NA	53 (1)

[a]CSF, cerebrospinal fluid; NA, not available.

of 1% to 5% of all neonatal intensive care admissions (91). To date, the precise mechanisms involved in this disease are not fully understood. Several potential causes are often suggested, like diet, inflammation, or infection. An infectious etiology is suspected for NEC outbreaks. In their study, Wendelboe and colleagues described a cluster of NEC cases in a neonatal ICU in New Mexico in 2007 and suggested the potential involvement of *B. cereus* in this outbreak (90).

Finally, as previously suggested, it is important to note that all of these invasive infections related to *B. cereus* can occur in the form of epidemic nosocomial outbreaks in health care centers (2). Some of these outbreaks occur seasonally, with summer peaks, as shown in several studies (60, 92). These reports suggest a link between high ambient temperature, environmental dissemination, particularly within the hospital environment, and the epidemic spread of nosocomial infections. Indeed, these findings rely on the hypothesis that the growth of *B. cereus* is enhanced when temperatures are higher, which could explain the transient increase in number of infections especially during the summer.

Collectively, all these data suggest that premature infants are particularly susceptible to *B. cereus* invasive nosocomial infections. These infections can occur through bacterial transmission from the environmental reservoir of *B. cereus* to the neonate. The various environmental sources of infection in preterm neonates are discussed below.

ENVIRONMENTAL SOURCES OF INFECTION IN PRETERM NEONATES

As previously suggested, *B. cereus* invasive infections can be fatal in preterm infants hospitalized in neonatal ICUs and sometimes even despite early and appropriate antimicrobial drug therapy (8, 51, 52, 70, 75). Considering the virulence potential of *B. cereus* in this population and the natural habitat of this bacterium in the environment, the question of the source of infection is of major concern in pediatric public health. Indeed, increasing our understanding of the origin of infection could help to prevent the transmission of *B. cereus* from the environmental reservoir and thus limit invasive infections in premature infants. In some studies, the authors were able to identify the source of contamination by showing a clonal link between patient and environmental strains. In preterm neonates, the main proven environmental

TABLE 4 Main features of reported cases of *B. cereus* bacteremia in neonates[a]

Reference (*n*, no. of cases)	Term of birth (wks + days of gestation)	Wt at birth (g)	Underlying condition(s)	Clinical presentation	Disseminated infection	Suspected source(s) of Infection	Antibiotic treatment[b]	Outcome
Liao and Tsai, 2021 (54) (*n* = 1)	33 + 2	1490	Respiratory distress	Sepsis	No	Mother's breast milk	VCM, AMK	Recovery
Lewin et al., 2019 (88) (*n* = 2)	25	590	Hyaline membrane disease, pulmonary hypertension	Septic shock	No	Banked human milk	LNZ, MRP, VCM	Death
	24	560	Chorioamnionitis, CBD, patent ductus arterioses	Septic shock	No	Banked human milk	AMP, TBM, VCM, MRP, PTZ, CTX	Death
Bar-Meir et al., 2019 (51) (*n* = 3)	32	NA	Twin pregnancy	Septic shock	Brain abscesses	Construction-related dust	VCM, MRP, CRP	Death
	31	NA	No	Sepsis	No	Construction-related dust	VCM, MRP	Recovery
	31	NA	CBD	Contamination	No	Construction-related dust	None	Recovery
Papan et al., 2019 (52) (*n* = 1)	37 + 5	2,700	Congenital diaphragmatic hernia closure	Septic shock	Pneumonia, pyogenic tracheobronchitis, necrotizing bronchiolitis	Undetermined	VCM, MRP, FSF	Death
Samarasekara et al., 2020 (55) (*n* = 1)	30	NA	No	Sepsis	Brain abscess	Undetermined	VCM, MRP, AMP, FCX	Recovery
Glasset et al., 2018 (53) (*n* = 6)	NA	NA	NA	Sepsis	Meningitis, pulmonary and liver infection	Surface in medical ward	None	Death
	NA	NA	NA	Sepsis	Brain abscess	Surface in medical ward	VCM, CFT	Recovery
	NA	NA	NA	Sepsis	No	Surface in medical ward	VCM	Recovery
	NA	NA	NA	Sepsis	No	Surface in medical ward	VCM, AMK, AMX	Recovery
	NA	NA	NA	Sepsis	No	Surface in medical ward, central catheter	VCM	Recovery
	NA	NA	NA	Sepsis	Kidney and urinary infection	Undetermined	CFX, GTM	Recovery
Fournier et al., 2017 (7) (*n* = 9)	30 + 2	750	Intrauterine growth restriction, hemorrhagic brain lesions	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Death
	29 + 2	1,075	Twin pregnancy, transfused transfusion syndrome	Sepsis	Extensive brain damage	Banked human milk, parenteral nutritional solutions	NA	Death
	37 + 2	2,815	Atresia of the small intestine	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
	31	1,380	Atresia of the duodenum	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
	29 + 4	1,025	Umbilical hernia	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
	27 + 5	750	Enterocolitis	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Death
	31	1,720	Twin pregnancy	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
	38 + 6	3,515	Neonatal respiratory distress	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
	39	3,240	Polymalformation	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Recovery
Lotte et al., 2017 (8) (*n* = 1)	29 + 4	1,480	Maternal malignancy	Septic shock	Brain empyema, abscesses and necrosis, cranial hemorrhages	Central catheter, surface in medical ward	VCM, GTM, CFT	Death
Ramarao et al., 2014 (56) (*n* = 2)	24 + 5	650	CBD	Sepsis	No	Central catheter	VCM, AMK, CFT	Recovery
	26 + 5	615	No	Septic shock	Brain and pulmonary abscesses	Central catheter	None	Death
Horii et al., 2012 (57) (*n* = 1)	NA	800	Bowel perforation, CBD	Sepsis	Late meningitis	Hospital linens	VCM, MRP, LNZ, CLD	Recovery
Shimono et al. 2012, (58) (*n* = 3)	29	476	NA	Sepsis	No	Surface in medical ward	NA	Recovery
	30	876	NA	Sepsis	No	Surface in medical ward	NA	Recovery
	28	1,018	NA	Sepsis	No	Surface in medical ward	NA	Recovery

