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FOODBORNE PATHOGENS (S JOHLER, SECTION EDITOR)

Bacillus cereus—a Multifaceted Opportunistic Pathogen

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Abstract

Purpose of Review This review provides a short overview on the role of *Bacillus cereus* group organisms as foodborne pathogens and summarizes the current scientific knowledge on *B. cereus* as causative agent of non-gastrointestinal diseases.

Recent Findings *B. cereus* is a well-known causative agent of foodborne bacterial intoxications in particular linked to the restaurant and catering sector. This endospore forming bacteria can cause two different types of foodborne illness, the emetic and the diarrheic syndrome, which are usually self-limiting. However, severe intoxications, requiring hospitalization and including even fatalities, are on a rise. Furthermore, *B. cereus* is also increasingly reported as causative agent of non-gastrointestinal diseases, especially in clinical settings.

Summary Over the last decades, substantial progress has been made in understanding the role of *B. cereus* in foodborne outbreaks, while information on non-gastrointestinal diseases, often linked to hospital acquired infections, caused by *B. cereus* is rather limited.

Keywords *Bacillus cereus* · Extraintestinal disease · Systemic infection

Introduction

The *Bacillus (B.) cereus* group, a subdivision of the genus "*Bacillus*" also known as "*Bacillus cereus sensu lato (s.l.)*," comprises a growing list of genetically closely related Gram-positive, spore-forming bacterial species. The most prominent members are as follows: *B. anthracis*, *B. cereus sensu stricto (s.s.)*, *B. thuringiensis*, *B. weihenstephanensis*, *B. mycoides*, *B. pseudomycoides*, *B. cytotoxicus*, and *B. toyonensis*. Members of the *B. cereus* group are widely distributed in diverse environments worldwide. They can grow under highly variable conditions (aerobic as well as anaerobic) over a broad temperature range. Due to the formation of endospores highly resistant to heat, pH, and desiccation, they are hard to inactivate and eradicate from food production and processing chains as well as from clinical settings. The pathogenic potential of *B. cereus s.l.* is quite variable, ranging from strains used as plant growth promoter and biopesticides to strains causing fatal diseases.

B. cereus is well known as important foodborne pathogen, which can cause two different types of gastrointestinal (GI) diseases: the emetic and the diarrheal syndrome. The emetic form of *B. cereus* food poisoning, resembling *Staphylococcus aureus* intoxications, is caused by cereulide, a small heat stable depsipeptide that is (pre-) formed directly in the food matrix. The emetic syndrome is characterized by nausea and vomiting 0.5 to 6 h after consumption of contaminated food. Usually, symptoms last not more than 1 day, but occasionally, hospitalization is required and intoxications with fatal outcomes are increasingly reported (reviewed in [1, 2]). Severe intoxications can lead to acute liver failure and encephalopathy [3, 4]. Recently, several isoforms of the cereulide toxin have been described, including one isoform showing tenfold cytotoxicity of the known cereulide in vitro [5]. These isoforms are produced under food production and processing conditions, but their exact contribution to intoxications still needs to be elucidated [6, 7•]. Furthermore, results from in vitro studies using low levels of cereulide suggest a potential role of cereulide in the induction of diabetes [8]. Thus, even subemetic doses of cereulide may pose a risk, which needs to be studied in more detail. The symptoms of the diarrheal form of *B. cereus* food poisoning, which is characterized

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by abdominal pain and watery diarrhea, resemble the symptoms of a *Clostridium perfringens* infection. In contrast to the emetic toxin, the diarrhea-associated enterotoxins are not produced in the food matrix itself, but in the intestine, upon ingestion of the toxin-producing *B. cereus* strains with the food. Two tripartite protein toxin complexes, the non-hemolytic enterotoxin complex (Nhe) and the hemolytic enterotoxin complex (Hbl), and the single protein cytotoxin K (CytK) have been linked to the diarrheal syndrome. In addition, several other virulence factors have been discussed, which may contribute to the enterotoxicity of *B. cereus* group strains (for review, see [9]). For instance, it has been shown in vitro and in vivo that the sphingomyelinase (SMase) of *B. cereus* synergistically interacts with Nhe as well as with Hbl; thus, it is tempting to speculate that SMase contributes to the severity of the disease [10, 11]. However, further studies are necessary to decipher the exact role of SMase and other putative virulence factors in *B. cereus* pathogenicity.

