CLINICAL MICROBIOLOGY REVIEWS, Oct. 1993, p. 324–338
0893-8512/93/040324-15$02.00/0

Vol. 6, No. 4

Bacillus cereus and Related Species

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INTRODUCTION

Members of the bacterial genus *Bacillus*, which are ubiquitous in the environment, are aerobic or facultatively anaerobic gram-positive or gram-variable spore-forming rods. The vegetative cells range from 0.5 by 1.2 to 2.5 by 10 μm in diameter (169) and can grow at optimal temperatures ranging from 25 to 37°C, although thermophilic and psychrophilic members are capable of growth at temperatures as high as 75°C or as low as 3°C. Some species can flourish at extremes of acidity and alkalinity, ranging from pH 2 to 10. The extreme heterogeneity of the genus is reflected in the wide variety of ecological niches that the many species occupy and in the debate over their taxonomic status. The G+C content of the DNA of species within the genus can vary from 32 to 69%, and many species may subsequently be reclassified into different taxonomic groupings (169, 171). Most strains are catalase positive, possess peritrichous flagella, and sporulate in air, differentiating members of this genus from the clostridia (169, 171). The identification and classification of *Bacillus* species are considered below.

The pathogenicity of *Bacillus anthracis*, the causative agent of anthrax, is well known for mammals, as is the virulence of *Bacillus thuringiensis*, *Bacillus sphaericus*, and some other species for insects (30, 34–36, 40, 74, 157). Nonanthrax species within clinical material, which were previously considered contaminants, have increasingly been identified as pathogens since Farrar's landmark review in 1963 (42). *Bacillus* infections (probably *Bacillus cereus* in most cases) have been documented since the beginning of this century and probably earlier (8, 42, 47, 81, 107, 110, 132, 136, 180). Clinical infections caused by *B. cereus* fall into six broad groups: (i) local infections, particularly of burns, traumatic or postsurgical wounds, and the eye (1, 2, 7, 14, 25, 29, 38, 39, 56, 69, 73, 79, 84, 88, 92, 105, 131, 133, 137, 159, 165, 172, 178, 182); (ii) bacteremia and septicemia (9, 24, 42, 121, 123, 129, 144, 146, 162, 165, 177); (iii) central nervous system infections, including meningitis, abscesses, and shunt-associated infections (11, 21, 42, 43, 50, 72, 85, 104, 121, 128, 134, 144, 162, 165, 176); (iv) respiratory infections (15, 20, 22, 42, 44, 49, 53, 89, 94, 103, 121, 123, 128, 144, 146, 152, 162); (v) endocarditis and pericarditis (17, 26, 42, 48, 119, 144, 146, 153, 162, 174, 177); and (vi) food poisoning, characterized by toxin-induced emetic and diarrheagenic syndromes (58, 62, 96, 138, 158, 170, 171).

The incidence of non-food-poisoning-related infections is likely to increase because of greater recognition of *B. cereus* as a pathogen outside the gut and the greater likelihood of infection in neonates (121, 144), intravenous drug users (52, 146, 161, 162, 177), the immunologically compromised, including patients with AIDS and malignant disease (9, 24, 42, 123, 129, 144, 162), and those with artificial prostheses, including orthopedic implants and cerebrospinal shunts (42, 128, 144, 162, 165). Intravenous drug users are at risk both from the injection paraphernalia and from the heroin itself, which contains several contaminating organisms, including *B. cereus* (161).

One study has demonstrated heavy contamination of topical and therapeutic medicaments with *B. cereus* and other *Bacillus* species, posing a potential source of infection in wounds and burns (52). Any combination of the above factors, such as intravenous drug abuse in individuals infected with the human immunodeficiency virus, increases the risk of infection significantly.

B. cereus elaborates several toxins, including a necrotizing enterotoxin, an emetic toxin, phospholipases, proteases, and hemolysins. They are important pathogenic determinants, and in this review, new data available since the comprehensive reviews by Turnbull (163, 164) concerning

their properties, mode of action, and contribution to the spectrum of disease caused will be discussed.

TAXONOMY

The genus *Bacillus* is divided into three broad groups, depending on the morphology of the spore and sporangium, a scheme that was originally proposed by Smith et al. (147) and developed further in 1973 (66). *B. cereus*, *Bacillus megaterium*, *B. anthracis*, *B. thuringiensis*, and *B. cereus* var. mycoides are all found in the large-cell subgroup (bacillary cell width, ≥1 μm) of group 1, i.e., gram-positive rods that produce central or terminal ellipsoid or cylindrical spores that do not distend the sporangia. Protoplasmic inclusions of poly-beta-hydroxybutyrate are found in the large-celled species but not in the small-celled subgroup comprising *Bacillus subtilis*, *Bacillus pumilus*, and *Bacillus licheniformis*, which form a separate subgroup (66, 147, 169, 171). Most of the clinically important *Bacillus* isolates are found in group 1. Group 2 species are gram-variable and have swollen sporangia with central or terminal ellipsoid spores (171). This group contains mainly *Bacillus circulans*, *Bacillus macerans*, *Bacillus polymyxa*, *Bacillus popillae*, *Bacillus larvae*, *Bacillus lentimorbus*, *Bacillus alvei*, *Bacillus stearothermophilus*, and *Bacillus brevis* (171). Group 3 is dominated by the heterogeneous and gram-variable *Bacillus sphaericus* species. The sporangia are swollen, with spherical terminal or subterminal spores (171).

The taxonomic relationship between many species is not entirely clear. Studies of DNA-DNA hybridization, despite some inconsistencies in the overall relatedness of strains and technical difficulties, suggest considerable chromosomal similarity between *B. anthracis* and some nonanthrax *Bacillus* species (90, 135, 149). This similarity has prompted the view that *B. anthracis*, *B. thuringiensis*, and *B. cereus* are all varieties of a single species. In a comparative study of 16S rRNA sequences from *B. anthracis* var. Sterne and *B. cereus* emetic strain NCTC 1143, 1,446 bases, or 94% of the total sequences, were found to be identical (6). *B. thuringiensis* and *B. cereus* var. mycoides differed from each other and from *B. anthracis* and *B. cereus* by fewer than nine nucleotides (6). Sequencing of the 23S rRNA genes derived from polymerase chain reaction amplification of chromosomal DNA from *B. anthracis* and an emetic strain of *B. cereus* showed them to be almost identical (5). Other studies have emphasized the close relationship between these species by enzyme electrophoretic patterns and numerical phenetic analysis (10, 126, 183). Significant cross-agglutination also occurs between the spore antigens of *B. cereus*, *B. anthracis*, and *B. thuringiensis* (100, 101) and the flagellar antigens of *B. cereus* and *B. thuringiensis* (163).