(Continued on next page)

TABLE 4 (Continued)

Reference (*n*, no. of cases)	Term of birth (wks + days of gestation)	Wt at birth (g)	Underlying condition(s)	Clinical presentation	Disseminated infection	Suspected source(s) of Infection	Antibiotic treatment[b]	Outcome
Campbell et al., 2011 (59) (*n* = 8)	31	1,650	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	29	1,148	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	28	1,515	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	24	710	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	25	945	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	29	1,015	NA	Contamination	No	Endotracheal intubation, central catheter, construction excavation	None	Recovery
	40	4,184	NA	Contamination	No	Endotracheal intubation, central catheter, construction excavation	None	Recovery
	30	870	NA	Contamination	No	Endotracheal intubation, central catheter, construction excavation	None	Recovery
Sasahara et al., 2011 (60) (*n* = 2)	NA	NA	Mitral regurgitation	Septic shock	No	Hospital linens, central catheter, parenteral solutions	AMP/SBT, MRP, VCM, PNP	Death
	NA	NA	Patent ductus arteriosus	Septic Shock	No	Hospital linens, central catheter, parenteral solutions	CFZ	Death
Saito et al., 2010 (61) (*n* = 1)	27	740	Intrauterine growth restriction, patent ductus arteriosus, severe pregnancy-induced hypertension	Septic shock	Meningitis, intraventricular hemorrhage, pulmonary hemorrhage	Undetermined	CFZ	Death
Drazin et al., 2010 (62) (*n* = 1)	32 + 4	1,910	Mild dysmorphic features, patent foramen ovale, twin pregnancy, preeclampsia	Sepsis	Meningoencephalitis, brain abscesses	Undetermined	VCM, AMK, GTM, MRP	Recovery
Pawlik et al., 2009 (63) (*n* = 1)	27	730	NA	Sepsis	Brain abscesses	Undetermined	NA	Recovery
Evreux et al., 2007 (64) (*n* = 1)	31	1,670	Thyroid agenesis	Septic shock	Meningitis, brain abscesses and necrosis	Central catheter	CFT, AMX, MTZ, AMK	Death
John et al., 2006 (65) (*n* = 1)	32	1,512	Ruptured bicornuate uterus, severe fetal distress	Sepsis	Subependymal hemorrhage, cerebral edema	Undetermined	PTZ, AMK, VCM	Recovery
Adler et al., 2005 (66) (*n* = 8)	25	680	*Candida* sepsis, chronic lung disease, retinopathy	Sepsis	No	Air	MRP	Recovery
	34	2,010	*Escherichia coli* peritonitis	Sepsis	No	Air	MRP	Recovery
	37	2,000	*Klebsiella* peritonitis and sepsis	Sepsis	No	Air	VCM	Recovery
	36	1,735	Necrotizing enterocolitis	Sepsis	No	Air	MRP	Recovery
	30	1,226	Necrotizing enterocolitis	Sepsis	No	Air	MRP	Recovery
	29	1,508	No	Sepsis	No	Air	VCM	Recovery
	32	1600	No	Sepsis	No	Air	VCM	Recovery
	27	870	No	Sepsis	No	Air	VCM	Recovery

(Continued on next page)

TABLE 4 (Continued)

