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Bacillus cereus invasive infections in preterm neonates : an up-to-date review of the literature

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THESE POUR L'OBTENTION DU
DIPLÔME D'ETAT DE DOCTEUR EN MEDECINE

Discipline : **Biologie Médicale**

INFECTIONS INVASIVES A *BACILLUS CEREUS*
DU NOUVEAU-NE PREMATURE :
REVUE DE LA LITTERATURE

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Par **CHEVALIER Alicia**
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TABLE DES MATIERES

INTRODUCTION.....	10
OBJECTIFS DE LA REVUE DE LA LITTERATURE.....	12
REVUE DE LA LITTERATURE.....	13
Introduction.....	14
Taxonomy and phylogeny.....	15
Species identification within the <i>Bacillus cereus</i> group.....	16
Habitat and epidemiology.....	18
Extra-digestive and invasive <i>Bacillus cereus</i> infections.....	20
Emergence of <i>Bacillus cereus</i> infections in preterm neonates.....	21
Invasive infections with <i>B. cereus sensu lato</i> bacteremia.....	21
Other severe invasive infections caused by <i>B. cereus</i> in neonates.....	26
Environmental sources of infection in preterm neonates.....	27
Invasive infections in neonates: pathophysiology.....	30
Virulence factors of <i>B. cereus sensu stricto</i>	30
Innate immunity in preterm neonates.....	31
Antimicrobial susceptibility testing and antibiotic treatment.....	31
Conclusion.....	34
References.....	35
Supplemental data.....	42
CONCLUSION ET PERSPECTIVES.....	44
Serment d’Hippocrate.....	46

INTRODUCTION

Le groupe *Bacillus cereus* aussi appelé *Bacillus cereus sensu lato*, comprend à ce jour 22 espèces dont 18 sont reconnues. Elles sont très proches phylogénétiquement. Ce sont des bactéries sporulées à Gram positif qui sont largement disséminées dans l'environnement. Leur réservoir est principalement tellurique. Ces espèces bactériennes sont connues pour impacter de façon importante à la fois les domaines de la santé humaine, de l'agriculture ou de l'industrie alimentaire. Chez l'homme, *B. cereus sensu stricto* est classiquement responsable d'infections gastro-intestinales et représente la troisième cause de toxi-infections alimentaires collectives en Europe. Parmi les autres espèces du groupe, *Bacillus anthracis* est l'agent responsable de l'anthrax, une pathologie mortelle chez l'homme en l'absence de traitement. *Bacillus thuringiensis* est un insecticide utilisé en agriculture biologique. Chez les sujets à risque, notamment les sujets immunodéprimés mais aussi les nouveau-nés prématurés, *B. cereus sensu lato* peut être responsable d'infections invasives et peut entraîner sepsis et choc septique. Chez les nouveau-nés prématurés, le taux de mortalité de ces infections peut atteindre les 30%.

Les espèces du groupe *B. cereus* ont un potentiel de pathogénicité variable. L'identification précise au niveau de l'espèce lors de l'isolement de cette bactérie dans un prélèvement clinique est donc primordiale. Cependant, il est important de noter que les méthodes d'identification phénotypique couramment utilisées dans les laboratoires de microbiologie clinique, telle que la spectrométrie de masse type MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight), ne permettent pas de distinguer *B. cereus sensu stricto* des autres espèces du groupe (à l'exception de *B. anthracis*). Par conséquent, toutes les infections invasives attribuées à *B. cereus* ne sont pas nécessairement dues à *B. cereus sensu stricto*, mais probablement à d'autres espèces étroitement apparentées du groupe *B. cereus*.

Par ailleurs, les infections invasives à *B. cereus* sont probablement sous-estimées. Lorsque cette bactérie est isolée dans un prélèvement clinique et que le patient ne présente pas de signes d'infection, elle est très souvent considérée comme un contaminant environnemental des cultures. Des études récentes ont pourtant suggéré l'émergence ou la réémergence d'infections invasives à *B. cereus* chez les nouveau-nés prématurés. Au centre hospitalier universitaire (CHU) de Nice, deux nouveau-nés prématurés sont décédés successivement en 2013 malgré une antibiothérapie à large spectre précoce et adaptée.

Egalement, en 2016, une enquête épidémiologique a montré une augmentation de l'incidence des bactériémies à *B. cereus* dans le service de réanimation néonatale de l'*Assistance Publique des Hôpitaux de Paris* (APHP), en France. Le nombre croissant de cas publiés d'infections à *B. cereus* chez les nouveau-nés prématurés et la description de cas groupés au sein d'un même établissement de soins en font une préoccupation majeure en santé publique pédiatrique.

Concernant le traitement, il n'existe actuellement aucune recommandation claire pour l'antibiothérapie probabiliste des infections invasives à *B. cereus*. Le choix du traitement empirique nécessite de connaître les données de sensibilité *in vitro* du pathogène d'intérêt. De nombreux articles étudient la sensibilité aux antibiotiques pour les souches environnementales de *B. cereus*, mais peu d'articles concernent les souches cliniques. Pour ces dernières, les données d'antibiorésistance se limitent souvent à celles liées aux études de cas dont il est difficile mais nécessaire de faire la synthèse.

Pour répondre à ces différentes problématiques, il nous a semblé important de réaliser une revue exhaustive de la littérature sur les infections à *B. cereus sensu lato* chez les nouveau-nés prématurés.

OBJECTIFS DE LA REVUE DE LA LITTÉRATURE

Les infections invasives à *Bacillus cereus* touchent en très grande majorité des sujets immunodéprimés. Chez les nouveau-nés prématurés, le nombre de cas publiés a nettement augmenté au cours des dernières années. Ces études récentes posent la question d'une éventuelle émergence ou réémergence de ces infections, rares mais potentiellement très graves, chez ces patients.

Cette revue de la littérature a pour objectif de faire l'état des connaissances actuelles sur les infections à *B. cereus* chez les nouveau-nés, en particulier les nouveau-nés prématurés. Ce travail a également pour objectifs de :

- Revoir la taxonomie des espèces du groupe *B. cereus* en intégrant les nouvelles espèces récemment décrites ;
- Souligner la problématique de l'identification bactérienne au laboratoire de bactériologie clinique ;
- Déterminer les caractéristiques microbiologiques et cliniques des infections invasives à *B. cereus* chez le nouveau-né ;
- Rapporter les interactions hôte-pathogène mises en jeu dans ces infections (virulence et immunité) ;
- Faire le point sur les sources environnementales des infections des nouveau-nés afin d'aborder la question de la prévention ;
- Décrire la résistance aux antibiotiques pour les souches cliniques de cette bactérie.

Notre revue fait actuellement l'objet d'une première révision dans le journal *Clinical Microbiology Reviews* (Revue de rang A, Impact Factor 26.132).

***Bacillus cereus* invasive infections in preterm neonates: An up-to-date review of the literature**

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Abstract (207 words)

Bacillus cereus group comprises eighteen species that are a widespread, Gram-positive, spore-forming environmental bacterium. *B. cereus sensu stricto* is the third most common cause 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 do not distinguish *B. cereus sensu stricto* and the other members of the group (excluded *B. anthracis*). As a result, all the invasive infections attributed to *B. cereus* are not necessarily due to *B. cereus sensu stricto* but likely to others closely related species of *B. cereus* group. NGS should be used to confirm if 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 its isolation in human bacteriological samples had for a long time been regarded as a contaminant. Recent studies have questioned the emergence or re-emergence 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 source of contamination and antimicrobial resistance.

INTRODUCTION

The *Bacillus cereus* group, also called *Bacillus cereus sensu lato*, consist of large, sporulating, Gram-positive, rod-shaped aerobic or facultative anaerobic bacteria that are widespread in the environment and can be isolated from soil, food and human skin ^(1,2). This group initially comprised six closely related species that were described during the 20th century and it has now reached 18 valid species. These bacterial species are known to have a significant impact on human health, agriculture or food industry, especially for *Bacillus anthracis*, *B. cereus sensu stricto*, and *Bacillus thuringiensis* ^(2,3). In human, *B. cereus sensu stricto* is mainly involved in gastrointestinal (GI) infections and represents the third most common bacteria involved in food poisoning outbreaks in Europe ⁽⁴⁾. Furthermore, *B. cereus sensu stricto* is involved in various invasive and frequently fatal infections, particularly in immunocompromised patients, patients with substance use disorders, post-surgical patients, and preterm neonates. It is important to keep in mind two important points. Firstly, it is difficult to distinguish between *B. cereus sensu stricto* and the other members of the group with phenotypic identification methods routinely used in clinical microbiology laboratory. Therefore, most human infections attributed to *B. cereus* in the literature should be considered as *B. cereus sensu lato* infections. Secondly, *B. cereus* invasive infections have probably been overlooked since its isolation in human bacteriological samples, especially in blood culture bottles, as for a long time been regarded as an environmental contaminant ⁽⁵⁾. Recent studies have suggested the emergence or re-emergence of *B. cereus sensu stricto* 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 ⁽⁶⁾. In our tertiary care center in Nice, France, we reported the death of two premature neonates in 2013 despite an appropriate wide spectrum antibiotic treatment ⁽⁷⁾. 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