In the diagnostic laboratory, differentiating between *Bacillus* species can be difficult, and a large number of phenotypic tests are used to distinguish between them, although sometimes only a single feature separates species. For example, the entomopathogenic *B. thuringiensis* produces an insecticidal crystalline inclusion, the delta-endotoxin, which can be seen by phase-contrast microscopy (30, 35, 40, 74). However, acrystalliferous mutants arise after plasmid loss and are practically indistinguishable from *B. cereus*.

ISOLATION AND IDENTIFICATION OF *B. CEREUS*

With isolates from infected blood or tissue, overnight incubation on nutrient or blood agar produces bacilli in large numbers (169). Typical isolates of *B. cereus* on blood agar form large, flat, granular, "ground-glass," beta-hemolytic colonies. The organism produces several toxins, and although assays are available for their detection, the diagnosis of infection still rests on the identification of large numbers of organisms in clinical specimens.

Clinical specimens in gastrointestinal illness are usually feces or vomitus, accompanied ideally by the suspected foodstuffs (58, 62, 138, 171), and these have a polymicrobial flora requiring selective techniques to isolate *Bacillus* species. Initial selection can make use of the relative thermostability and resistance to chemical agents of *Bacillus* spores. In environmental and food specimens in which *B. cereus* may be present in spore form, non-spore-forming contaminants may be removed by treating the sample with 50% sterile ethanol for 60 min or by heating the specimen with an equal volume of deionized water at 62.5°C for 15 min (169) before plating onto selective medium at 32 to 35°C. Psychrophilic and thermophilic strains are able to grow at temperatures ranging from 5 to 50°C (96). Clinical specimens such as vomitus may contain spores, but other specimens will contain only vegetative cells, and gentler selection methods are required.

A variety of media have been used successfully, including mannitol-egg yolk-polymyxin, Kim and Goepfert medium, and polymyxin-pyruvate-egg yolk-mannitol plus bromothymol blue or bromocresol purple. These media use polymyxin B as the selective agent and permit presumptive identification by the lecithinase reaction on the egg yolk and the inability of *B. cereus* to catabolize mannitol (75, 93, 115). The low peptone content of the last two media promotes sporulation. Growth can occur at a wide range of pHs from 4.9 to 9.3 (93, 96). Incubation for 48 h is optimal with or without prior enrichment in brain heart infusion or Trypticase-soy-polymyxin broth.

Enumeration of *B. cereus* in specimens is performed by surface plating techniques or by a most probable number method if fewer than 1,000 organisms per gram of material are expected (96). The details of medium composition have been described by Turnbull et al. (171) and Kramer and Gilbert (96), and photographs of typical cellular and colonial morphology can be found in both Turnbull et al. (171) and Parry et al. (120).

The principal distinguishing characteristics of *B. cereus* and the related species in group 1 are listed in Table 1. The distinction between *B. cereus* and *B. anthracis* and their separation from nonpathogenic species are the most important clinically. In general, *B. cereus* is motile, hemolytic on blood agar, penicillin resistant, and resistant to bacteriophage gamma, whereas *B. anthracis* is not. However, there can be considerable strain variation; nonmotile *B. cereus* variants are morphologically identical to *B. anthracis*, which in turn may be weakly hemolytic. Nevertheless, if *B. anthracis* is suspected, suspect colonies can be inoculated into defibrinated horse or sheep blood and incubated for 8 h at 37°C, and smears can be prepared and examined for the presence of encapsulated bacilli with India ink or a stain such as polychrome methylene blue (M'Fadyean stain) (96, 171). Smears prepared from mucoid colonies grown overnight on nutrient agar containing 0.7% sodium bicarbonate, under CO_2, can be stained in the same way. Anthrax toxin may be detected immunologically, and plasmids pXO1 and pXO2, which encode the anthrax toxin and capsule, respectively, can also be identified on agarose gels and by recombinant DNA techniques, although usually only in specialist laboratories. Serological studies for differentiating strains of *B. cereus* by spore, somatic, and, in particular, flagellar

TABLE 1. Principal distinguishing characteristics of *B. cereus* and related species[a]

Species	Characteristic[b]											
	Colony on blood agar	Motility[c]	Hemolysis[d]	Lysis by gamma phage	Penicillin susceptibility	Crystalline parasporal inclusion	Citrate utilization	Growth in 7% NaCl	Tyrosine decomposition	Elaboration of anthrax toxin and capsule and possession of plasmids pXO1 and pXO2	Virulence in mice	M'Fadyean reaction in killed mice
B. cereus	Slight green tinge	+	+	−	−	−	+[c]	+[c]	+[c]	−	−	−
B. anthracis	Gray-white to white; generally smaller than *B. cereus*	−	−	+	+	−	b	+[c]	−[c]	+	+	+
B. thuringiensis	As *B. cereus*	+	+	−	−	+	+[c]	+[c]	+[c]	−	−	−
B. cereus var. mycoides	Spreading rhizoid colonies with marked tailing	−	(+)	−	−	−	a	a	a	−	−	−

[a] Reprinted from reference 169 with the permission of the authors and publisher.
[b] Symbols: +, ≥85% of strains positive; a, 50 to 84% positive; b, 15 to 49% positive; −, <15% positive; (+), usually weakly positive.
[c] Data from Gordon et al. (66).
[d] On sheep or horse blood agar at 24 h.

antigens have been used extensively, especially in reference laboratories, and have been reviewed elsewhere (96, 116, 155, 171). Characteristically, 23 of 42 flagellar (H) serotypes have been associated with *B. cereus*-related disease (96, 97, 155), and serology combined with biotyping (based on biochemical properties) and phage typing has proved useful epidemiologically (95, 96, 108, 138). Novel techniques such as pyrolysis mass spectrometry and gas-liquid chromatography of whole-cell fatty acids are showing promise for the future (102, 145).