Reference (*n*, no. of cases)	Term of birth (wks + days of gestation)	Wt at birth (g)	Underlying condition(s)	Clinical presentation	Disseminated infection	Suspected source(s) of Infection	Antibiotic treatment[b]	Outcome
Lequin et al., 2005 (67) (*n* = 3)	30 + 6	NA	No	Sepsis	Hemorrhagic meningoencephalitis	Undetermined	NA	Death
	28 + 3	NA	No	Sepsis	Hemorrhagic meningoencephalitis	Undetermined	NA	Death
	34 + 1	NA	No	Sepsis	Hemorrhagic meningoencephalitis, ventriculitis	Undetermined	NA	Death
Heep et al., 2004 (68) (*n* = 1)	27	950	Intrauterine growth restriction, triplet pregnancy, intraventricular hemorrhage	Sepsis	Ventriculitis, hemorrhagic necrotizing lesions end brain abscesses	Central catheter	VCM, GTM, MRP	Recovery
Hilliard et al., 2003 (69) (*n* = 1)	24	585	Chorioamnionitis	Septic shock	No	Undetermined	VCM, TBM, CLD, MRP	Recovery
Chu et al., 2001 (70) (*n* = 1)	26	1,580	Hyaline membrane disease, CBD, patent ductus arteriosus, MV, parenteral nutrition	Sepsis	Meningitis, brain necrosis and edema	Undetermined	AMP, CFT, AMK, VCM	Death
Van Der Zwet et al., 2000 (71) (*n* = 3)	28 + 5	895	MV, patent ductus arteriosus	Septic shock	Hemorrhagic meningoencephalitis	Ventilator equipment, hands of medical staff	AMX, CFT	Death
	26+4	1,000	MV	Sepsis	Knee arthritis	Ventilator equipment, hands of medical staff	VCM, MRP	Recovery
	37+3	2,780	MV, hepatosplenomegaly	Sepsis	Meningitis	Ventilator equipment, hands of medical staff	VCM, MRP	Recovery
Tuladhar et al., 2000 (72) (*n* = 1)	24	735	MV, CNS hemorrhage	Sepsis	Bone marrow	Undetermined	CPF, CLD, GTM, IMP, VCM	Death
Tokieda et al., 1999 (73) (*n* = 1)	37	3,764	Hydrops fetalis, MV	Sepsis	Meningitis, brain hemorrhages	Peripheral catheter	AMP, GTM	Death
Jevon et al., 1993 (74) (*n* = 2)	27	920	Intrauterine growth restriction, hyaline membrane disease, MV, transfused transfusion syndrome, cerebral hemorrhage	Septic shock	Necrotizing pneumonia, necrosis of the larynx, thyroid and trachea, meningitis, subendocardial hemorrhage with focal necrosis	Resuscitation devices, drugs or hands of medical staff	AMP, GTM	Death
	25	690	Hyaline membrane disease, MV, CNS hemorrhage	Septic shock	Necrotizing pneumonia	Resuscitation devices, drugs or hands of medical staff	AMP, GTM	Death
Patrick et al., 1989 (75) (*n* = 1)	26	830	MV, thalamic hemorrhage	Septic shock	Meningitis, brain necrosis	Undetermined	AMK, VCM	Death
Turnbull et al., 1979 (77) (*n* = 1)	NA	NA	NA	Sepsis	Meningitis	Undetermined	NA	NA
Turnbull et al., 1977 (76) (*n* = 1)	32	1,320	Necrotizing enterocolitis	Sepsis	Brain, lung and respiratory tract necrosis	Central catheter	AMP, GTM	Death

[a]CBD, chronic bronchial disease; MV, mechanical ventilation; CNS, central nervous system; NA, not available.

[b]VCM, vancomycin; AMK, amikacin; LNZ, linezolid; MRP, meropenem; AMP, ampicillin; TBM, tobramycin; PTZ, piperacillin/tazobactam; CTX, cefotaxime; CRP, chloramphenicol; FSF, fosfomycine; FCX, flucloxacilline; AMX, amoxicillin; GTM, gentamicin; CLD, clindamycin; AMP/SBT, ampicillin/sulbactam; PNP, panipenem; CFZ, cefazolin; MTZ, metronidazole; CPF, cefozopran; IMP, imipnem; CPF, ciprofloxacin; CFA, ceftazidime; ETY, erythromycin.

TABLE 5 Environmental sources of infections in neonates

Suspected source of contamination[a] (no. of cases) (references)	Proven source of contamination[b] (%) (no. of proven cases/total no. of suspected cases)	Mode of transmission
Intravascular catheters (*n* = 5) (8, 53, 60, 68)	60 (3/5)	Inoculation
Ventilator equipment (*n* = 17) (71, 83, 93)	53 (9/17)	Inhalation
Human milk (*n* = 16) (7, 53, 54, 85)	6 (1/16)	Ingestion
Surfaces in medical ward (*n* = 16) (8, 53, 58, 84)	37 (6/16)	Unknown
Hands of medical staff (*n* = 5) (58, 71, 84)	60 (3/5)	Unknown
Hospital linens (*n* = 3) (57, 60)	33 (1/3)	Unknown
Parenteral nutritional solutions (*n* = 11) (7, 60); air, airborne dust, construction (*n* = 2) (58)	0 (0/13)	Unknown

[a]Study of *Bacillus cereus* strains isolated from patients and hospital environments.
[b]Same strain isolated from the patient and the hospital environment.

sources of systemic infection are airborne contaminations through resuscitation devices (mechanical or manual ventilation equipment) (71, 83, 93) and inoculation via intravascular catheter (8, 53). Other environmental sources of infection have been described, including hospital linen, surfaces in medical wards, and hands of medical staff, and should be investigated in cases of *B. cereus* nosocomial outbreaks in pediatric ICUs (53, 58, 60, 71). The various suspected sources of infection that are investigated using various genotyping methods in cases of *B. cereus* invasive infections in neonates previously reviewed are summarized in Table 5 and Fig. 3.