Besides its potential to cause gastrointestinal diseases, members of the *B. cereus* group are increasingly linked to nosocomial non-gastrointestinal infections. Usually, these diseases are associated with immunosuppression of the affected patient, but there are also cases reported from immunocompetent persons. The extraintestinal diseases caused by members of the *B. cereus* group range from local (eye infections, traumatic and surgical wound infections) to systematic infections, e.g., fulminant septicemia [12]. The virulence factors contributing to non-gastrointestinal infections are largely unknown, and the role of the known, GI-associated toxins in non-gastrointestinal infections is still cryptic.

Members of the *Bacillus cereus* Group as Foodborne Pathogens

In the European Union (EU), every year 500 to 700 confirmed human cases of foodborne diseases caused by *B. cereus s.l.* are reported (see Fig. 1). In 2016, bacterial toxins ranked second among the causative agents in foodborne and waterborne outbreaks, and 17.7% of the reported foodborne outbreaks were caused by bacterial toxins, including *B. cereus* emetic and diarrheal toxins [13]. Concerning the food matrices, involved in these outbreak situations, “mixed food” was reported in 23%, “other food” in 17%, and “cereal products and legumes” in 14% of the outbreaks [13]. In routine diagnostics, the members of the *B. cereus* group will not be differentiated; instead, the whole group will be identified as *B. cereus s.l.* (formally called presumptive *B. cereus*). Thus, the numbers of outbreaks reported, including the ones shown in Fig. 1, usually refer to *B. cereus s.l.* (Fig. 1).

Even though the number of reported outbreaks and illnesses caused by members of the *B. cereus* group is increasing over the last decade, the true incidence of *B. cereus* food poisoning is still unknown for a number of reasons, including misdiagnosis of the illness, which may be symptomatically similar to other types of food poisoning and diagnostic deficiencies with regard to this foodborne pathogen, both in clinical and food microbiology [14]. So far, diagnostics of the *B. cereus* group are mainly based on phenotypic characteristics. However, in the light of consumer protection, it is expected that in the future, the focus will move toward risk-orientated differential diagnostics by including methods for detection of toxins, toxin genes, and virulence markers. Indeed, in the context of foodborne outbreak investigations, molecular typing and toxin gene profiling are already of much higher importance than the differentiation between the species of the *B. cereus* group (for review, see [15]). The cytotoxin K exists in two variants, cytotoxin K_1 (CytK-1) and cytotoxin K_2 (CytK-2). CytK-1 is a highly potent toxin that is restricted to a very distinct group of *B. cereus s.l.* strains, which was recently reclassified to *B. cytotoxicus* [16]. In contrast, the CytK-2 protein, which is found frequently among *B. cereus* group members, exhibits only one fifth of the toxicity of the CytK-1 protein in vitro [17], thus putting into question its role as bona fide toxin in foodborne illness [18, 19•]. Thus, for the investigation of foodborne outbreaks linked to *B. cereus s.l.*, the molecular differentiation of the two variants of CytK is essential for a correct indication of the possible virulence of the detected strains.

The emetic toxin cereulide is found in a specific subgroup of *B. cereus s.s.*, while the enterotoxin genes and other virulence factors are broadly distributed among the members of the *B. cereus*. It is assumed that Nhe is produced by 91 to 100% of *B. cereus s.s.* and also by other *B. cereus* group species, such as *B. thuringiensis and B. weihenstephanensis*. The ability for Hbl production was found in 44 to 60% of the *B. cereus s.s.* and also in other *B. cereus* species such as *B. thuringiensis* and *B. weihenstephanensis* [9, 20, 21]. Frequently, isolates possess the ability to produce not only one but also two or more enterotoxins [22]. In this context, the current discussion about the safety of *B. thuringiensis*, which is widely used as biopesticide, should be considered [23•]. Several *B. thuringiensis* strains are able to produce the two enterotoxin complexes Nhe and HBL, which are known to play a pivotal role in the diarrheal syndrome. Therefore, it would be of utmost importance to gather more data on the occurrence of toxin producing *B. thuringiensis* strains in foods and in foodborne outbreaks to assess the actual risk related to the increasing use of *B. thuringiensis* as biopesticide and *B. thuringiensis* contaminations in foods. The use of *B. thuringiensis* as biopesticide might have no substantial impact on human health. However, due to the lack of data, it cannot be ruled out that *B. thuringiensis* plays a much more greater risk for human health than currently assumed [23•]. Thus, novel risk-orientated diagnostic tools, including (apart from the known toxins) additional virulence markers, will be necessary to close the current gap of data and pave the way for