Figure 1 is a diagnostic scheme for suspected *B. cereus* infections, incorporating both standard clinical laboratory investigations and those likely to be conducted in research or reference laboratories. Further information on the technical details of media, growth conditions, isolation, and identification can be found elsewhere (58, 62, 93, 97, 115, 138, 169, 171).

NONGASTROINTESTINAL DISEASE

Clinical infection with *B. cereus* can be categorized broadly into gastrointestinal and nongastrointestinal disease (Fig. 2), and the latter can be separated into infections that are either local or systemic. The production of toxins, tissue invasion, and bacterial multiplication contribute to the range of diseases seen. *B. cereus* spores are found ubiquitously, including in the hospital environment; the detection of *B. cereus* in the environment may not always signify a likelihood of increased clinical disease. However, contamination of dressings, intravenous catheters, or linens provides an opportunity for infection. In one recent study, contamination of operating theater scrub suits led to two cases of meningitis after neurosurgical procedures (11). Subsequent contamination of health workers by linens, particularly in neonatal and other special units, is of importance because alcohol-based handwashing solutions are ineffective against *Bacillus* spores (11).

Local Infection

Local disease manifests primarily as postsurgical or traumatic wound, burn, or ocular infections (1, 7, 39, 73, 84, 88, 92, 122, 131, 159, 165, 166, 171a, 178). Primary cutaneous infections, with the formation of necrotic bullae, have been noted (73, 92). Interpretation of the presence of *B. cereus* recovered from wound specimens is difficult, as mixed cultures are common. Nevertheless, pathogenicity should always be considered when large, gram-positive rods are found, or "clostridial species" are suspected, on microscopy. The pathogenicity of bacilli in wounds is supported by their presence in surgical biopsy specimens, where they can be stained with periodic acid-Schiff's reagent (92). In one recent study of wound complications following total hip arthroplasty, *Bacillus* species were isolated from 25% of the patients (1). All patients had received preoperative prophylactic benzylpenicillin, flucloxacillin, cloxacillin, or cefuroxime treatment. Although half the isolates were susceptible to flucloxacillin and related antibiotics in vitro, these agents did not appear to be effective clinically. In 4 of the 24 cases described (1), plaster of Paris casts had been applied and could have been the source of the organism. Orthopedic cases may be particularly vulnerable, as plaster of Paris-impregnated gauze rolls have been shown to be contaminated with *B. cereus* (131). Although many cases of local infection are mild, severe deep infections such as necrotizing fasciitis and gangrene occur. Cases of acute and chronic osteomyelitis have been described: the former is more typical of drug abusers, the latter of trauma (16, 45, 88, 146). The production of exotoxins, including hemolysins, is likely to be of importance in the establishment of these severe infections (38, 39, 166). Prolonged intravenous antimicrobial agent therapy with adequate surgical debridement is required, but morbidity and mortality are high (146).

Ocular Infection

B. cereus is a major cause of severe keratitis, endophthalmitis, and panophthalmitis (2, 4, 14, 18, 19, 25, 28, 29,

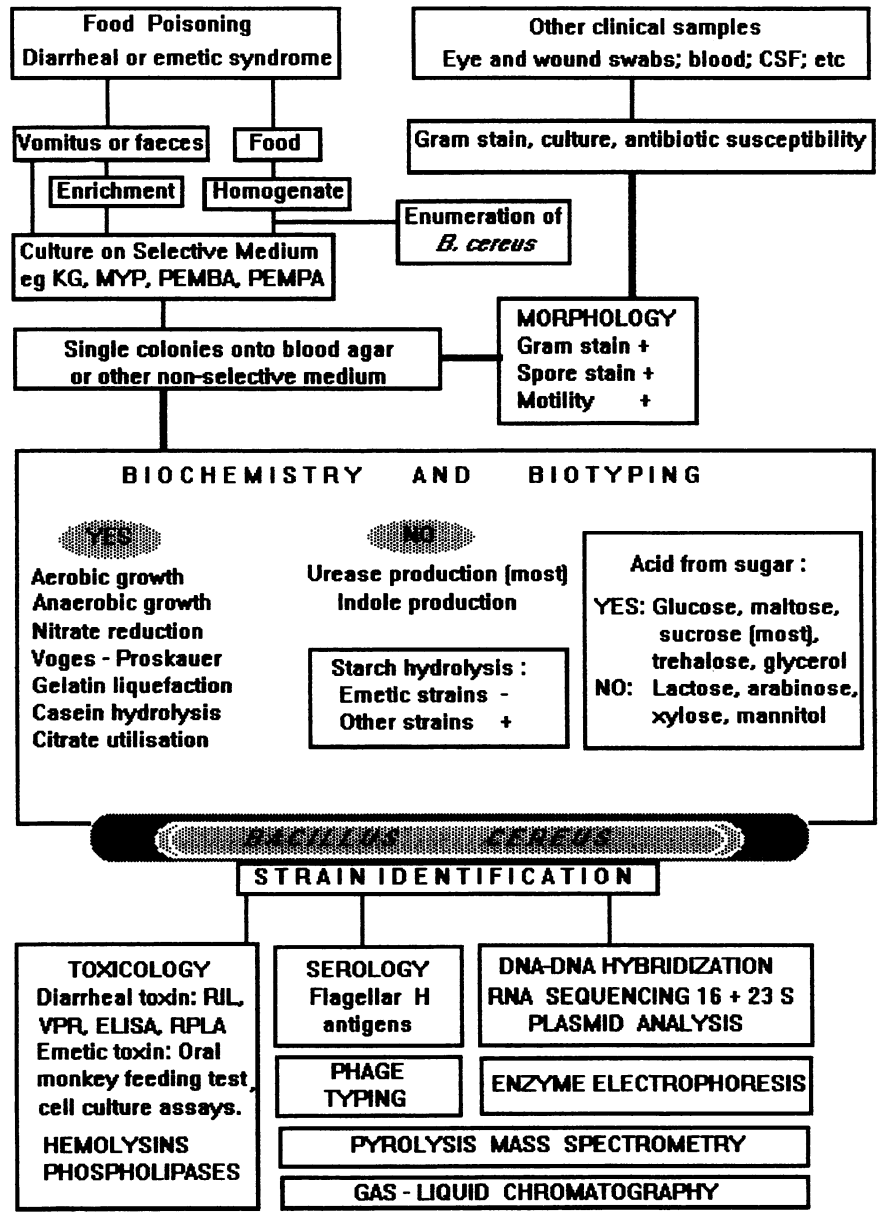

FIG. 1. Isolation and identification of *B. cereus* in clinical specimens. CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; RPLA, reverse passive latex agglutination. Media: KG, Kim and Goepfert; MYP, mannitol-egg yolk-polymyxin; PEMBA and PEMPA, polymyxin-pyruvate-egg yolk-mannitol with bromothymol blue or bromocresol purple, respectively.