Enteral feeding contamination by *B. cereus* can result in either a GI infection or a bactere-

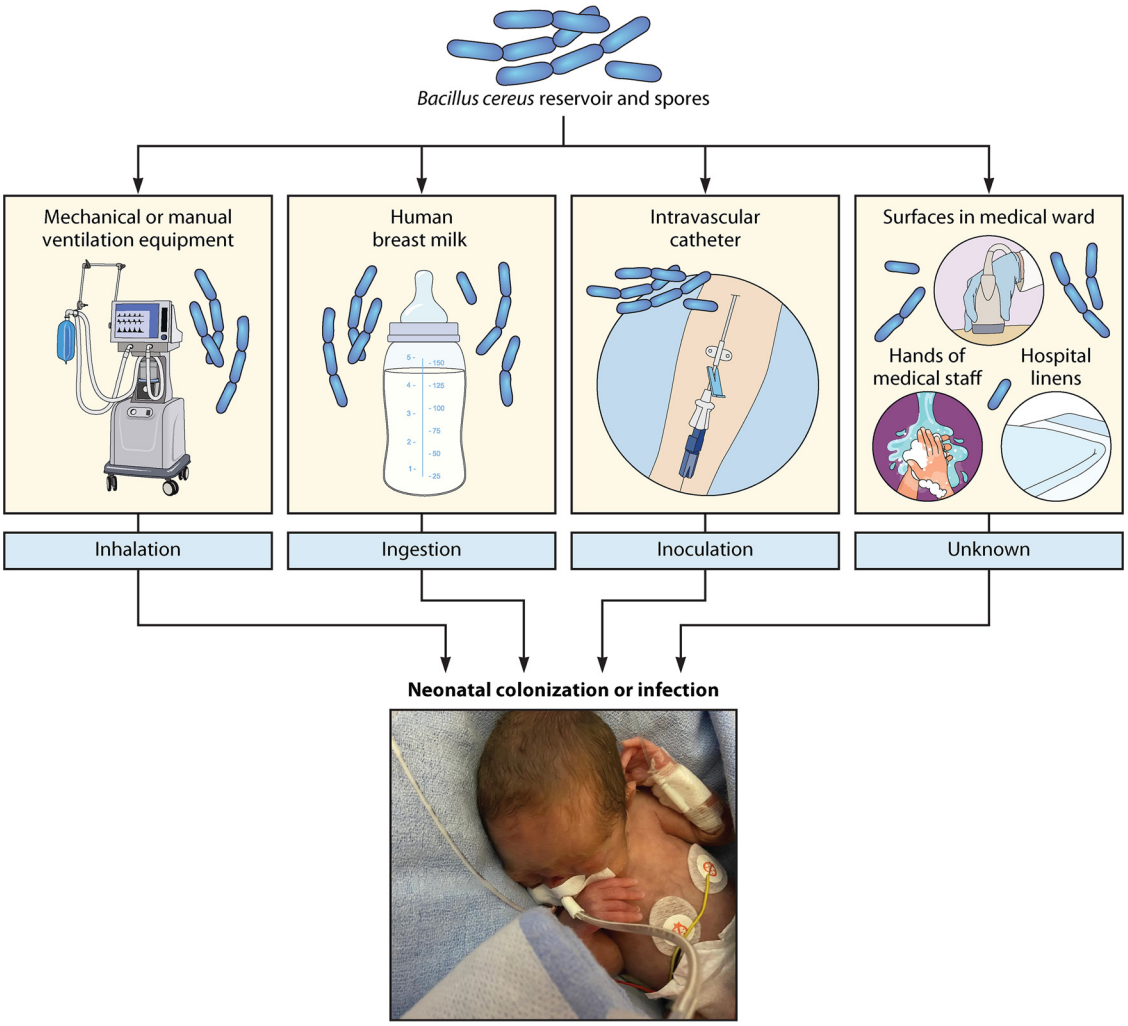

FIG 3 Schematic representation of the various potential environmental sources of infection in preterm neonates infected by *Bacillus cereus*.