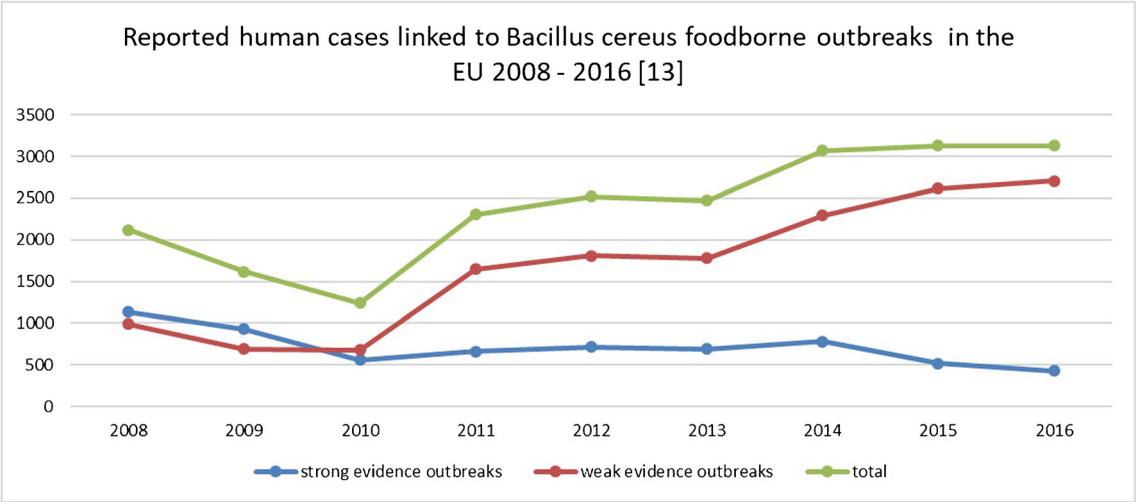

Fig. 1 Reported human cases linked to *B. cereus* foodborne outbreaks in the EU between 2008 and 2016 [13]

evidence-based decision-making regarding the risk potential related to a certain *B. cereus* group strain.

Non-Gastrointestinal Diseases Caused by Members of the *Bacillus cereus* Group

In addition to the well-known role of *B. cereus* group members in foodborne gastrointestinal infections or intoxications, these organisms can also cause a wide range of extraintestinal diseases. This is primarily the case in immunocompromised persons, but reports of *B. cereus* infections from immunocompetent persons are on a rise. In contrast to the foodborne diseases linked to *B. cereus*, the key virulence determinant of extraintestinal diseases is largely unknown, although a panoply of potential virulence factors of *B. cereus* has been described [24]. Using a mouse model, it could be shown that *B. cereus* sphingomyelinase is a crucial factor in the outcome of septicemia [25], and in vitro studies suggest an essential role of the immune inhibitor protein A in macrophage escape [26]. Nevertheless, substantial research will be necessary to fully unravel the role of the different virulence factors in the growing list of extraintestinal diseases linked to *B. cereus* infections.

The most relevant risks factors for an extraintestinal *B. cereus* infection in immunocompromised patients are:

- Intravenous drug abuse
- Indwelling catheters
- Traumatic or surgical wounds
- Leukemia

In addition, extraintestinal *B. cereus* infections are found frequently in premature infants. The spectrum of symptoms related to non-gastrointestinal *B. cereus* infections depends on the port of entry and ranges from gas gangrene-like cutaneous infections, endophthalmitis, and pneumonia to fulminant bacteremia, including meningitis and brain abscesses [12]. Based on case reports of recent years (see Table 1), extraintestinal infections caused by members of the *B. cereus* group can be split in the following groups:

- Systemic infections (bacteremia and septicemia)
- Infections in the eye area (panophthalmitis, endophthalmitis)
- Infections in the brain area (brain abscess, meningoencephalitis)
- Infections in the heart area (endocarditis)

Similar to foodborne gastrointestinal diseases caused by members of the *B. cereus* group, the true incidence of non-gastrointestinal *B. cereus* diseases is unknown most probably underreported for several reasons. One reason might be that in medical microbiology, members of the *B. cereus* group are generally rather considered a “laboratory” or “environmental contamination” than a causative pathogenic agent. This is particularly the case when *B. cereus s.l.* is isolated from open wounds or from blood cultures. Usually, these bacteria are not further differentiated and toxin profiles are not determined routinely. Furthermore, most often, the strains are not kept for sequencing and genetic subtyping at a later stage. Thus, not only the true incidence but also the source of the strains and the pathophysiological mechanisms of the infections are largely unknown. This general lack of information from differential diagnostics is also reflected in the case reports from the last 5 years listed in Table 1. Furthermore, as shown recently, antibiotic treatment can induce the formation of small colony variants (SCVs) of *B. cereus*, which are at risk of misdiagnosis due to their altered metabolism and slow growth [51].