B. cereus sensu stricto belong to the subdivision of the *Bacillus* genus called *B. cereus sensu lato*. To date, it comprises eighteen validly published species, which are phylogenetically closely related. In the early 2000s, only six species have been described in the *B. cereus* group: *Bacillus anthracis*⁽⁸⁾, *Bacillus cereus sensu stricto*⁽⁹⁾, *Bacillus thuringiensis*⁽¹⁰⁾, *Bacillus mycoides*⁽¹¹⁾, *Bacillus pseudomycoides*⁽¹²⁾, and *Bacillus weihenstephanensis*^(1, 2). These six species have classically been defined based on the presence of species' specific phenotypic and biochemical characters and on a similarity value lower than 70% using DNA/DNA hybridization methods. However, *B. cereus sensu stricto*, *B. thuringiensis* and *B. anthracis* have been validated as distinct species while these three species display a similarity value greater than 70%. Historically, the distinction between these three species was made because they display various pathogenic properties and diverse ecological lifestyles due to the presence or absence of plasmid harboring various toxins genes. *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 *pXOI*-like plasmid⁽¹³⁾. *B. thuringiensis* has insecticidal properties due to a crystal encoded by the *cry* gene on a plasmid position. *B. anthracis* is the etiologic agent of anthrax. Pathogenic strains of *B. anthracis* harbor two virulent plasmids *ie pXOI* and *pXO2*⁽¹⁴⁾.

In 2008, Guinebretière and colleagues, questioned the group's delineation in six species by using an approach combining molecular analyzes including fluorescent amplified fragment length polymorphism, and phenotypic analyzes on a collection of 425 strains⁽¹⁵⁾. In this study, seven phylogenetic groups were defined including three groups where the three species *B. cereus sensu stricto*, *B. anthracis* and *B. thuringiensis* were randomly distributed. Others molecular based approaches such as Multi-locus sequence typing (MLST) and Multilocus enzyme electrophoresis have confirmed that the three species could be considered to be a single species with different lineages displaying various phenotypic and pathogenic properties depending on the acquisition of plasmids of various sizes⁽¹⁶⁾. Over the past ten years, the group's composition of *B. cereus sensu lato* has been revised and enriched by the description of several novel species using a new criterion of DNA-DNA hybridization (average nucleotide identity) based on the whole-genome sequencing (WGS) of the strains. *B. weihenstephanensis* was reclassified as a later heterotypic synonym of *B. mycoides*⁽¹⁷⁾. Four species have also been published but not yet validated ("*Bacillus gaemokensis*", "*Bacillus manliponensis*", "*Bacillus bingmayongensis*", and "*Bacillus clarus*")⁽¹⁸⁻²¹⁾.

Twelve more valid new species were described in the *B. cereus* group: *Bacillus cytotoxicus*, *Bacillus toyonensis*, *Bacillus wiedmannii* ⁽²²⁻²⁴⁾ followed by *Bacillus albus*, *Bacillus luti*, *Bacillus mobilis*, *Bacillus nitratireducens*, *Bacillus pacificus*, *Bacillus paramycoides*, *Bacillus paranthracis*, *Bacillus proteolyticus* and *Bacillus tropicus* ⁽¹⁷⁾. The last nine have been isolated recently from seawater and marine sediments ⁽¹⁷⁾. More recently, a new species has been isolated from spent mushroom substrate: *Bacillus fungorum* ⁽²⁵⁾ (Supplemental Table).

The taxonomic history of the *B. cereus* group has been recently reviewed ⁽²⁶⁾. The phylogenetic relationships between the species composing *B. cereus sensu lato* using MLST is summarized in Figure 1 ⁽²⁷⁾. The comparison of three phylogenetic methods (neighbor-joining, maximum likelihood and maximum parsimony), as well as bootstrap replications (x1000), revealed a solid group consisting of all the *B. cereus* species except two valid species, *B. pseudomycoides* and *B. cytotoxicus*, and four not valid species “*B. gaemokensis*”, “*B. bingmayongensis*”, “*B. manliponensis*” and “*B. clarus*”. Given that many new species have been described since the early 2000s and in light of the new phylogenetic analyses, we could propose to delineate *B. cereus sensu lato* to those species brought together in the solid phylogenetic group shown in Figure 1. Recently, Carroll and colleagues suggested to reconcile genomic definition of bacterial species with clinical and industrial phenotypes ⁽²⁸⁾. In their study, they propose a new nomenclature based on eight genomospecies, two subspecies and three biovars.

The description of twelve new species in the *B. cereus* group makes it necessary to reconsider if the strains implicated in the different *B. cereus* group infections belong to specific or individual emerging species. In 2019, by using WGS, Carroll and colleagues have shown that *B. paranthracis* was implicated in an emetic outbreak ⁽²⁹⁾.

SPECIES IDENTIFICATION WITHIN THE *BACILLUS CEREUS* GROUP

The bacteria belonging to the *B. cereus* group are Gram-positive rods that produce central or terminal spores. The members of the *B. cereus* group, excluding *B. anthracis*, display various morphological forms depending upon the milieu in which they are observed ⁽²⁾. Gram stains of blood culture typically yield straight to slightly curved bacilli with square ends either singly or arranged in pairs or short chains (Figure 2A). *B. cereus* group species are aerobic or facultatively anaerobic bacteria and can grow over a broad temperature range ^(2, 30). Colonies are usually dull gray and opaque with a rough surface and are surrounded by a zone of β -hemolysis when grown at 37°C on enriched blood agar media under aerobic atmosphere (Figure 2B).

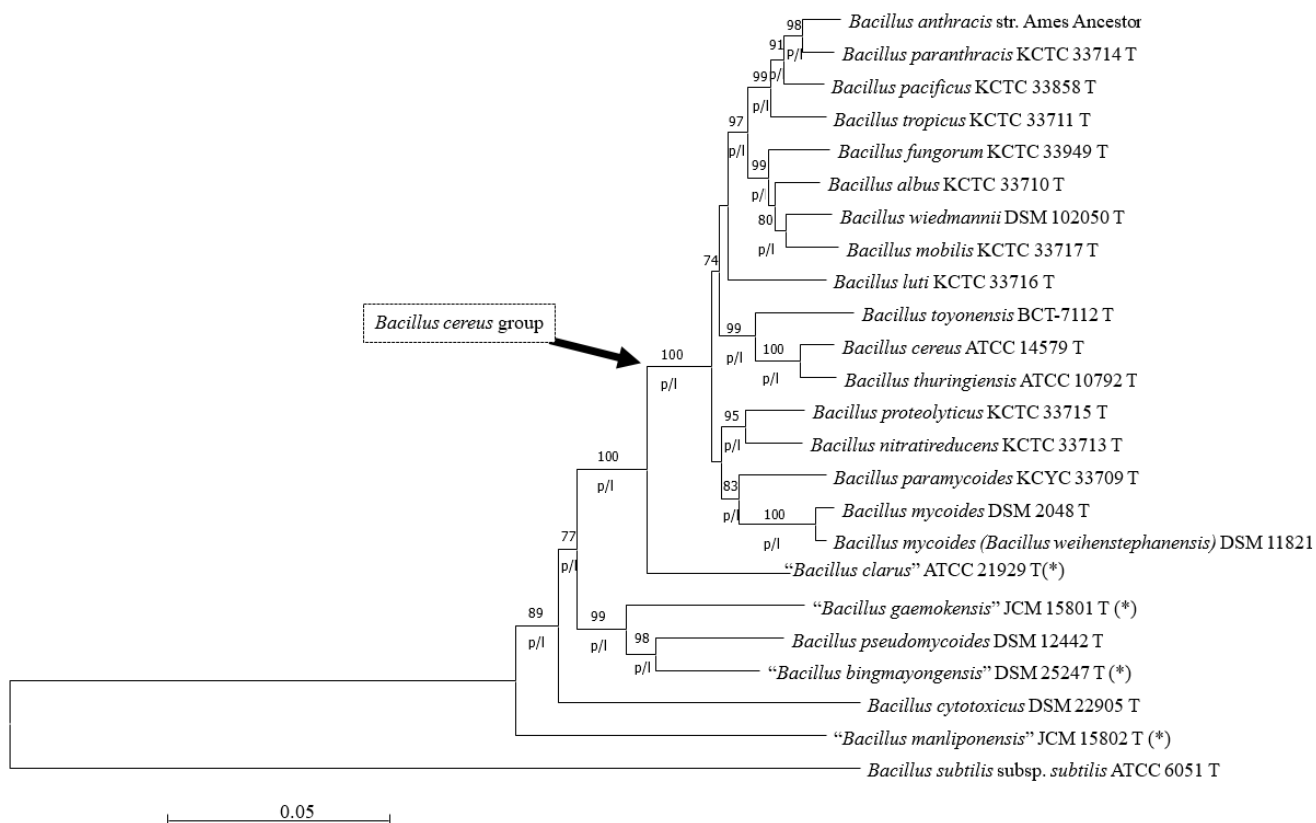


Figure 1: Phylogenetic relationships between the species of the *Bacillus cereus* group with *Bacillus subtilis* subsp. *subtilis* used as the outgroup.