mia consecutive to gut translocation, especially in the context of neutropenia (94). Therefore, *B. cereus* invasive infection in neonatal ICUs associated with the ingestion of contaminated milk has been commonly suspected and investigated. In two different studies reporting severe intestinal infections related to *B. cereus* in preterm neonates, the putative role of contaminated, pulled breast milk has been suggested but not proven by typing of strains (85, 90). In another study, nine cases of *B. cereus* bacteremia were described in five neonatal resuscitation units (NRUs) of the APHP between August and December 2016 (7). Interestingly, *B. cereus* was isolated from various batches of pasteurized breast milk produced by the same manufacturers who delivered to the NRUs. However, a comparison of the strains showed great genotypic diversity and the implication of a batch contamination of the milk has not been proven. No common source could be identified. The lack of evidence regarding the origin of *B. cereus* in human breast milk was recently highlighted by a recent literature review (95). Recently, Liao and Tsai reported for the first time a case of *B. cereus* bacteremia in a preterm infant caused by consumption of contaminated breast milk using pulsed-field gel electrophoresis (54). Airborne contamination can occur by inhalation of *B. cereus* spores from contaminated air or dust or through the presence of contaminated respiratory equipment. Indeed, airflow sensors from contaminated mechanical ventilation devices have been proven to be responsible for outbreaks of *B. cereus* respiratory colonization (positive endotracheal aspiration) in newborns (71, 83, 93). Moreover, in other studies, the presence of construction work adjacent to the NRUs has led to dissemination of *B. cereus* spores in the air likely responsible for airborne contamination of premature neonates (51, 59, 66). Unfortunately, this last hypothesis has not been proven via molecular typing. Other potential sources of nosocomial infections caused by *B. cereus*, for example, contamination of gloves, hydroalcoholic gels, and hygiene procedure negligence in health care practices which could be responsible for the colonization of catheters, should not be neglected by the hygiene control team in cases of a nosocomial outbreak.

Finally, in most of the health care-associated infection clusters caused by *B. cereus*, a comparative analysis between clinical and environmental strains using various genotyping methods failed to prove the precise origin of the infection, as these strains were genotypically different. Indeed, the molecular investigations revealed that the clustered cases of infection were linked to a wide variety of bacterial clones (7, 8, 51, 94). The retrospective nature of the environmental sampling performed by hygiene control teams in cases of nosocomial outbreaks and the wide genetic diversity of *B. cereus* strains present in the environment could also explain the failure to identify the precise source of infection. We can therefore hypothesize that *B. cereus* can, from various elements of the environment, colonize the skin and the respiratory or digestive tract and under certain conditions (immunosuppression and/or acquisition of virulence factors) lead to true infection.

INVASIVE INFECTIONS IN NEONATES: PATHOPHYSIOLOGY

Given the emergence and potential severity of invasive infections caused by *B. cereus* in preterm neonates, it is crucial to understand the host-pathogen interactions and to decipher the molecular mechanisms involved in this disease. In this at-risk population, the severity of the infection can be explained by the high virulence potential of some strains of *B. cereus* or by a defect in the innate immune response capacity of the host, as premature neonates have an immature immune system, or by a combination of these two factors.

Virulence Factors of *B. cereus sensu stricto*

Some *B. cereus sensu stricto* strains produce several compounds that could contribute to their virulence associated with GI infections. The emetic toxin cereulide, present in food products, can be responsible for food intoxication characterized by emesis in humans. The pore-forming toxins hemolysin BL (HBL), nonhemolytic enterotoxin (NHE), and CytK can cause GI infections characterized by diarrhea (96, 97). The differential level of expression of the various potential enterotoxin genes could be a contributing factor to the broad spectrum of strain virulence. However, little is known about the virulence factors associated with non-GI invasive infections (32, 98, 99).

Recently, using a mouse model of infection, our team has shown that the pore-forming toxin α-hemolysin of *Escherichia coli* counteracts the innate immune response during bacteremia

(100). Interestingly, the pore-forming HlyII of *B. cereus* has been shown to counteract the host immune system (101, 102) and is therefore suggested to play a role in invasive opportunistic infection. More recently, Mathur and colleagues (103) attempted to decipher the role of the multicomponent enterotoxin Hbl, which is highly conserved among *B. cereus sensu stricto* strains. The secretion of this toxin engages the activation of the NLRP3 inflammasome. Moreover, Hbl-producing *B. cereus* induces pyroptosis and cellular lysis in bone marrow-derived macrophages and rapid inflammasome-mediated mortality in a mouse model (C57BL/6). Furthermore, the authors showed that pharmacological inhibition of the NLRP3 inflammasome using MCC950 reduced the mortality of the mice infected by Hbl-producing *B. cereus* strains (103).

Together, these recent observations suggest that hypervirulent strains of *B. cereus sensu stricto* producing virulence factors such as HlyII or Hbl could be responsible for severe invasive infections in at-risk populations such as neonates. These studies also shed light on the potential relevance of pharmacological inhibitors of the inflammasomes as new drugs for the treatment of life-threatening bacterial infections.

Innate Immunity in Preterm Neonates

At birth, anti-infectious immunity is based mainly on the efficiency of the innate immune system (IS). Premature infants have immature ISs with reduced adaptive immune response capacities, which increases the risk of invasive infections. The preterm IS is also characterized by its lower capacity for neutralization and phagocytosis of infectious agents caused by a reduced activation of complement pathways, an impaired migration capacity of neutrophils to the site of infection, an impaired production of neutrophil extracellular traps (NETs), and also defective antigen presentation by monocytes and macrophages (104).

Premature birth is an increasing health care problem worldwide (105, 106). This increase in preterm births may partly account for the emergence of invasive bacterial infections in premature infants.