32, 38, 56, 69, 70, 79, 91, 105, 109, 118, 130, 133, 137, 166, 172, 182). In one U.S. study of posttraumatic endophthalmitis, *Bacillus* species were the second most common organism isolated after *Staphylococcus epidermidis* (29). More alarming, ocular infections due to *B. cereus* appear to have increased over the last 15 years, particularly among the immunocompromised and intravenous drug abusers (69, 182). The organism is introduced into the eye by foreign bodies, which is usually a consequence of traumatic injury. However, trauma is not always required, as acute keratitis has been caused by contact lenses cleaned in solutions contaminated with the organism (172). Hematogenous seeding of the eye may also occur, particularly in intravenous drug abusers, among whom contamination of heroin and injection equipment (70, 137, 182) is the likely source. In two cases, ocular infection was associated with blood transfusion and injection of vitamin B complex (137).

Regardless of the source, the classic ophthalmic lesion is a corneal ring abscess, the formation of which is accompanied by pain, chemosis, proptosis, retinal hemorrhage, and perivasculitis, depending on the exact site of infection. Systemic symptoms, including fever, are common, and blood samples should always be taken for culture. Ideally, intraocular fluid should also be cultured. Table 2 lists the significant ocular infections caused by *B. cereus* reported during this century.

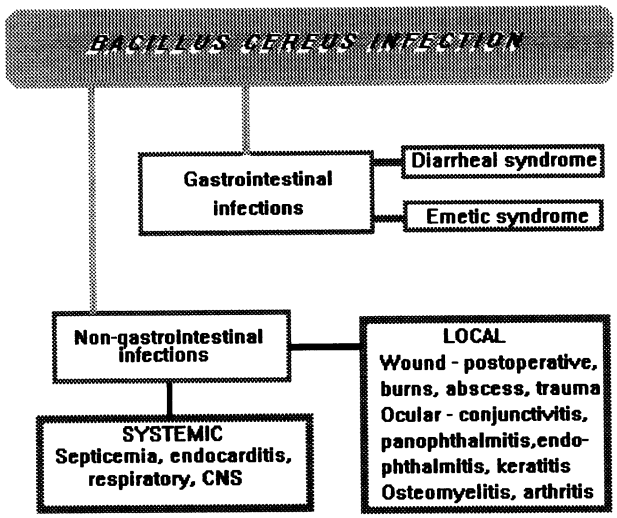

FIG. 2. Schematic representation of *B. cereus* infections. CNS, central nervous system.

Systemic Disease

Systemic disease is associated with the presence of a portal of entry into the system concerned, e.g., ventricular shunts with meningitis or intravenous cannulae with bacteremia and septicemia. Infections caused by *B. cereus* tend to be necrotizing, which implicates the necrotizing enterotoxin as a virulence determinant (167); it is probable that phospholipases and hemolysins play a role in establishing pathogenic foci, and their properties are discussed in a later section.

Diagnosis is hampered because *Bacillus* species are common contaminants of blood cultures, with estimates varying from 0.1 to 0.9% of submitted cultures (122). In many infections, *B. cereus* has been dismissed initially as a contaminant before clinical deterioration necessitated a reappraisal of its significance. The actual number of clinical cases attributable to *B. cereus* is probably higher; in many of the reported studies, the *Bacillus* strains were not identified to the species level.

The most significant episodes of severe disease associated with *B. cereus* for which full treatment and outcome were documented are listed in Table 3.

Bacteremia and septicemia. The majority of bacteremias are transient and not clinically significant. Most cases of significant clinical illness have occurred in intravenous drug abusers, patients receiving hemodialysis or continuous intravenous infusions, neonates, and those with an underlying malignancy. Bacteremia may be complicated by ocular and pulmonary infection, abscess formation, and endocarditis (9, 24, 27, 42, 121, 123, 129, 144, 146, 162, 165, 166, 177).

Bacterial endocarditis. *B. cereus* is a small but significant cause of endocarditis, particularly when associated with intravenous drug administration (161) or an underlying valvular disease. The source of the organism is usually either the drug or the injection equipment, with the tricuspid valve being affected in most patients. Three cases were associated with either a pacemaker or a prosthetic valve. Antimicrobial therapy with prophylaxis for thrombosis was usually effective, although valve replacement was needed in two cases and two patients died (17, 26, 42, 48, 119, 144, 146, 153, 162, 174). A single case of pericarditis was reported in a drug addict who had also received hemodialysis, the postulated source of the organism in this case (48).

Central nervous system infection. There have been almost 30 documented cases of *Bacillus* meningitis and encephalitis reported in the literature for both adults and children, with the majority attributable to *B. cereus* (11, 21, 42, 43, 50, 72, 85, 104, 121, 128, 134, 144, 146, 162, 166, 176). Risk of infection is associated with conditions that reduce immunity and provide access to the central nervous system, including spinal anesthesia and shunts. One quarter of pediatric cases had ventricular shunts in situ (176), but an additional 25% of infections occurred in apparently normal neonates (176). Aggressive antimicrobial therapy and removal of foreign bodies is essential, but the condition is associated with a high mortality. Brain abscesses have also occurred, but extremely rarely, as a consequence of *B. cereus* infection elsewhere (82, 85, 171a).

Respiratory infection. Respiratory infections involving both the lung and pleural space are uncommon but are potentially life-threatening (15, 22, 42, 44, 144, 152, 166). Pneumonia, abscess, and pleuritis have occurred in the typical at-risk groups, who in a minority of cases had a documented bacteremia. Complications can be severe. One patient's pneumonia was followed by massive hemoptysis, acute respiratory failure, tension pneumothorax, empyema, and a bronchopleural fistula (15).

The local production of proteases may also act as an irritant or precipitant of asthma, as appeared to be the case when detergent manufacturing workers were shown to respond to inhaled proteases from *B. subtilis* (46, 124).