The tree was obtained by the neighbor-joining method based on the comparison of the concatenated sequences of seven housekeeping genes (*glpF*, *gmk*, *ilvD*, *pta*, *pur*, *pycA*, *tpi*). The Kimura two-parameter distance measure was used as implemented in MEGA X (10). Values above the lines indicate how the tree's branches are supported by the results of bootstrap analysis (X100 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 (10). Scale bar = accumulated changes per nucleotide. (*) indicates the species published but not yet validly.

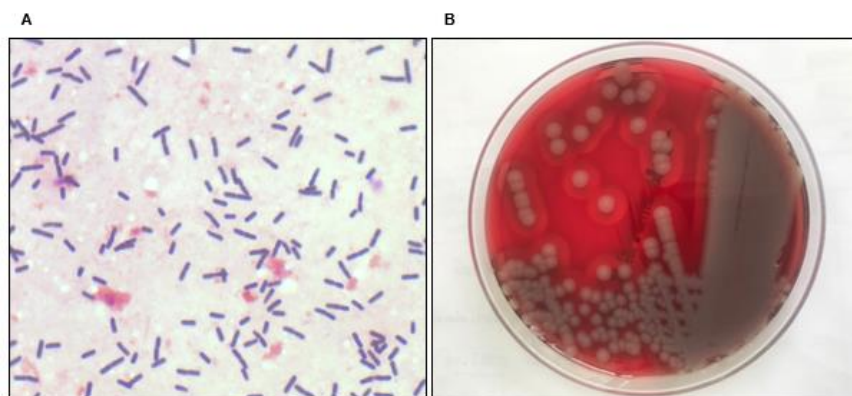


Figure 2: Direct examination and culture of *Bacillus cereus* strains

- Gram staining (1000X) showing large and straight Gram-positive bacilli with square ends.
- Colonial morphology of *B. cereus* grown on Columbia agar with 5% sheep blood after 24 hours of incubation under aerobic condition. The colonies are surrounded by a typical zone of β -hemolysis.

Several biochemical and phenotypic characteristics of the different species can differentiate the species of the *B. cereus* group⁽³¹⁾. The main differences between positive biochemical characteristics of the type strains for the different proposed species in the *B. cereus* group and species out of the *B. cereus* group are detailed in Table 1^(17, 20, 25).

In a routine clinical microbiology laboratory, the 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 Microflex database (Bruker Daltonics, Bremen) that is widely used in routine clinical microbiology laboratories, only contains microbial reference spectra for five species of the *B. cereus* group: *B. cereus sensu stricto* (4 spectra), *B. cytotoxicus* (4 spectra), *B. mycoides* (3 spectra), *B. pseudomycoides* (1 spectrum), *B. thuringiensis* (1 spectrum). Some of the newly described species of the *B. cereus* group are still missing from this database. Moreover, MALDI-TOF MS could misidentify strains belonging to the *B. cereus sensu lato*. For example, the food-born 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 only differ by the presence or absence of the Cry-toxin encoding plasmid. 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^(32,33). Finally, it is now crucial to update the available MALDI-TOF MS databases with high-quality reference strains identified by WGS in order to enhance the identification human pathogen species belonging to the *B. cereus* group.

HABITAT AND EPIDEMIOLOGY

B. cereus sensu lato is widespread in nature. The natural environmental reservoir for *B. cereus sensu lato* consists of decomposing organic matter, fresh and marine water, plants and the intestinal tracts of invertebrates^(2, 34). From this natural habitat, the microorganism is able to contaminate soil and a wide variety of food products and this can lead to the transient colonization of the human gut⁽³⁵⁾. Moreover, *B. cereus sensu lato* is capable of growing quickly in a wide variety of conditions, which explains its ubiquitous worldwide distribution regardless of the environment. *B. cereus sensu lato* also produces endospores that enable it to withstand desiccation, temperature and pH variations, and anaerobic conditions⁽³⁰⁾.

	Acetoin production (+)	Arbutin (+)	Citrate utilization (+)	D-mannose (+)	Glycogen (+)	Oxidase (+)	Salicin (+)	Starch hydrolysis (+)	Sucrose (+)	Trehalose (+)	Urease (+)
<i>Bacillus cereus</i> group (n=17) ^a	94%	82%	82%	19%	82%	94%	82%	78%	53%	94%	0%
<i>Bacillus cereus</i> outgroup (n=6)	60%	50%	33%	17%	67%	50%	67%	33%	50%	50%	33%
Species validly published only (n=2) ^b	100%	100%	0%	50%	50%	100%	100%	0%	0%	50%	0%
Species not validly published (n=4) ^c	33%	25%	50%	0%	75%	25%	50%	50%	75%	50%	50%

Table 1: Main positive biochemical characteristics of type strains for proposed species in *B. cereus* group and species out of *B. cereus* group (validated and not validated) ^(17, 20, 25)

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

^b *Bacillus pseudomycooides* DSM 12442T; *Bacillus cytotoxicus* NVH 391-98T

^c “*Bacillus bingmayongensis* FJAT 13831T”; “*Bacillus manliponensis* BL4-6T”; “*Bacillus gaemokensis* JCM 15801T”; “*Bacillus clarus* ATCC 21929”

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 ⁽³⁶⁾. Some *B. cereus* strains are also able to form diverse biofilms that allow them to resist bio-cleaning procedures ⁽³⁷⁾. Biofilm formation and sporulation are therefore responsible for the persistence of *B. cereus* in the environment. In general, human *B. cereus sensu lato* infections occur *via* ingestion of contaminated food or soil, inhalation of spores or direct inoculation into the skin.

EXTRA-DIGESTIVE AND INVASIVE *BACILLUS CEREUS* INFECTIONS

B. cereus sensu lato is an opportunistic pathogen responsible for extra-digestive, localized or systemic, nosocomial infections, frequently occurring in immunocompromised patients and in newborns (premature or full-term). In these populations, *B. cereus sensu lato* causes various types of infections including sepsis, septic-shock, central nervous system infections and even eye infections ⁽²⁾. Recently, Messelhäuser & Ehling-Schulz have summarized the main cases of extra-digestive infections described in the literature between 2012 and 2017. In this review, they report cases of bacteremia or sepsis, central nervous system (CNS) infections with cerebral damages (abscess, meningoencephalitis), endocarditis and eye infections, two cases of necrotizing fasciitis and one case of peritonitis and hepatic abscess ⁽³⁰⁾. In immunocompromised subjects, the main risk factors for infection are malignant hemopathies, intravascular devices, intravenous drug injections and traumatic or surgical lesions ^(38, 39). In immunocompetent patients, systemic *B. cereus sensu lato* infections such as anthrax-like disease type and catheter-related bloodstream infections (CRBSI) have also been reported ^(40, 41). In immunocompetent adults, systemic *B. cereus sensu lato* 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 ⁽⁶⁾.

Overall, there is a wide clinical spectrum of human *B. cereus sensu lato* infections. Indeed, extra-digestive infections are probably overlooked because *B. cereus* has, for a long time, been regarded as a 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 sensu lato* 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 elderly, immunocompromised patients and preterm neonates. In this review, we focus on *B. cereus* invasive infections in infants that are being increasingly reported in the literature (Supplemental figure). A newborn is considered premature when birth occurs before the start of the 37th week of pregnancy⁽⁴²⁾. Invasive infections in these patients occur sporadically, or in outbreaks. The very recent description of nosocomial outbreaks in France, Germany and Israel led to a reconsideration of the global risk of this potentially serious risk^(6, 43-45). Therefore, improving the current knowledge regarding *B. cereus sensu lato* 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 sensu lato* infections in neonates 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%)^(6, 7, 44-70), 36 CNS infections (25%)^(7, 43, 44, 47, 49, 50, 54-57, 60, 61, 63, 64, 66-75), 18 respiratory tract infections (12%)^(7, 43, 45, 49, 67, 69, 76), 13 cases of skin infections (9%)^(43, 77), six cases of GI infections (4%)^(43, 78, 79), two cases of osteo-articular infections (1%)^(64, 65) and one single case of urinary tract infection (UTI) (1%)⁽⁴³⁾ (see Table 2 for details). *B. cereus sensu lato* infection was fatal in 33 out of 106 patients (31%). Regarding treatment, the implementation of the antibiotic treatment, based on vancomycin for *B. cereus sensu lato* invasive infection⁽⁸⁰⁾, did not prevent patient death in eleven out of thirty-three cases (33%) considering only patients for whom antibiotic therapy information was available^(44, 45, 53, 63, 65, 68, 72, 81).

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

Invasive infections with *B. cereus sensu lato* bacteremia

We further analyzed a total of 69 cases of *B. cereus sensu lato* bacteremia in newborns^(6, 7, 44-70, 81) (Table 3). The selection criterion was the presence of at least one positive blood culture for *B. cereus sensu lato* 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 weight of birth was 1392 g.