ANTIMICROBIAL SUSCEPTIBILITY TESTING AND ANTIBIOTIC TREATMENT

B. cereus (*B. anthracis* excluded) is frequently resistant to β-lactams, with the exception of carbapenems (47, 48, 51–53, 57, 66, 78, 87, 92, 94, 107–123). It is resistant to penicillin G and aminopenicillin, including ampicillin, ampicillin-sulbactam, amoxicillin, and amoxicillin-clavulanic acid. *B. cereus* is susceptible to third- and fourth-generation cephalosporins in 8% of cases (51 of 632 isolates) (53, 57, 66, 78, 87, 108, 109, 111, 112, 117, 119, 121, 122, 124). Little is known about the molecular mechanisms of antibiotic resistance of these bacteria. However, some authors have tried to decipher the main resistance mechanisms to β-lactams. *B. cereus* strains are intrinsically resistant to penicillins and cephalosporins by producing up to three chromosomal β-lactamases, named I, II, and III (125, 126). *B. cereus* β-lactamases I and III are serine-β-lactamases encoded by the *blaI* and *blaIII* genes, while β-lactamase II is a metallo-β-lactamase encoded by the *blaII* gene. Recently, Godič Torkar and Bedenic found that all 66 *B. cereus* isolates in their collection expressed *blaII* genes (122). Only two possessed the *blaIII* genes, and none possessed the *blaI* gene. If *B. cereus* strains are widely resistant to different classes of β-lactams including penicillins and cephalosporins, they are susceptible to various molecules that can be used as therapeutic agents as described below. Interestingly, carbapenems are active against *B. cereus*. Eighty-seven percent (254/290) and 94% (106/113) of the strains are susceptible to imipenem and meropenem, respectively. *B. cereus* is susceptible to glycopeptides, with 95% (575/606) and 100% (51/51) of the isolates being susceptible to vancomycin and teicoplanin, respectively (20, 47, 48, 51, 53, 57, 66, 69, 78, 87, 92, 94, 107–112, 114–119, 121–124, 127, 128). It is also susceptible to fluroquinolones, with 99% and 96% of the strains being susceptible to ciprofloxacin and levofloxacin, respectively (47, 48, 51, 53, 78, 87, 92, 94, 108–110, 112, 114, 115, 117–119, 121–123, 127). *B. cereus* is also susceptible to linezolid (57, 87, 92, 115–117, 123) and aminoglycosides (47, 48, 53, 57, 78, 87, 92, 107–109, 112, 115–121, 123, 124). In the literature, *B. cereus* has been reported to be frequently susceptible to macrolides and related antibiotics, with 75% (212/286), 85% (161/189), 89% (48/54), 74% (235/316), and 97% (29/30) of strains being susceptible to erythromycin, azithromycin,

clarithromycin, clindamycin, and pristinamycin, respectively (47, 53, 57, 66, 78, 92, 107–112, 114, 117, 118, 121, 123, 124). All the current knowledge about *in vitro* antimicrobial susceptibility of *B. cereus* clinical isolates is reported in Table 6.

Of note, if guidelines for *B. cereus* spp. (exclusive of *B. anthracis*) were provided by the Clinical and Laboratory Standards Institute, only a few authors used these recommendations to perform antimicrobial susceptibility testing (AST) in their studies. All the AST results collected from the literature were obtained by using various AST methods, inocula, and clinical breakpoints (see Table 6 for details) (129–135).

Very recently, in April 2021, specific recommendations for *Bacillus* species (exclusive of *B. anthracis*) were established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for the standardization of AST methods and clinical breakpoint interpretation (136). AST can be performed using broth microdilution in Mueller-Hinton broth with an inoculum of 5×10^5 CFU/mL and incubation for 24 h under aerobic conditions or by the disk diffusion method with a MacFarland 0.5 inoculum. EUCAST also provides clinical breakpoints for AST interpretation for the following eight antibiotics: imipenem, meropenem, ciprofloxacin, levofloxacin, vancomycin, erythromycin, clindamycin, and linezolid.

As of today, no specific treatment guidelines concerning *B. cereus*-related infections have been published. In the literature and considering only patients for whom antibiotic therapy information was available, 63% (33/52) of neonates with *B. cereus* bacteremia were treated with antibiotic therapy, including intravenous vancomycin (8, 51–57, 59, 60, 62, 65, 66, 68–72, 75, 88). The treatment was vancomycin monotherapy in 12 cases out of 33 (36%), and all these patients had favorable outcomes. In the 21 cases of multitherapy including vancomycin, 12 patients with favorable outcomes received a wide variety of antibacterial combinations: bitherapy with amikacin ($n = 1$), meropenem ($n = 4$), ampicillin ($n = 1$), or cefotaxime ($n = 1$); tritherapy with aminoglycosides and β-lactams (cefotaxime, meropenem, or piperacillin-tazobactam) ($n = 4$); or a combination of four antibiotics for one patient (vancomycin, tobramycin, clindamycin, and meropenem). Among the 33% of patients treated with vancomycin, a total of 73% (24/33) had favorable clinical and microbiological outcomes (51–53, 55–58, 60, 62, 65, 66, 68–72, 75, 78, 79, 83, 85, 88). These findings, along with the large percentage of vancomycin-susceptible strains and the pharmacological properties of this antibiotic, make vancomycin the treatment of choice in sepsis caused by *B. cereus*. Furthermore, given the very high susceptibility rate of *B. cereus* strains to aminoglycosides, the synergistic action with glycopeptides, and the history of successful treatment of neonates with these two antibiotics classes, we could propose the association of vancomycin with an aminoglycoside as the treatment of choice for *B. cereus* invasive infections in neonates. β-Lactams are widely used in the treatment of sepsis or septic shock due to their wide antibacterial array and pharmacological properties but should not be recommended alone in the treatment of *B. cereus* invasive infections because of high MICs and history of treatment failures. In particular, 40% of neonates treated with β-lactams without vancomycin died in the days or weeks following the beginning of infection (60, 61, 64, 71, 73, 74, 76, 82, 89).