TREATMENT

B. cereus, unlike nearly all *B. anthracis* isolates, produces β-lactamases, and so it is resistant to β-lactam antimicrobial agents (23), including the third-generation cephalosporins. It is usually susceptible to aminoglycosides, clindamycin, vancomycin, chloramphenicol, and erythromycin (9, 23, 121, 146, 162, 167, 176, 179).

Ocular infections can be very aggressive; blindness can occur within 12 to 18 h, with enucleation of the eye and blindness as frequent sequelae (29, 79, 105, 133, 137, 182), although complete recovery has been reported (14). Prompt antimicrobial therapy, which should begin before culture results are known, with systemic, topical, and possibly intravitreal antibiotics is essential if function is to be preserved (56). Clindamycin plus gentamicin and vancomycin alone have been used successfully, and imipenem may also be useful. Multiple therapeutic routes are needed to ensure adequate antimicrobial concentrations in different parts of the eye. For example, topical clindamycin gives good drug levels in the anterior compartment of the eye but not always posteriorly (29); aminoglycosides are removed from the eye via an anterior route and so have a high aqueous-to-vitreous humor drug ratio (29). This may explain why focal cases of endophthalmitis and those of the anterior segment have better prognoses than those in the posterior segment, which usually end in blindness (69). Though β-lactams distribute preferentially into the vitreous humor (29), the β-lactamases produced by *B. cereus* render them ineffective and inappropriate for treating *B. cereus* infections. However, there has been little conclusive research concerning drug penetration into the inflamed eye, and most regimens are empirical.

Ciprofloxacin has been reported to be effective in the treatment of a patient with a rare case of bronchiectasis (53). In cases of meningitis and severe systemic infections, empirical therapy with vancomycin and an aminoglycoside is

TABLE 2. Ocular infections with *B. cereus* reported during this century

No. of cases	Disease	Antibiotics[a]	Host risk factor	Notes[b]	Reference
1	Panophthalmitis	Aureomycin	Metallic foreign body	Enucleation	28
1	Panophthalmitis		Recent blood transfusion; contaminated transfusion?	Enucleation	91
1	Endophthalmitis	Gentamicin, nafcillin	IV[c] drug abuse	Enucleation	109
1	Panophthalmitis	Gentamicin, penicillin	IV drug abuse	Enucleation	70
1	Endophthalmitis	Nafcillin, gentamicin, chloramphenicol, erythromycin	IV drug abuse	Enucleation	162
1	Panophthalmitis	Gentamicin, chloramphenicol	Vitamin B injection	Organism cultured from ocular fluid and vitamin ampoule	18
3	Panophthalmitis	Gentamicin, penicillin, cefazolin, clindamycin	IV drug abuse and foreign body	Corneal perforation, acute closed-angle glaucoma, enucleation	182
	Panophthalmitis	Gentamicin, clindamycin	IV drug abuse	Enucleation	
	Panophthalmitis	Methicillin, ampicillin, gentamicin	Trauma and foreign body	Corneal laceration repaired; enucleation	
1	Endophthalmitis	Amoxycillin, gentamicin, chloramphenicol	Trauma by thorn	Sector iridectomy, gentamicin via subconjunctival injection	4
6	Panophthalmitis	Clindamycin, gentamicin, penicillin	Trauma and metallic foreign body	Ring abscess, intravitreal antibiotic, enucleation in 4 cases	118
3	Panophthalmitis	Clindamycin, gentamicin, cephalothin, oxacillin	IV drug abuse	Also retrobulbar abscess; evisceration and abscess drainage	137
	Panophthalmitis	Gentamicin, clindamycin, cefazolin	IV drug abuse	Also angle closure glaucoma, enucleation	
	Panophthalmitis	Vancomycin, chloramphenicol	IV drug abuse	Also cavernous sinus thrombosis; evisceration and orbital exploration	
3	Endophthalmitis	Clindamycin, gentamicin, cefazolin	Trauma	Diagnostic vitrectomy and anterior chamber taps; intraocular antibiotic blindness in affected eye	130
1	Endophthalmitis	None	Trauma, metallic foreign body	Enucleation; endophthalmitis noted in 4 other cases with *B. subtilis* and *B. circulans*	19
1	Endophthalmitis	Gentamicin, cefazolin, clindamycin	Trauma, metallic foreign body	Partial vitrectomy; intravitreal antibiotics; enucleation	29
1	Endophthalmitis		Foreign body	Corneal ring abscess; enucleation	79
3	Endophthalmitis/ panophthalmitis		IV drug abuse	Fulminant, retinal hemorrhages, perivasculitis	25
1	Endophthalmitis	Gentamicin, clindamycin	Trauma	Ring abscess; enucleation	105
1	Endophthalmitis	Gentamicin, clindamycin	Trauma	Reduced visual acuity; a *Bacillus* sp. caused 6 of 13 cases of endophthalmitis in this study	133
1	Panophthalmitis	Gentamicin, cefazolin, chloramphenicol	Trauma, metallic foreign body, intraocular gas bubble	Intravitreal antibiotics; enucleation	2
2	Acute keratitis		Contaminated contact lens	Recovery	172
1	Endophthalmitis	Clindamycin, gentamicin, cefazolin	Trauma	Corneal laceration closed; pars plana sclerotomy, intravitreal antibiotic; good recovery after 1 yr	14
1	Panophthalmitis	Gentamicin, cefazolin, chloramphenicol	IV drug abuse	Enucleation	146

[a] The antibiotics listed include initial therapies, which were usually ineffective.
[b] Visual loss occurred in nearly all cases, ranging from mild loss of acuity to blindness in the affected eye. François (47) reported 41 cases of *Bacillus*-associated posttraumatic eye infections, most of which were probably *B. cereus*.
[c] IV, intravenous.

the most appropriate combination. However, the common combination of ampicillin and gentamicin used to treat *Listeria* infections when gram-positive rods are identified in the cerebrospinal fluid will provide adequate cover for most *Bacillus* species.