Type of infection	Cases, <i>n</i> (%) (<i>n</i> =145)	Source of positive clinical specimens	References (cases, <i>n</i>)
Bacteremia	69 (48%)	Blood culture	(46) (1), (81) (2), (44) (3), (45) (1), (47) (1), (43) (6) (6)(9), (7) (1),(49) (2), (50) (1),(51) (3), (52) (8), (53) (2), (54) (1),(55) (1), (56) (1), (57) (1), (58) (1), (59) (8), (60) (3), (61) (1),(62) (1),(63) (1),(64) (3),(65) (1) (66) (1),(67) (2)(68) (1), (70)(1),(69) (1)
CNS infection	36 (25%)		
Meningitis, meningoencephalitis	23 (16%)	CSF, meninges, brain tissue	(43) (1), (50) (1), (54) (1), (55) (1),(57) (1),(60)(3)(61) (1), (63) (1),(64) (2),(66) (2),(67) (1), (68) (1),(70) (1) (71) (1),(72) (1), (73), 2)3 (1),(75)(1)
Brain abscesses, empyema or necrosis	13 (9%)	Brain tissue, necrosis	(44) (1),(47) (1), (43)(1), (7) (1) (49) (1), (55) (1), (56) (1), (57) (1)(61) (1),(63) (1),(68) (1),(67) (1) (69)(1)
Respiratory infection	18 (12%)		
Pneumonia	11 (8%)	Tracheal aspiration, pleural fluid, lung tissue	(45) (2), (43) (1), (67) (2), (82) (1), (7) (1),(76) (4)
Pulmonary abscesses or necrosis	6 (4%)	Lung tissue, pleural fluid	(45) (1),(49) (1), (67), (2), (69)(1), (82)(1)
Tracheobronchitis	1 (0.7%)	NA	(45) (1)
Cutaneous infection	13 (9%)	Skin, armpit, umbilical cord stump swab	(77) (12), (43)(1)
Gastrointestinal infection	6 (4%)		
Digestive tract	5 (3.5%)	Gastric fluid, stomach tube feeding, sample from abdominal cavity	(43) (2),(78) (2),(79) (1)
Liver	1 (0,7%)	NA	(43) (1)
Osteoarticular infection	2 (1%)		
Arthritis	1 (0.7%)	Synovial fluid	(64) (1)
Osteitis	1 (0,7%)	Bone, bone marrow	(65) (1)
Kidneys and urinary infection	1 (1%)	NA	(43) (1)

Table 2: Type of infection due to *B. cereus* in neonates.

CSF: cerebrospinal fluid, NA: not available

Table 3: Main features of reported cases of *Bacillus cereus* bacteremia in neonates.

Reference (n, number of cases)	Term of birth (weeks + days of gestation)	Weight at birth (g)	Underlying conditions	Clinical presentation	Disseminated infection	Suspected Source(s) of Infection	Antibiotic treatment	Outcome
Liao and Tsai, 2020 ⁽⁴⁶⁾ (n=1)	33 + 2	1490	Respiratory distress	Sepsis	No	Mother breast milk	VCM, AMK	Recovery
Lewin <i>et al.</i> , 2019 ⁽⁸¹⁾ (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				AMP, TBM, VCM, MRP, PTZ, CTX	
Bar-Meir <i>et al.</i> , 2019 ⁽⁴⁴⁾ (n=3)	32	NA	Twin pregnancy	Septic shock	Brain abscesses	Construction related dust	VCM, MRP, CRP	Death
	31		No	Sepsis	No		VCM, MRP	Recovery
	31		CBD	Contamination	No		None	Recovery
Papan <i>et al.</i> , 2019 ⁽⁴⁵⁾ (n=1)	37 + 5	2700	Congenital diaphragmatic hernia closure	Septic shock	Pneumonia, Pyogenic tracheobronchitis, necrotizing bronchiolitis	Undetermined	VCM, MRP, FSF	Death
Samarasekara <i>et al.</i> , 2019 ⁽⁴⁷⁾ (n=1)	30	NA	No	Sepsis	Brain abscess	Undetermined	VCM, MRP, AMP, FCX	Recovery
					Meningitis, pulmonary and liver infection	Surface in medical ward	None	Death
					Brain abscess	Surface in medical ward	VCM, CFT	Recovery
Glasset <i>et al.</i> , 2018 ⁽⁴³⁾ (n=6)	NA	NA	NA	Sepsis	No	Surface in medical ward	VCM	Recovery
					No	Surface in medical ward	VCM, AMK, AMX	Recovery
					No	Surface in medical ward, central catheter	VCM	Recovery
					Kidneys and urinary infection	Undetermined	CFX, GTM	Recovery
Fournier <i>et al.</i> , 2017 ⁽⁶⁾ (n=9)	30 + 2	750	Intrauterine growth restriction, hemorrhagic brain lesions	Sepsis	No	Banked human milk, parenteral nutritional solutions	NA	Death
	29 + 2	1075	Twin pregnancy, transfused transfusion syndrome		Extensive brain damage			Death
	37 + 2	2815	Atresia of the small intestine		No			Recovery
	31	1380	Atresia of the duodenum		No			Recovery
	29 + 4	1025	Umbilical hernia		No			Recovery
	27 + 5	750	Enterocolitis		No			Death
	31	1720	Twin pregnancy		No			Recovery
	38 + 6	3515	Neonatal respiratory distress		No			Recovery
39	3240	Polymalformation	No	Recovery				
Lotte <i>et al.</i> , 2017 ⁽⁷⁾ (n=1)	29 + 4	1480	Maternal malignancy	Septic shock	Brain empyema, abscesses and necrosis, cranial hemorrhages	Central catheter, surface in medical ward	VCM, GTM, CFT	Death
Ramarao <i>et al.</i> , 2014 ⁽⁴⁹⁾ (n=2)	24 + 5	650	CBD	Sepsis	No	Central catheter	VCM, AMK, CFT	Recovery
	26 + 5	615	No	Septic shock	Brain and pulmonary abscesses		None	Death

Reference (n, number of cases)	Term of birth (weeks + days of gestation)	Weight at birth (g)	Underlying conditions	Clinical presentation	Disseminated infection	Suspected Source(s) of Infection	Antibiotic treatment	Outcome
Horii <i>et al.</i> , 2012 ⁽⁵⁰⁾ (n=1)	NA	800	Bowel perforation, CBD	Sepsis	Late meningitis	Hospital linens	VCM, MRP, LNZ, CLD	Recovery
Shimono <i>et al.</i> ⁽⁵¹⁾ (n=3)	29	476	NA	Sepsis	No	Surface in medical ward	NA	Recovery
	30	876						
Campbell <i>et al.</i> , 2011 ⁽⁵²⁾ (n=8)	28	1018	NA	Sepsis	No	Endotracheal intubation, central catheter, construction excavation	VCM	Recovery
	31	1650						
	29	1148						
	28	1515	NA	Contamination	No	Endotracheal intubation, central catheter, construction excavation	None	Recovery
	24	710						
	25	945						
Sasahara <i>et al.</i> , 2011 ⁽⁵³⁾ (n=2)	29	1015	Mitral regurgitation Patent ductus arteriosus	Septic shock	No	Hospital linens, central catheter, parenteral solutions	AMP/SBT, MRP, VCM, PNP, CFZ	Death
	40	4184						
Saito <i>et al.</i> , 2010 ⁽⁵⁴⁾ (n=1)	30	870	Intrauterine growth restriction, patent ductus arteriosus, severe pregnancy-induced hypertension	Septic shock	Meningitis, intraventricular hemorrhage, pulmonary hemorrhage	Undetermined	CFZ	Death
	27	740						
Drazin <i>et al.</i> , 2010 ⁽⁵⁵⁾ (n=1)	32 + 4	1910	Mild dysmorphic features, patent foramen ovale, twin pregnancy, preeclampsia	Sepsis	Meningoencephalitis, brain abscesses	Undetermined	VCM, AMK, GTM, MRP	Recovery
Pawlik <i>et al.</i> , 2009 ⁽⁵⁶⁾ (n=1)	27	730	NA	Sepsis	Brain abscesses	Undetermined	NA	Recovery
Evreux <i>et al.</i> , 2007 ⁽⁵⁷⁾ (n=1)	31	1670	Thyroid agenesis	Septic shock	Meningitis, brain abscesses and necrosis	Central catheter	CFT, AMX, MTZ, AMK	Death
John <i>et al.</i> , 2006 ⁽⁵⁸⁾ (n=1)	32	1512	Ruptured bicornuate uterus, severe fetal distress	Sepsis	Subependymal hemorrhage, cerebral edema	Undetermined	PTZ, AMK, VCM	Recovery
	25	680	Candida sepsis, chronic lung disease, retinopathy	Sepsis	No	Air	MRP	Recovery
Adler <i>et al.</i> , 2005 ⁽⁵⁹⁾ (n=8)	34	2010	<i>Escherichia coli</i> peritonitis				MRP	
	37	2000	<i>Klebsiella</i> peritonitis and sepsis				VCM	
	36	1735	Necrotizing enterocolitis				MRP	
	30	1226	Necrotizing enterocolitis				MRP	
	29	1508	No				VCM	
	32	1600	No				VCM	
27	870	No	VCM					
Lequin <i>et al.</i> , 2005 ⁽⁶⁰⁾ (n=3)	30 + 6	NA	No	Sepsis	Hemorrhagic meningoencephalitis	Undetermined	NA	Death
	28 + 3				Hemorrhagic meningoencephalitis			
	34 + 1				Hemorrhagic meningoencephalitis, ventriculitis			