CONCLUSIONS

To date, the *B. cereus* group proposed in our study encompasses 16 validly published species that are involved in sepsis and other life-threatening infections in preterm neonates. Around 33% of these infections are fatal despite an early and appropriate wide-spectrum antibiotic treatment active against the isolated strains. The high virulence potential of some *B. cereus* strains and the host innate immune response play a crucial role in patient outcomes in this at-risk population. In preterm neonates, the main proven environmental sources of *B. cereus* and gateways to systemic infection are airborne contaminations through resuscitation devices (mechanical or manual ventilation equipment) (71, 83, 93) and inoculation via intravascular catheter (8, 53). A very recent study has shown for the first time a case of *B. cereus* bacteremia in a preterm infant caused by consumption of contaminated breast milk (54). Hygiene control teams should be particularly reactive in order to identify the previously known or new environmental sources of infants' nosocomial infections and to avoid the epidemic spread of *B. cereus* clones in neonatal intensive care units. Of note,

TABLE 6 *In vitro* activity of antimicrobial agents against *B. cereus* clinical isolates[a]

	Susceptibility determined by AST guidelines (% susceptible strains) (no. of susceptible strains/total no.)													
	EUCAST (129)			CLSI/NCCLS (130–135)							Overall susceptibility			
Antibiotics	*Staphylococcus* spp.	Gram-positive bacteria	PK/PD breakpoints	*Staphylococcus* spp.	*Bacillus* spp. (not *Bacillus anthracis*)	*Bacillus anthracis*	Mycobacteria, nocardiae, other actinomycetes	*Corynebacterium* spp.	Gram-positive bacteria	Unspecified reference	Total no. of categorized strains	MIC range (mg/L)	% Susceptible	Reference(s)
Beta-lactams														
Penicillin G				1 (2/137)	0 (0/63)	1 (1/67)			0 (0/3)	0 (0/126)	396	0.012–>256	1	47, 48, 66, 78, 108–112, 116–119, 122–124
Ampicillin				0 (0/8)	2 (4/179)				0 (0/1)	0 (0/112)	300	0.016–256	1	48, 53, 57, 87, 92, 107–112, 114, 115, 117, 123, 124
Ampicillin - sulbactam				4 (1/28)							28	<0.25–>8	4	87, 111
Amoxicillin				4 (2/48)	5 (2/42)						90	0.016–>256	6	116, 117, 137
Amoxicillin – clavulanic acid									22 (15/68)	0 (0/90)	158	0.5– 64	9	66, 112, 119, 124
Cloxacillin										0 (0/60)	60	NA	0	124
Oxacillin				7 (3/43)							43	0.094–>256	7	110, 117, 123
Ceftriaxone				11 (9/82)	5 (2/42)				0 (0/1)		125	8–>256	9	47, 66, 117, 122
Cefotaxime				1 (1/69)	2 (2/78)				28 (19/68)	0 (0/112)	327	0.1–>64	7	53, 78, 87, 108–112, 119, 122, 124
Ceftazidime				0 (0/69)	0 (0/22)					10 (2/20)	111	2–>256	2	57, 87, 111, 121, 122
Cefepime				23 (16/69)							69	>32	23	94, 111, 122
Cefazolin				0 (0/1)	42 (34/80)						81	1–64	42	48, 87, 92, 110
Imipenem		0 (0/1)	100 (2/2)	100 (79/79)	99 (135/136)				100 (5/5)	49 (33/67)	290	0.004–>16	87	47, 48, 52, 53, 57, 66, 87, 92, 108, 110–115, 122
Meropenem				94 (104/111)	100 (1/1)				100 (1/1)		113	0.012–32	94	51, 57, 66, 111, 115, 117, 122
Aminoglycosides														
Amikacin					100 (46/46)				100 (1/1)	100 (20/20)	67	0.25–16	100	78, 87, 118, 121
Gentamicin				99 (124/125)	99 (197/199)		100 (1/1)		100 (68/68)	100 (101/101)	494	0.016–16	99	47, 48, 53, 57, 78, 87, 92, 107–109, 112, 116–119, 122–124
Tobramycin					100 (20/20)				100 (1/1)	100 (30/30)	51	0.125–2	100	78, 112, 118
Glycopeptides														
Vancomycin			100 (2/2)	94 (136/144)	98 (204/208)		100 (1/1)		87 (65/75)	95 (167/176)	606	0.06–24	95	20, 47, 48, 51, 53, 57, 69, 78, 87, 92, 94, 107–112, 114–122, 124, 127, 128
Teicoplanin								100 (51/51)			51	0.125–2	100	92, 110, 113
Cyclic lipopeptide														
Daptomycin				80 (68/85)				16 (8/51)			136	0.032–8	56	87, 92, 117, 118, 123, 127
Quinolones														
Ciprofloxacin				99 (75/76)	98 (120/122)	98 (131/133)	100 (1/1)		100 (1/1)	100 (127/127)	460	0.008–>4	99	47, 48, 53, 78, 94, 107–109, 111, 112, 114, 116–119, 121–123, 127
Levofloxacin			100 (2/2)	100 (20/20)	92 (74/80)					100 (60/60)	162	0.064–32	96	47, 57, 87, 92, 108, 111, 115, 117, 123
Macrolides and related														
Azithromycin				74 (49/66)	100 (56/56)				83 (56/67)		189	0.016–128	85	53, 119, 122
Clarithromycin				98 (41/42)						58 (7/12)	54	<0.12–4	89	108, 117
Clindamycin				69 (9/13)	80 (142/178)		0 (0/1)		100 (7/7)	66 (77/117)	316	0.032–16	74	47, 48, 53, 57, 66, 78, 87, 92, 107–111, 117, 121, 123
Erythromycin				25 (1/4)	72 (89/123)		100 (1/1)		78 (53/68)	75 (68/90)	286	0.032–24	75	48, 78, 87, 92, 107, 109, 110, 112, 114, 117–119, 124
Pristinamycin										97 (29/30)	30	NA	97	112
Cyclins														
Doxycycline				96 (46/48)							48	<0.03–16	96	116, 118
Tetracycline				97 (70/72)	100 (98/98)	84 (56/67)			100 (1/1)		238	0.016–128	95	53, 107, 109, 111, 117, 119, 122, 123
Tigecycline	100 (1/1)			100 (42/42)							43		100	117, 123
Oxazolidinone														
Linezolid			100 (2/2)	100 (116/116)				94 (48/51)			169	0.125–4	98	57, 87, 92, 115–117
Others														
Rifampicin				94 (47/50)	99 (113/114)		100 (1/1)			87 (26/30)	195	0.002–8	96	53, 87, 107, 112, 114, 116, 117, 123
Sulfamethoxazole-trimethoprim				62 (8/13)	72 (107/149)				100 (1/1)		163	0.064–>32	71	47, 48, 53, 92, 109, 114, 117, 123