FOOD POISONING

Although anecdotal evidence for *B. cereus* food poisoning had existed in Europe for some time, it was not until Hauge's remarkable experiments of the 1950s that *B. cereus* was

TABLE 3. Major case reports of systemic nongastrointestinal *B. cereus* infections with clinical details[a]

Disease	Host risk factor	Notes and therapy[b]	Reference
Pneumonia	None	Died	Stapler et al. (152)
Bacteremia, septicemia	Renal failure	Two cases; both recovered	Curtis et al. (27)
	Pyelonephritis	Recovered	
	Glomerulonephritis	Recovered; treated with vancomycin, erythromycin, cephaloridine	
	Polycystic kidney disease	Recovered; treated with vancomycin, erythromycin, cephaloridine	
Meningitis	Ventricular shunt	Recovered; shunt removed, unspecified antibiotics	Leffert et al. (104)
Pneumonia	Lymphatic leukemia	Septicemic; penicillin, methicillin, gentamicin; died	Coonrod et al. (22)
Pneumonia	Leukemia	Septicemic; gentamicin, oxacillin, carbenicillin; died	Ihde and Armstrong (82)
Endocarditis	IV[c] drug abuse; cardiac catheterization	Treated with clindamycin, erythromycin, penicillin, lincomycin; died	Craig et al. (26)
Pneumonia	Leukemia	Died	Feldman and Pearson (44)
Meningitis + pneumonitis	Hydrocephalus and ventricular shunt	Recovered; treated with ampicillin, gentamicin, and shunt removal	Raphael and Donaghue (128)
Encephalitis	Neonate, bowel perforation, cerebral hemorrhage	Treated with ampicillin and gentamicin; died	Turnbull et al. (165)
Cavitating pneumonia	Acute lymphoblastic leukemia	Recovered; gentamicin, penicillin, cephalothin, carbenicillin, tetracycline	Leff et al. (103)
Endocarditis	Prosthetic valve	Treated with tobramycin and chloramphenicol; died	Block et al. (17)
Endocarditis	IV drug abuse	Recovered; ampicillin, oxacillin, clindamycin, gentamicin	Weller et al. (177)
Endocarditis	Rheumatic heart disease	Treated with streptomycin, penicillin, gentamicin; died	Wanvarie and Rochanawaton (174)
Endocarditis	IV drug abuse	Recovered; four cases treated with nafcillin, clindamycin, gentamicin, chloramphenicol	Tuazon et al. (162)
Bacteremia	Diabetes	Recovered; ventriculoatrial shunt infected; clindamycin	Tuazon et al. (162)
Meningitis	Leukemia; neutropenia	Septicemic; treated with gentamicin and penicillin; died	Colpin et al. (21)
Meningoencephalitis	Neonate; central venous line; respiratory distress	Treated with ampicillin, gentamicin, chloramphenicol; died	Hendrickx et al. (72)
Endocarditis	Prosthetic valve	Recovered; treated with clindamycin and valve removal	Oster and Kong (119)
Meningitis	Cancer, immunosuppression	Treated with penicillin and chloramphenicol; died	Siegman-Igra et al. (144)
Pneumonia + pleural effusion	None	Recovered; treated with penicillin, chloramphenicol, thoracotomy, and lung resection	Jonsson et al. (89)
Meningitis	Lymphoblastic lymphoma	Bacteremic; implanted Ommaya reservoir; died	Garcia et al. (50)
Pneumonia	Alcohol abuse	Recovered; developed empyema, hemoptysis, bronchopulmonary fistula requiring resection	Bekemeyer and Zimmerman (15)
Endocarditis	Pacemaker, breast implants	Recovered; clindamycin; implants and pacemaker removed	Sliman et al. (146)
Pneumonia	Leukemia, neutropenia	Recovered; septicemic; nafcillin and tobramycin	Sliman et al. (146)
Meningitis	Neonate; IV catheter	Recovered but suffered ventricular hemorrhage; residual cerebral palsy	Feder et al. (43)
Bacteremia	Cancer, Hickman catheters, neutropenia	Eight cases, treated by catheter removal, gentamicin, imipenem, vancomycin, chloramphenicol, piperacillin	Banerjee et al. (9)
Brain abscesses	Acute lymphocytic leukemia, thrombocytopenia	Recovered; gentamicin, vancomycin, rifampin, oxacillin, mezlocillin	Jenson et al. (85)
Encephalitis	Neonate, bilateral thalamic hemorrhage	Treated with vancomycin and amikacin; died	Patrick et al. (121)
Pneumonia	Infant, prior infections	Recovered; also septicemic	Kovacs and Jozsef (94)
Pneumonia	None	Recovered; treated with ciprofloxacin	Gascoigne et al. (53)
Meningitis	Neonate	Recovered; myelingomeningocele present; vancomycin	Weisse et al. (176)
Pericarditis	IV drug abuse, hemodialysis	Pericardiocentesis and pericardial window created; clindamycin, vancomycin, gentamicin	Fricchione et al. (48)
Endocarditis	Artificial cardiac valve	Recovered; treated with vancomycin	Steen et al. (153)
Pneumonia	Aplastic anemia	Empyema occurred; died	Funada et al. (49)
Meningitis	Ventricular drain	Postoperative; treated with vancomycin; died	Barrie et al. (11)
Meningitis	Ventricular drain	Postoperative; treated with chloramphenicol and vancomycin; died	Barrie et al. (11)

[a] Data drawn from references indicated. Cases were not included if species identification was not made or clinical information about treatment or outcome was incomplete or if they may have involved *B. cereus* rather than the species quoted, including some of those referred to by Farrar (42).
[b] The antibiotics listed include initial therapies, which were usually ineffective.
[c] IV, intravenous.

established as a cause of food poisoning (71). Hauge consumed vanilla sauce containing 92×10^6 organisms per ml, and within 16 h he was suffering from one of the two types of food poisoning associated with this organism, profuse diarrhea accompanied by cramping abdominal pain.

B. cereus is a significant cause of food-related disease, the incidence of which varies appreciably around the world. In the United Kingdom and United States in the late 1970s and early 1980s, *B. cereus* accounted for 1 to 3% of reported outbreaks of bacterial food poisoning (about 1% of actual cases); in the Netherlands, by contrast, 22% of outbreaks (about 11% of cases) were caused by *B. cereus* (96). In Canada, 7% of outbreaks and more than 2% of bacterially related food-poisoning cases were reported as being due to *B. cereus* (96). Confirmed outbreaks in the United States date from the end of the 1960s. Since then, there have been several outbreaks in which rice, meat loaf, turkey loaf, sprouts, mashed potatoes, beef stew, and apples were implicated (31, 55, 76, 113, 114, 125, 156).