In principle, non-gastrointestinal infections caused by members of the *B. cereus* group can be divided in two categories: exogenous, originating from entry of the bacteria through a trauma, an open wound, or a medical intervention; or endogenous. In case of an exogenous entry, the source of infection can

Table 1 Selected case reports of the last five years

Year	Country	Disease	Source			Relevant risk factors/medical history	Number of patients	Literature
			Intravenous drug abuse	Postoperative/ posttraumatic	Spontaneous/ unknown source			
2017	China	Bacteremia		X			744	[27]
2016	India	Intratumoral brain abscess		X			1	[28]
2016	USA	Endocarditis			X		1	[29]
2016	Denmark	Peritonitis		X			1	[30]
2013–2015	USA	Bacteremia	X				3	[31]
2015	USA	Progressive, hemorrhagic meningoencephalitis			X (foodborne?)	Acute myeloid leukemia	5	[32]
2015	USA	Cerebral abscess			X	Acute lymphoblastic anemia	1	[33]
2014	India	Bacteremia			X	Acute myeloid leukemia	1	[34]
2014	China	Endophthalmitis			X		1	[35]
2014	Japan	Septicemia and necrotizing fasciitis			X	Liver cirrhosis and diabetes mellitus	1	[36]
2014	USA	Endogenous endophthalmitis	X				1	[37]
2014	Australia	Bacteremia and multiple brain abscesses			X	Acute lymphoblastic leukemia	1	[38]
2013	France	Systemic infection			X	Neonates	2	[39]
2013	France	Endocarditis			X		1	[40]
2013	Japan	Septicemia and meningoencephalitis			X	Myelodysplastic syndrome	1	[41]
2013	Taiwan	Septicemic syndrome			X	Acute lymphoblastic leukemia	1	[42]
2013	USA	Fasciitis of the right lower extremity		X			1	[43]
2012	UK	Hepatic abscess			X		1	[44]
2012	France	Panophthalmitis		X			1	[45]
2012	France	Endocarditis				Pacemaker	1	[46]
2012	Malaysia	Endocarditis	X				1	[47]
2012	USA	Septicemia		X		Chronic myelogenous leukemia	1	[48]
2012	India	Keratitis and panophthalmitis		X			1	[49]
2012	Japan	Sepsis and multiple organ failure			X	Acute lymphoblastic leukemia	1	[50]

be normally detected, and in case of an endogenous entry, the source mostly remains unclear except for patients with a clear history of intravenous drug abuse. In some cases, there are indications that also non-gastrointestinal *B. cereus* infections could be traced back to contaminated food. In one case report from 2015, bananas were considered as a possible food source of five cases of progressive, hemorrhagic meningoencephalitis caused by *B. cereus* in patients with acute myeloid leukemia [32•]. Therefore, there is the possibility that also non-gastrointestinal infections caused by members of the *B. cereus* group can be food-related diseases.

Conclusion

Members of the *B. cereus* group are well-known opportunistic human pathogens, which can cause two different types of foodborne illnesses, emesis and diarrhea. Although the three

main diarrhea-associated toxins, Nhe, HBL, and CytK, as well as the emetic toxin cereulide, are known over a decade and considerable progress has been made on the understanding of toxin gene regulation, the exact mechanisms of toxin syntheses and toxin actions are far from understanding. Furthermore, it becomes increasingly evident that additional virulence factors, such as SMase, could contribute to the pathogenicity of certain strains and the severity of the illness. Hitherto, a suitable animal model has neither been established for studying the mechanisms of *B. cereus* enterotoxicity nor translocation, potential metabolization or mechanisms of cereulide toxicity within the host in detail. Such models would also be of special importance to assess the actual risk of foodborne infections related to a particular *B. cereus s.l.* strain.

Besides the classical known foodborne infections and intoxications, members of the *B. cereus* group can also cause extraintestinal infections in both immunocompromised and immunocompetent patients. The source of these infections remains often unclear, partially due to a lack of awareness of the multifaceted role of *B. cereus* in a variety of local and systemic diseases and partially due to the limited information currently available on mechanisms of *B. cereus* pathogenicity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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