Reference (n, number of cases)	Term of birth (weeks + days of gestation)	Weight at birth (g)	Underlying conditions	Clinical presentation	Disseminated infection	Suspected Source(s) of Infection	Antibiotic treatment	Outcome
Heep <i>et al.</i> , 2004 ⁽⁶¹⁾ (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 <i>et al.</i> , 2003 ⁽⁶²⁾ (n=1)	24	585	Chorioamnionitis	Septic shock	No	Undetermined	VCM, TBM, CLD, MRP	Recovery
Chu <i>et al.</i> , 2001 ⁽⁶³⁾ (n=1)	26	1580	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 <i>et al.</i> , 2000 ⁽⁶⁴⁾ (n=3)	28 + 5	895	MV, patent ductus arteriosus	Septic shock	Hemorrhagic meningoencephalitis	Ventilator equipment, hands of medical staff	AMX, CFT	Death
	26+4	1000	MV	Sepsis	Knee arthritis		VCM, MRP	Recovery
	37+3	2780	MV, hepatosplenomegaly	Sepsis	Meningitis		VCM, MRP	Recovery
Tuladhar <i>et al.</i> , 2000 ⁽⁶⁵⁾ (n=1)	24	735	MV, CNS hemorrhage	Sepsis	Bone marrow	Undetermined	CPF, CLD, GTM, IMP, VCM	Death
Tokieda <i>et al.</i> , 1999 ⁽⁶⁶⁾ (n=1)	37	3764	Hydrops fetalis, MV	Sepsis	Meningitis, brain hemorrhages	Peripheral catheter	AMP, GTM	Death
Jevon <i>et al.</i> , 1993 ⁽⁶⁷⁾ (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		Necrotizing pneumonia			
Patrick <i>et al.</i> , 1989 ⁽⁶⁸⁾ (n=1)	26	830	MV, thalamic hemorrhage	Septic shock	Meningitis, brain necrosis	Undetermined	AMK, VCM	Death
Turnbull <i>et al.</i> , 1979 ⁽⁷⁰⁾ (n=1)	NA	NA	NA	Sepsis	Meningitis	Undetermined	NA	NA
Turnbull <i>et al.</i> , 1977 ⁽⁶⁹⁾ (n=1)	32	1320	Necrotizing enterocolitis	Sepsis	Brain, lung and respiratory tract necrosis	Central catheter	AMP, GTM	Death

MRP: meropenem, VCM: vancomycin, FCX: fluclloxacilline, FSF: fosfomycin, CFT: cefotaxime, AMK: amikacin, AMP/SBT: ampicillin/sulbactam, AMX: amoxicillin, CFX: ceftriaxone, GTM: gentamicin, CRP: chloramphenicol, LNz: linezolid, CLD: clindamycin, AMP: ampicillin, PNP: panipenem, CFZ: ceftazidime, PTZ: piperacillin/tazobactam, TBM: tobramycin, CPF: ciprofloxacin, IMP: imipenem, MTZ: metronidazole, CFA: ceftazidime, ETY: erythromycin, CBD: chronic bronchial disease, CNS: central nervous system, MV: mechanical ventilation, NA: not available

The presence of *B. cereus sensu lato* in the blood culture was considered to be contamination in only four cases (4/69) (6%)^(44, 52). In all other reports, *B. cereus* was responsible for sepsis 50/69 (72%)^(6, 44, 46-50, 52, 53, 55, 58-61, 63-66, 69, 70, 75) or septic shock 15/69 (22%)^(7, 44, 45, 49, 53, 54, 57, 62, 64, 67, 68, 81). A peculiarity of *B. cereus sensu lato* sepsis in neonates is the secondary meningeal or cerebral dissemination. Indeed, meningitis or meningoenzephalitis^(43, 50, 54, 55, 57, 60, 63, 64, 66-68, 70) and brain abscesses or necrosis^(6, 7, 43, 44, 47, 49, 55-57, 61, 68, 69) were reported in 19/65 (29%) and 12/65 (18%) of the neonate presenting with *B. cereus sensu lato* related sepsis or septic shock, respectively. Pneumonia was associated in six out of sixty-five patients (9%)^(45, 48, 49, 67, 69).

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 sensu lato* can be responsible for severe neurological^(71, 72), respiratory^(76, 82), digestive^(78, 83) and primary cutaneous infections⁽⁷⁷⁾. 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⁽⁸²⁾. Interestingly, *B. cereus sensu lato* 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 of 1-5% of all neonatal intensive care admission⁽⁸⁴⁾. To date, the precise mechanisms involved in this disease are not fully understood. Several potential causes are often evocated like diet, inflammation or infection. An infectious etiology is suspected for NEC outbreaks. In their study, Wendelboe and colleagues described a cluster of NEC in a neonatal ICU in New Mexico in 2007, and suggested the potential involvement of *B. cereus* in this outbreak⁽⁸³⁾.

Finally, as previously suggested, it is important to note that all these invasive infections related to *B. cereus sensu lato* 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^(53, 85). 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 sensu lato* is enhanced when temperatures are higher, which could explain the transient increase in the number of infections especially during summer.

Collectively, all these data suggest that premature infants are particularly susceptible to *B. cereus sensu lato* invasive nosocomial infections. One of the main reasons for this susceptibility is that preterm neonates are exposed to various environmental sources of *B. cereus sensu lato* contamination.

ENVIRONMENTAL SOURCES OF INFECTION IN PRETERM NEONATES

As previously suggested, *B. cereus sensu lato* invasive infections can be fatal in preterm infants hospitalized in neonatal ICU and sometimes, even despite early and appropriate antimicrobial drug therapy^(7, 44, 45, 63, 68). Considering the virulence potential of *B. cereus sensu lato* in this population and the natural habitat of this bacterium in the environment (soil, food, or decomposing organic matter), the question of the source of contamination is of major concern in pediatric public health. Indeed, increasing our understanding of the origin of infection could help preventing the transmission of *B. cereus sensu lato* 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 sources of contamination and the gateways to systemic infection are air born contaminations through resuscitation devices (mechanical or manual ventilation equipment)^(64, 76, 86), and inoculation *via* intravascular catheter^(7, 43). Other environmental sources of contamination have been described, including hospital linen, surfaces in medical wards and hands of medical staff and should be investigated in the case of *B. cereus sensu lato* nosocomial outbreak in pediatric ICU^(43, 51, 53, 64). The various suspected sources of contamination that are investigated using various genotyping methods in the cases of *B. cereus sensu lato* invasive infections in neonates previously reviewed are summarized in the Table 4 and Figure 3.

Enteral feeding contamination by *B. cereus sensu lato* can result in either a GI infection or a bacteremia consecutive to gut translocation, especially in the context of neutropenia⁽⁸⁷⁾. Therefore, *B. cereus sensu lato* invasive infection in neonatal ICU 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 sensu lato* in preterm neonates, the putative role of contaminated, pull breast milk has been suggested but not proven by typing of strains^(78, 83). In another study, nine cases of *B. cereus sensu lato* bacteremia occurred in five neonatal resuscitation units (NRU) of the APHP between August and December 2016⁽⁶⁾.

Suspected source of contamination ^a (n = number of cases)	Proven source of contamination ^b	Mode of transmission
Intravascular catheters (n=5) (7, 43, 53, 61)	60% (3/5)	Inoculation
Ventilator equipment (n=17) (64, 76, 86)	53% (9/17)	Inhalation
Human milk (n=16) (6, 43, 46, 78)	6% (1/16)	Ingestion
Surfaces in medical ward (n=16) (7, 43, 51, 77)	37% (6/16)	
Hands of medical staff (n=5) (51, 64, 77)	60% (3/5)	Unknown
Hospital linens (n=3) (50, 53)	33% (1/3)	
Parenteral nutritional solutions (n=11) (6, 53)		
Air, airborne dust, construction (n=2) (51)	0% (0/13)	Unknown

Table 4: Environmental source of preterm infections in neonates.

^a Study of *Bacillus cereus* strains isolated from patients and hospital environments.

^b Same strain isolated from patient and hospital environment.