There is a high level of asymptomatic fecal carriage of *B. cereus* (14% of 711 healthy adult British volunteers in one study [54], 43% of 120 African school children in another [168]). Therefore, proof that a sample of food is responsible for an outbreak requires that the strain of *B. cereus* isolated from both the clinical specimen and the foodstuff should be of the same serotype (and/or biotype or phage type) and be present in significant numbers ($>10^5$ CFU/g) (97). The outbreak should be considered in the context of its epidemiology, including incubation times, clinical symptoms, and appropriate toxin production by the strain of *B. cereus*. In episodes of emetic food poisoning, failure to recover *B. cereus* from foodstuffs does not entirely rule it out as the causative organism, since heating after contamination could kill the organism but leave preformed stable emetic toxin intact. The time interval between the onset of symptoms and the collection and examination of specimens may also partly explain why the organism is not always detected in specimens.

Although the spore is not particularly thermostable, spores of some strains are able to withstand relatively high temperatures, particularly if the food has a high fat content, which seems to have a protective effect (96). Fecal carriage is also related to spore survivability and the widespread presence of *B. cereus* in many foodstuffs, including rice, other vegetable dishes, various desserts, turkey, and other meats. One study demonstrated a contamination rate of approximately 52% in meat, vegetable, and food ingredient samples (117). Therefore, diagnosis is complicated by the natural contamination of many foodstuffs with spores, and the detection of *B. cereus* in the absence of clinical symptoms may not always signify food-borne disease. When symptoms and isolation of the organism from foodstuffs coincide, the case for *B. cereus* food poisoning is stronger. For example, it has been suggested that the high incidence of cases in Hungary during the period from 1960 through 1968 (15% of all cases of bacterial food poisoning) was due to the consumption of highly spiced meats prepared with traditional spices that were heavily contaminated with *Bacillus* spores. Some of these would have survived cooking, germinated on the meat during storage, and produced enterotoxin (96). Conversely, some additives to food, such as garlic extract, have an inhibitory effect on bacterial growth (96).

Diarrheal Syndrome and Enterotoxin

B. cereus is the etiological agent of two clinical food-poisoning syndromes. The diarrheal syndrome resembles *Clostridium perfringens* food poisoning and is due to the effects of an enterotoxin that is immunologically unrelated to the *C. perfringens* enterotoxin. The enterotoxin may be preformed in the food or may be produced within the small intestine. Patients experience profuse diarrhea with abdominal pain and cramps, but only rarely vomiting or fever, which begins 8 to 16 h (typically 10 h) after ingestion of the contaminated food. Symptoms resolve within approximately 12 h. Supportive therapy is rarely if ever needed, and there is no role for antimicrobial therapy. Although a variety of foods may be responsible, proteinaceous ones such as meat-based dishes are the most common.

Epidemiologically, the flagellar (H) serotypes most commonly involved in this syndrome are 1, 2, 6, 8, 10, 12, and 19 (60, 97). In one study, nine strains isolated from episodes of diarrheal illness hydrolyzed starch, whereas 82 strains associated with the emetic syndrome did not (138). It has been suggested that starch hydrolysis and enterotoxin production may be linked to the diarrheal syndrome (140).

The biological activities of the enterotoxin form the basis of most assays, although the isolation of toxic fractions with some but not all of these activities has caused confusion. The development of immunological assays has consequently been hampered by a debate as to what, exactly, the assay was detecting. Rapid screening methods such as fluorescence-based immunodot and reverse passive latex agglutination assays have recently been evaluated and found to have adequate sensitivity and specificity (68, 83). Toxin assays are complicated because different strains produce various degrees of fluid accumulation in rabbit ileal loops (RIL), young rabbits are more sensitive than old rabbits, and strains grown in nutrient broth rather than in brain heart infusion broth are negative in the RIL test regardless of bacterial numbers. The test methods have been reviewed recently (96, 138).

In brain heart infusion broth supplemented with 1% (wt/vol) starch or glucose, the enterotoxin is synthesized during the late logarithmic growth phase at an optimum temperature of 32 to 37°C and at a pH of 7.5 (51, 59). It comprises two or three protein components, with isoelectric points of 5.1 to 5.6 and molecular masses of 38 to 57 kDa, which together, but not individually, produce the known properties of the enterotoxin (41, 67, 96, 141, 151, 158, 170). Enterotoxin activity is susceptible to proteolytic degradation and is thermolabile. Whole-cell suspensions, cell-free culture filtrates, and purified enterotoxin complex produce fluid accumulation in RIL tests and in mouse intestinal loops, and it has been suggested that the fluid accumulation may be due to activation of adenylate cyclase, although the evidence is conflicting (164). An increased vascular permeability reaction (VPR), with necrosis, and cytotoxicity in cell cultures (64, 97, 150, 158, 164, 170) can also be demonstrated. The cell-free culture filtrate and the purified enterotoxin complex are also lethal to mice when given intravenously (158). Therefore the toxins described as mouse-lethal factor 1, diarrheagenic factor, necrotic factor, vascular permeability factor, and edema factor are all part of the same enterotoxin complex.

The VPR is another standard assay for the enterotoxin, in which 50 μl of test material is injected intradermally into the back of an adult rabbit; 3 h later, the rabbit is injected intravenously with Evans blue dye, and after 1 h, the diameter of the blue zones around the intradermal sites is

measured (138). There is good correlation between the RIL and VPR assays, the assays used most often in reference laboratories, when purified toxic entities from culture filtrates are evaluated (64, 138, 158, 164, 170). However, when crude filtrates are tested, this may not always be the case (78).