[a]AST, antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NCCLS, National Committee for Clinical Laboratory Standards; PK/PD, pharmacokinetic/pharmacodynamic; NA, not available.

infections caused by *B. cereus* might have been overlooked since *B. cereus* isolated in human clinical samples has, for a long time, been regarded as a contaminant of the culture from the environmental reservoir. Our work questions the emergence or reemergence of these infections in preterm neonates. Furthermore, our review sheds light on recently described species thanks to advances in molecular identification methods using WGS. Interestingly, routine identification methods usually based on MALDI-TOF MS technology in routine clinical microbiology laboratories do not allow one to discriminate between these species. For example, the foodborne human pathogen *B. cereus sensu stricto* differs from *B. thuringiensis*, an insect pathogen widely used as a biopesticide, only by the presence or absence of the Cry toxin-encoding plasmid. In addition, *B. paranthracis* was recently involved in an emetic outbreak (30) and invasive infections in newborns (31). Therefore, *B. paranthracis* could have a high virulence potential, and further studies using NGS methods are required to understand whether the clinical strains implicated in the different *B. cereus* group infections belong to preferential and individual formerly known species or to newly described and emerging species.

Finally, in the absence of specific recommendations and given high MIC levels and treatment failure with β-lactams, this class of antibiotics should not be recommended alone for the treatment of *B. cereus* invasive infections. Given the information provided above (see Antimicrobial Susceptibility Testing and Antibiotic Treatment), we recommend the combination of vancomycin and aminoglycosides for the treatment of *B. cereus* group-related invasive infections in neonates before AST results.

ACKNOWLEDGMENTS

We are grateful to Abby Cuttriss, Université Côte d'Azur, for the careful reading and English editing of the manuscript. We warmly thank Florence Casagrande (Neonatal Intensive Care Unit, CHU) for permission to take the picture of a premature newborn hospitalized in the neonatal intensive care unit at the Nice teaching hospital in France shown in Fig. 3.

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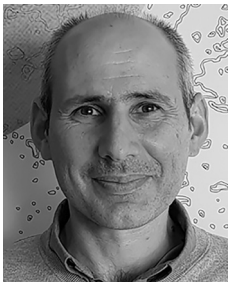

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