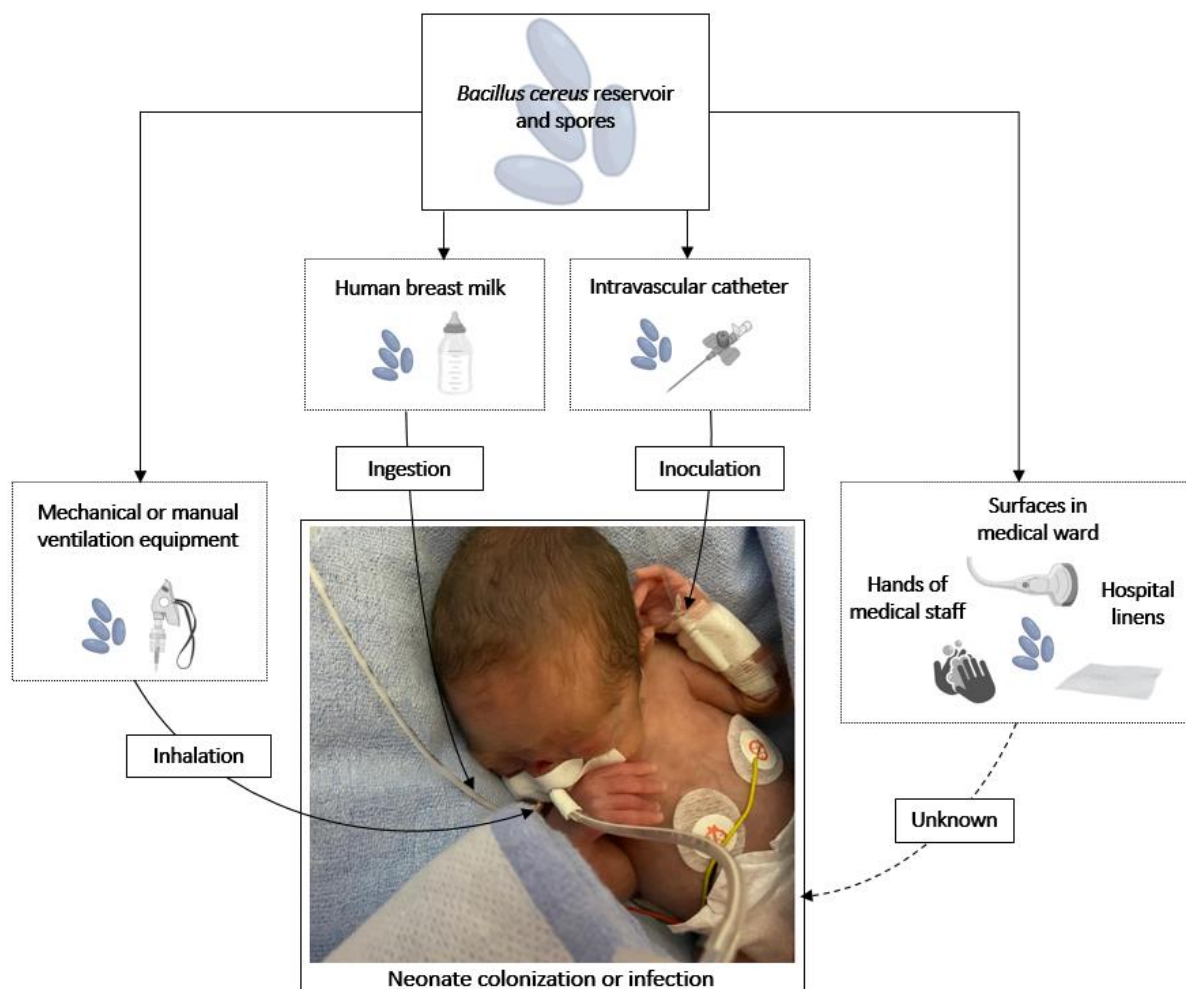


Figure 3: Schematic representation of the various potential environmental sources of contamination in preterm neonates infected by *Bacillus cereus*.

Interestingly, *B. cereus sensu lato* was isolated from various batches of pasteurized breast milk produced by the same manufacturers who delivered to the NRU. However, the 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 sensu lato* in human breast milk was recently highlighted by a recent literature review⁽⁸⁸⁾. Recently, Liao and Tsai reported for the first time a case of *B. cereus* bacteremia in a preterm infant caused by consumption of contaminated breastmilk using pulse field gel electrophoresis⁽⁴⁶⁾. Airborne contamination can occur by inhalation of *B. cereus* spores from contaminated air or dust, or through the presence of a contaminated respiratory equipment. Indeed, air flow sensors from contaminated mechanical ventilation devices have been proven to be responsible for outbreaks of *B. cereus sensu lato* respiratory colonization (positive endotracheal aspiration) in newborns^(64, 76, 86). Moreover, in other studies, the presence of construction works adjacent to the NRU have led to the dissemination of *B. cereus* spores in the air likely responsible for airborne contamination of premature neonates^(44, 52, 59). Unfortunately, this last hypothesis has not been proven *via* molecular typing. Other potential sources of nosocomial infections caused by *B. cereus sensu lato* should not be neglected by the hygiene control team in case of a nosocomial outbreak, for example, contamination of gloves, hydroalcoholic gels, and hygiene procedure negligence in healthcare practices which could be responsible for the colonization of catheters.

Finally, in most of the healthcare-associated infection clusters caused by *B. cereus*, the 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 are linked to a wide variety of bacterial clones^(6, 7, 44, 87). The retrospective nature of the environmental sampling performed by hygiene control teams in case of nosocomial outbreaks, and the wide genetic diversity of *B. cereus sensu lato* strains present in the environment could also explain the failure to identify the precise source of infection. We can therefore hypothesize that *B. cereus sensu lato* can, from various elements of the environment, colonize the skin, 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 the potential severity of invasive infections caused by *B. cereus sensu lato* 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 the patient *B. cereus sensu lato* strains 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*

B. cereus sensu stricto strains produce several compounds that could contribute to their virulence including (i) the emetic toxin, cereulide, present in food products causing food intoxication characterized by emesis in humans, (ii) the pore-forming toxins, hemolysin HBL, non-hemolytic enterotoxin (NHE) and Cyt K, responsible for GI infection characterized by diarrhea, and (iii) hemolysin I (HlyI, also known as cereolysin O), hemolysin II (HlyII) and hemolysin III (HlyIII) ⁽⁸⁹⁻⁹¹⁾. Despite that the GI pathogenesis of *B. cereus sensu stricto* is considered to be due to the production of toxins, such as Hbl, cereulide and Nhe, but little is known about the virulence factors associated with non-GI invasive infections ^(89, 92, 93).

Recently, using a mouse model of infection, our team has shown that the pore-forming toxin α -hemolysin of *E. coli* counteracts the innate immune response during bacteremia ⁽⁹⁴⁾. Interestingly, the pore-forming HlyII of *B. cereus* has been shown to counteract the host immune system ^(95,96) and is therefore suggested to play a role in invasive opportunistic infection. More recently, Mathur and colleagues 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 BMDM (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 ⁽⁹⁷⁾.

Altogether, 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 infection 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 mainly based on the efficiency of the innate immune system (IS). Premature infants have immature immune systems 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 NETs (Neutrophil Extra-cellular Traps) and also defective antigen presentation by monocytes and macrophages⁽⁹⁸⁾.

Premature birth is an increasing healthcare problem worldwide^(99,100). This increase in preterm births may partly account for the emergence of invasive bacterial infections in premature infants. The sensitivity of premature infants to *B. cereus sensu stricto* infections could reflect the capacity of *B. cereus sensu stricto* virulence factors to blunt the innate immune defenses that are critical in the context of an immature adaptive immune system.

ANTIMICROBIAL SUSCEPTIBILITY TESTING AND ANTIBIOTIC TREATMENT

B. cereus sensu lato (excluded *B. anthracis*) is frequently resistant to β -lactams with the exception of carbapenems^(39, 40, 43-45, 50, 59, 71, 80, 85, 87, 101-117). It is resistant to penicillin G and aminopenicillin including ampicillin, ampicillin-sulbactam, amoxicillin and amoxicillin-clavulanic acid. *B. cereus sensu lato* is susceptible to 3rd and 4th generation cephalosporins in 8% of cases (51 out of 642 isolates)^(43, 50, 59, 71, 80, 102, 103, 105, 106, 111, 113-116). For instance, only two strains have been reported susceptible to ceftazidime⁽¹¹⁵⁾. Clinical isolates have been reported to be either susceptible^(80, 85) or resistant^(40, 80, 85) to cefazolin. *B. cereus sensu lato* (excluded *B. anthracis*) is resistant to ureidopenicillin including piperacillin and piperacillin associated with a β -lactam inhibitor: piperacillin-tazobactam^(40, 104, 105). Interestingly, carbapenems are active against *B. cereus sensu lato*. Ninety percent (341/377) and 96% (175/182) of the strains are susceptible to imipenem and meropenem, respectively. The majority of *B. cereus* strains produce a type IIa chromosomal β -lactamase (*BlaII gene*) and some strains can express a gene encoding a chromosomal metallo- β -lactamase. *B. cereus* is susceptible to glycopeptides with 95% (635/670) and 100% (51/51) of the isolates being susceptible to vancomycin and teicoplanin, respectively^(31, 39, 40, 43, 44, 50, 59, 62, 71, 80, 85, 87, 101-106, 108-119).

Antibiotics	Number of tested strains	MICs range (mg/L)	Susceptibility (%)	References	
Beta lactams	Penicillin G	398	0.012 – > 256	0.1	(39, 40, 59, 71, 102-106, 110-114)
	Ampicillin	332	0.016 – 256	1	(40, 43, 50, 80, 85, 101-106, 108, 109, 111, 114, 117)
	Ampicillin/sulbactam	28	< 0,25 – > 8	4	(80, 105)
	Amoxicillin	91	0.016 – > 256	6	(110, 111, 123)
	Amoxicillin/clavulanic acid	158	0.5 – 64	10	(59, 106, 113, 114)
	Cloxacillin	60	NA	0	(114)
	Oxacillin	46	0.094 – > 256	7	(104, 111, 117)
	Ceftriaxone	125	8 – > 256	9	(39, 59, 111, 116)
	Cefotaxime	329	0.1 – > 64	7	(43, 71, 80, 102-106, 113, 114, 116)
	Ceftazidime	114	2 – > 256	2	(40, 50, 80, 104)
	Cefepime	73	> 32	23	(87, 105, 116)
	Cefazolin	83	1 – 64	42	(40, 80, 85, 104)
	Piperacillin	4	4	0	(104, 105)
	Piperacillin/tazobactam	4	NA	25	(40, 105)
	Aminosids	Imipenem	377	0.004 – > 16	90
Meropenem		208	0.012 – 32	96	(44, 50, 59, 105, 109, 111, 116)
Aztreonam		5	NA	60	(105, 108)
Amikacin		67	0.25 – 16	100	(71, 80, 112, 115)
Gentamicin		523	0.016 – 16	99.4	(39, 40, 50, 71, 80, 85, 101-103, 106, 109-114, 116, 117, 124)
Glycopeptids	Tobramycin	51	0.125 – 2	100	(71, 106, 112)
	Vancomycin	695	0.06 – 24	95	(39, 40, 43, 44, 50, 59, 62, 71, 80, 85, 87, 101-106, 108-111, 113, 114, 116-120, 125)
Cyclic lipopeptid	Teicoplanin	54	0.125 – 2	100	(85, 104, 107)
Quinolons	Daptomycin	136	0.032 – 8	59	(80, 85, 111, 112, 117, 118)
	Ciprofloxacin	464	0.008 – > 4	100	(39, 40, 43, 71, 87, 101-103, 105, 106, 108, 110-113, 115-118)
	Levofloxacin	191	0.064 – 32	96	(39, 50, 80, 85, 102, 105, 109, 111, 117)
Macrolids and related	Ofloxacin	7	0.072 – 1	100	(104, 105)
	Azithromycin	189	0.016 – 128	85	(43, 113, 116)
	Clarithromycin	54	< 0.12 – 4	89	(102, 111)
	Clindamycin	349	0.032 – 16	75	(39, 40, 43, 50, 59, 71, 80, 85, 101-105, 108, 111, 113, 115, 117)
	Erythromycin	310	0.032 – 24	75	(40, 71, 80, 85, 101, 103, 104, 106, 108, 111-114, 116)
Cyclins	Pristinamycin	30	NA	97	(106)
	Doxycycline	68	< 0.03 – 16	96	(110, 112)
	Tetracycline	237	0.016 – 128	95	(43, 101, 103, 105, 111, 113, 116, 117)
Oxazolidinone	Tigecycline	43	0.023 – 0.125	100	(111, 117)
	Linezolid	198	0.125 – 4	99	(50, 80, 85, 108, 111, 112, 117)
Others	Rifampicin	195	0.002 – 8	96	(43, 80, 101, 106, 108, 110, 111, 116)
	Sulfamethoxazole/Trimethoprim	162	0.064 – > 32	71	(39, 40, 43, 85, 103, 108, 111, 117)

Table 5: *In vitro* activity of antimicrobial agents against *Bacillus cereus* clinical isolates.

B. cereus is also susceptible to tetracycline^(43, 101, 103, 105, 110-112, 116, 117), linezolid^(50, 80, 85, 109-111, 117), rifampicin^(43, 80, 101, 106, 108, 110, 111, 116), aminoglycosides^(39, 40, 43, 50, 71, 80, 85, 101-103, 106, 109-117) and fluoroquinolones^(39, 40, 43, 44, 71, 80, 85, 87, 102-104, 106, 108, 109, 111-113, 115-118). In the literature, *B. cereus* has been reported to be frequently susceptible to macrolides and related antibiotics, with 75% (212/283), 85% (161/189), 89% (48/54), 75% (258/345), and 97% (29/30) of strains being susceptible to erythromycin, azithromycin, clarithromycin, clindamycin and pristinamycin, respectively^(39, 43, 50, 59, 71, 85, 101-106, 108, 111, 112, 114, 115, 117). *B. cereus* is more frequently susceptible to trimethoprim/sulfamethoxazole with 71% (115/162) of strains being susceptible^(39, 40, 43, 85, 103, 108, 111, 117). Of note, 41% of the isolates have been reported to be resistant to daptomycin^(80, 85, 111, 112, 117, 118). All the current knowledge about *in vitro* antimicrobial susceptibility of *B. cereus* clinical isolates is reported in Table 5.

To date, specific recommendations to perform antimicrobial susceptibility testing (AST) and clinical breakpoints to interpret minimal inhibitory concentrations (MICs) have not been published for *Bacillus cereus* group species. Due to the absence of specific rules, researchers have used either the E-test method, disk diffusion methods or broth microdilution methods to perform AST. In these studies, bacterial cultures were seeded on different types of media such as Mueller-Hinton agar^(43, 85, 106, 108, 110, 111, 113, 116), Mueller-Hinton broth^(109, 110, 115, 116, 120, 121), or Mueller-Hinton 5%-blood^(114, 119). Bacterial suspensions were generally adjusted to 0.5^(43, 106, 113, 115) or 1 McFarland^(109-111, 114, 119), and the medium was incubated in aerobic atmosphere for 24h. Finally, in the absence of specific breakpoints for the interpretation of MICs of *Bacillus cereus* group species, various guidelines were used to interpret AST results, as follows: Clinical & Laboratory Standards Institute (CLSI) guidelines for interpreting the breakpoints for *Staphylococcus* spp.^(39, 40, 62, 80, 103, 105, 108, 116, 120), for *Bacillus* spp. other than the *B. cereus* group^(43, 44, 80, 85, 118, 119), for Gram positive/aerobic bacteria^(59, 71, 113), or EUCAST breakpoints for *Staphylococcus* spp.⁽¹¹⁷⁾ or for Gram positive bacteria⁽³⁹⁾.

Considered together, these data show the necessity of establishing specific expert-validated AST guidelines for the *B. cereus* group species because *B. cereus* is increasingly reported in humans and can be responsible for disseminated and potential lethal infections in at-risk populations including preterm neonates. As of today, no specific treatment guidelines concerning *B. cereus sensu lato* related infections have been published. In the literature, the vast majority of preterm neonates treated for *B. cereus* invasive infections received various antibiotic combinations including intra-venous vancomycin. Seventy-one percent of these patients had favorable clinical and microbiological outcomes^{(43-45, 47, 49-51, 53, 55, 58, 59, 61-65, 68, 71,}

72, 76, 78, 81). 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 sensu lato*. 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 in the treatment of *B. cereus sensu lato* invasive infections because of high MICs and history of treatment failures. In particular, 40% of neonates treated by β -lactams without vancomycin died in the days or weeks following the beginning of infections (53, 54, 57, 64, 66, 67, 75, 82, 122).

CONCLUSION

To date, *B. cereus sensu lato* encompasses eighteen validly published species that could be involved in sepsis and other life-threatening infections in preterm neonates. Around 33% of these infections can be fatal despite an early and appropriate wide-spectrum antibiotic treatment active against the isolated strains. Host innate immune response play a crucial role in patient outcomes in this at-risk population. Therefore, hygiene control teams should be particularly reactive in order to identify the environmental source of infants' nosocomial infections (catheter or ventilator equipment) and to avoid the epidemic spread of *B. cereus* clones in neonatal intensive care unit. Of note, infections caused by *B. cereus* group species might have been overlooked since its isolation in human clinical samples has, for a long time, been regarded as a contaminant. Our work questions the emergence or reemergence of these infections in preterm neonates. Furthermore, our review sheds the light on recently described species thanks to the 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 food-born human pathogen *B. cereus sensu stricto* only differs from *B. thuringiensis*, an insect pathogen widely used as biopesticide, by the presence of absence of Cry-toxin encoding plasmid. In addition, *B. paranthracis* was recently involved in an emetic outbreak (29) and invasive infections in newborns. Further studies using next-generation sequencing (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, vancomycin appears to be efficient and should be recommended for the treatment of *B. cereus* group-related invasive infections before AST results.

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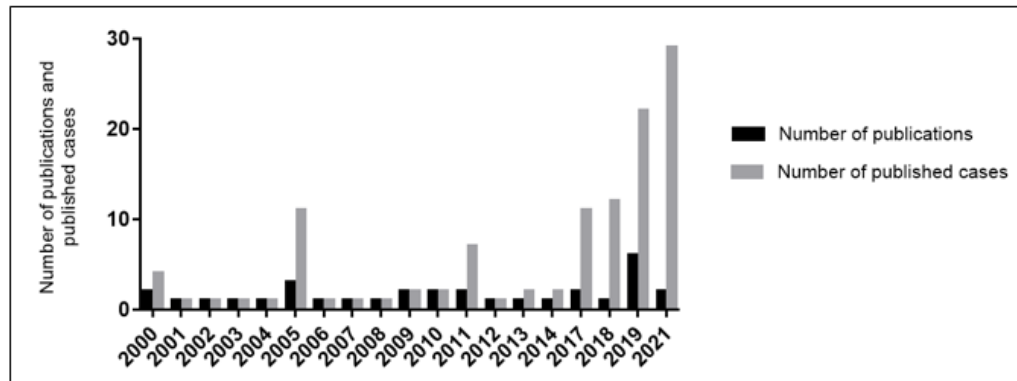
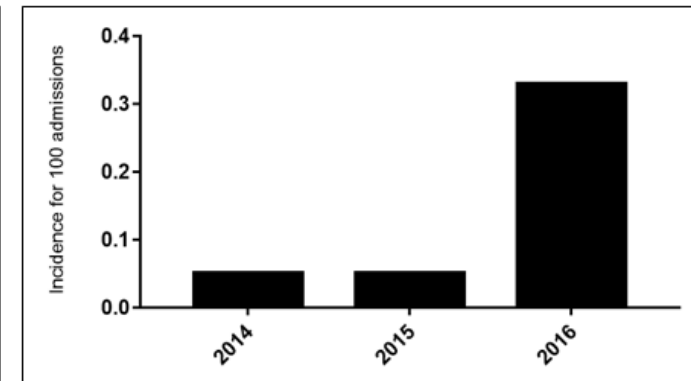
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Supplemental data

	Validly published	Location	Date of isolation	Sample type	References
<i>Bacillus anthracis</i> ATCC 14578T	yes	Germany	1872	NA	Cohn 1872
<i>Bacillus cereus</i> ATCC 14579T	yes	England	1887	Air	Frankland and Frankland 1887
<i>Bacillus mycoides</i> DSM 11821*	yes	Germany	1886	NA	Flügge 1886
<i>Bacillus thuringiensis</i> ATCC 10792T	yes	Germany	1915	Flour moth	Berliner 1915
<i>Bacillus toyonensis</i> BCT-7112T	yes	Japan	1966	Probiotic	Jiménez 2014
<i>Bacillus pseudomycooides</i> DSM 12442T	yes	USA	1995	Soil isolate	Nakamura 1998
<i>Bacillus cytotoxicus</i> NVH 391-98T	yes	France	1998	Vegetable puree	Guinebretière 2013
“ <i>Bacillus gaemokensis</i> ” BL3-6T	no	Korea	2010	Sediments from the Yellow Sea	Jung 2010
“ <i>Bacillus manliponensis</i> ” BL4-6T	no	Korea	2011	Sediments from the Yellow Sea	Jung 2011
<i>Bacillus wiedmannii</i> DSM 102050T	yes	USA	2012	Dairy products	Miller 2016
“ <i>Bacillus bingmayongensis</i> ” FJAT 13831T	no	China	2014	Soil isolate (Emperor Qin’s Terra-cotta warriors)	Liu 2014
<i>Bacillus luti</i> KCTC 33716T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus mobilis</i> KCTC 33717T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus nitratireducens</i> KCTC 33713T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus pacificus</i> KCTC 33858T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus paramycooides</i> KCYC 33709T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus paranthracis</i> KCTC 33714T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus proteolyticus</i> KCTC 33715T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus tropicus</i> KCTC 33711T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus albus</i> KCTC 33710T	yes	China	2017	Sediments and seawater (Pacific ocean)	Liu 2018
<i>Bacillus fungorum</i> KCTC 33949T	yes	China	2017	Spent mushroom substrate	Liu 2020
“ <i>Bacillus clarus</i> ” ATCC 21929T	no	Papua New Guinea	NA	Soil	Mendez Acevedo 2021

**Bacillus weihenstephanensis* isolated in 1998 from milk is a validly published by Lechner *et al* in 1998, is a synonym of *Bacillus mycoides* (2018)

Supplemental table: List of type strains taxonomical status for proposed species in *Bacillus cereus* group.

A**B****Supplemental figure:**

A. Evolution of the number of publications and number of published cases of *Bacillus cereus* infections in preterm neonates per year. 2000-2021.

B. Evolution of the incidence of *Bacillus cereus* bacteriemia in preterm neonates (Number per 100 admissions). 2014-2016, AP-HP, Paris, France

CONCLUSION ET PERSPECTIVES

Les nouveau-nés prématurés sont particulièrement à risque de bactériémie à *B. cereus*. Les dispositifs intravasculaires utilisés en réanimation néonatale sont les portes d'entrée majoritairement retrouvées. La gravité de ces infections est en partie liée aux formes secondaires neuro-méningées. De même, les infections respiratoires sont particulièrement représentées. Dans ce cas, ce sont les matériels de ventilation contaminés par *B. cereus* qui sont le plus souvent mis en cause. Le rôle du microbiologiste est d'alerter le clinicien en cas d'isolement de *B. cereus* dans une hémoculture ou un prélèvement respiratoire chez ces patients, afin de débiter rapidement une antibiothérapie probabiliste. Nous pouvons en cas de bactériémie à *B. cereus* proposer d'inclure un glycopeptide dans le traitement probabiliste, du fait de la très bonne sensibilité *in vitro* de cette bactérie vis-à-vis de ces molécules et de l'absence de contre-indication à l'administration de ces antibiotiques chez le nouveau-né prématuré. Le signalement d'un cas au service d'hygiène hospitalière pour enquête environnementale et mise en place rapide de mesures de prévention en réanimation néonatale doivent être sérieusement envisagées pour éviter la survenue d'épidémie.

Notre travail se poursuit actuellement selon trois axes : (i) l'identification par séquençage des souches de *B. cereus sensu lato* impliquées dans les infections du nouveau-né prématuré, (ii) l'étude de la virulence de ces souches et (iii) l'évaluation de la résistance aux antibiotiques.

La spectrométrie de masse utilisée pour l'identification bactérienne au laboratoire de bactériologie est actuellement insuffisante pour distinguer de façon fiable les espèces du groupe *B. cereus* entre elles. Ainsi, toutes les infections invasives attribuées à *B. cereus* ne sont pas nécessairement dues à *B. cereus sensu stricto*. L'approche par séquençage nouvelle génération (NGS) devrait permettre de confirmer l'identification des souches et de déterminer si les souches impliquées dans les infections invasives à *B. cereus* décrites à ce jour sont des espèces nouvellement décrites et émergentes. Dans cette optique, une collection multicentrique de 46 souches de *B. cereus sensu lato* responsables d'infections invasives chez des nouveau-nés prématurés et provenant de 15 centres hospitaliers en France a été constituée. Trente-trois de ces 46 souches ont déjà été séquencées par WGS (Whole Genome Sequencing) par une double approche Illumina® et Nanopore® et analysées bio-informatiquement. Les différentes approches d'analyses taxonomiques et phylogéniques ont permis de montrer de façon concordante la présence de 7 espèces différentes retrouvées dans plusieurs régions de France,

dont une majorité de *Bacillus paranthracis* (n=15 ; 45%) et *B. cereus sensu stricto* (n=7 ; 21%). Il s'agit de la première étude rapportant l'implication de 7 espèces du groupe *Bacillus cereus* dans des infections graves chez les prématurés.

Un tiers des nouveau-nés décédés (11/33) des suites de l'infection avait reçu une antibiothérapie incluant la vancomycine pour laquelle seules de très rares souches résistantes ont été décrites. Cette observation suggère que la virulence des souches, l'immaturation du système immunitaire du patient ou la combinaison de ces deux facteurs sont impliqués dans la sévérité de ces infections. Dans un travail préalable en cours d'écriture, le modèle de virulence *Drosophila melanogaster* a été utilisé pour rechercher des souches hypervirulentes de *B. cereus*. Cette étude a permis de montrer que les souches responsables de décès chez les patients étaient les souches les plus virulentes chez la drosophile infectée. Ces résultats ont permis de conforter l'hypothèse de l'existence de souches hypervirulentes. Ces données devront être confirmées par l'analyse de la virulence sur modèle murin. Également, grâce au NGS et au screening des gènes de virulence connus, nous avons pu montrer que les souches identifiées *B. cereus sensu stricto* parmi les 33 de la collection précédemment mentionnée possédaient davantage de gènes de virulence connus. Ces souches étaient également associées de façon statistiquement significative à un taux plus important de décès chez le nouveau-né prématuré.

Concernant l'antibiorésistance, nous avons pu montrer que le nombre de souches cliniques testées est variable selon les antibiotiques. De plus, avant la parution en avril 2021 des nouvelles recommandations du CASFM-EUCAST, aucune recommandation spécifique de méthodologie pour la réalisation des antibiogrammes et la mesure des concentrations minimales inhibitrices (CMI) n'était disponible pour *B. cereus*. Les auteurs ont donc utilisé différentes méthodes de détermination de l'antibiorésistance et d'interprétation des résultats. Nous avons donc de manière standardisée déterminer les profils de sensibilité à un panel important d'antibiotiques (n=17) sur une large collection nationale multicentrique de 85 souches de *B. cereus sensu lato* et 13 souches types de la Collection Institut Pasteur (CIP). Le NGS pourra dans un second temps permettre de rechercher s'il existe des profils d'antibiorésistance spécifique d'une espèce et aider à mieux caractériser le support moléculaire des résistances.

SERMENT D'HIPPOCRATE

« Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. »