Turnbull et al. (170) used isoelectric focusing to isolate a fraction which had VPR and RIL activity but also retained some hemolytic activity, which they thought might be due to a contaminant. As their preparation was highly necrotic, they were puzzled by the limited hemolytic activity (163). The combination of components used by Thompson et al. (158) produced an enterotoxin with greater hemolytic activity, although they did not comment on the reason for this. However, in a recent study, Beecher and Macmillan, using isoelectric focusing, fast protein liquid chromatography, and polyacrylamide gel electrophoresis, suggest that the enterotoxin is made up of three components that produce fluid in RIL assays (and therefore enterotoxicity), increased vascular permeability, and also hemolytic activity only when combined (12, 13). The study suggests that the hemolysin consists of a protein component B (35 kDa) that binds to or alters the cells, permitting lysis by the second subunit, called L. This is made up of two components, L1 and L2, with molecular weights of 36,000 and 45,000. Physicochemically, hemolysin BL resembles enterotoxin; the molecular masses and isoelectric points of hemolysin BL correlate with the values given for the multicomponent enterotoxin described above and differ from those of other known hemolysins. Hemolysin BL is not inhibited by cholesterol and so is not a thiol-activated cytolysin (see below). Assuming that it is the enterotoxin, its exact mode of action remains unclear, although it may act on target membranes in concert with phospholipases secreted by *B. cereus* (12). Indeed, components B and L may be sphingomyelinases that are not hemolytic individually (12). Alternatively, the binding component may be utilized by other toxic factors to produce fluid accumulation and thus diarrhea, with the BL hemolytic activity of importance in systemic or local infections. Immunofluorescent staining does confirm that component B binds to cells as an initial step before the L components bind (13). The production of multiple proteins with hemolytic activity should not necessarily be a surprise, as there is emerging evidence that the closely related species *B. thuringiensis* elaborates several immunologically distinct cytolysins that possess hemolytic activity and are insect gut enteropathogens. The cytolysin of one strain was also lethal to mice after parenteral administration (34–36, 74, 157). The recent purification to near homogeneity from a strain of *B. cereus* of a 45-kDa mouse-lethal toxin that causes fluid accumulation and vascular permeability in a mouse model but which has no hemolytic activity (142, 143) will need to be considered in light of the above findings. An immunological or molecular comparison may be the only way to completely settle the matter.

Emetic Toxin

The emetic toxin, or vomiting factor, is a highly stable peptide of less than 10 kDa which is thermostable (surviving 126°C for 90 min) and resistant to proteolytic degradation. It is formed during the late exponential to stationary growth phase (and may be associated with sporulation) at optimal temperatures of 25 to 30°C but not above 40°C. It has been suggested that it may be a breakdown product from foodstuffs supporting the growth of *B. cereus* (171). Assays of toxicity include a laborious and expensive monkey feeding test, which uses a rice-based culture medium (96, 111, 112, 164, 170, 171) and in vitro cell culture systems with HEp-2 or Chinese hamster ovary cells (80, 154).

The emetic syndrome is characterized by the ingestion of rice- and pasta-based foods. Of the 110 outbreaks reported in the United Kingdom between 1971 and 1978, rice, particularly from Chinese restaurants, was implicated in 108 (57). The association with rice relates to ecological, economic, and cultural factors: *B. cereus* is a common soil bacterium and contaminates rice plants in the paddy field; in restaurants, large amounts of rice that contain *B. cereus* spores are cooked, allowed to cool slowly, and used to make fried rice dishes the next day; the rice is usually left at room temperature, as refrigeration causes starch to clump the rice grains together. Spores germinate and vegetative cells produce toxin at room temperature. Toxin production is enhanced by the addition of protein in the form of egg or meat. Subsequent cooking is usually too brief to inactivate the toxin.

The emetic syndrome has a short incubation period of 1 to 5 h, during which the emetic toxin induces nausea, vomiting, abdominal cramps, and also diarrhea in about one-third of patients. Incubation periods as short as 15 min and as long as 12 h have been reported (96). Supportive therapy is rarely needed, but antimicrobial therapy is not required. The syndrome is self-limiting, and the patient recovers within 24 h. It resembles *Staphylococcus aureus* food poisoning in both its symptomatology and incubation period.

Epidemiological studies indicate that the H serotypes commonly associated with emesis are 1, 5, 8, 12, and 19 (60, 97), although there is some overlap with strains producing the diarrheal syndrome. Some strains are able to express both diarrheal and emetic toxins, although the extent to which they are produced is determined by the substrate and other growth conditions.

HEMOLYSINS AND PHOSPHOLIPASES

The nomenclature for hemolysins is confusing, as up to four hemolytic entities can be elaborated by *B. cereus*. As discussed above, the enterotoxin may possess hemolytic activity (12, 13). Hemolysin and phospholipase production is associated with successful local infections (29, 38, 137, 146) and undoubtedly is of importance in the establishment of systemic disease.

Cereolysin, which is also known as hemolysin I or mouse-lethal factor I, is a thiol-activated cytolysin of 49 to 59 kDa. Thiol-activated cytolysins are produced by several bacterial species; they are characterized by similar molecular weights and possess considerable sequence homology. They exert a broad cytolytic action on mammalian cells in vitro and in vivo, are hemolytic, and frequently have important sublytic effects on leukocyte and macrophage function. They are cross-neutralized by antisera prepared against other members of the group, are inactivated by cholesterol, the presumed membrane receptor, and are reversibly inactivated by oxidation. The exact mode of action is unclear, although membrane cholesterol is of importance in binding toxin monomers to the cell membrane. Subsequently, there is probably a process of lateral aggregation and monomer unfolding, with exposure of hydrophobic domains and penetration of the membrane, to form pores through which leakage of intracellular contents and cell lysis occurs (reviewed in references 3, 16, 33, 37, 148, 164, and 171).

The thiol-activated cytolysins have been rigorously purified from both *B. cereus* and *B. thuringiensis* by the same

methods and shown to be biologically, physicochemically, and immunologically identical. This reflects the close similarity of the two species (see above) (77).

B. cereus produces several phospholipases (e.g., phospholipase C and egg yolk turbidity factor) with preferences for different phospholipids (83, 96, 164, 171), including phosphatidylcholine (23 kDa, approximately), phosphatidylinositol (29 to 35 kDa, approximately), and a sphingomyelinase (29 kDa, approximately). Strains producing phospholipase C cause a dose-dependent release of lysosomal enzymes from neutrophils (175), which is probably a factor involved in mediating tissue damage, especially in wound and ocular infections. Resistance to phagocytosis may also be related to phospholipase production (127). The gene encoding the phosphatidylcholine-preferring enzyme has been cloned and sequenced and, like the phosphatidylinositol-specific enzyme, is synthesized with a signal sequence that is removed in the secreted enzyme (87). It has structural homology with the *C. perfringens* alpha-toxin, or lecithinase, which is also synthesized with a comparable signal peptide (106). The phosphatidylinositol-specific phospholipase has been cloned and purified of other contaminating phospholipases and has stretches of sequence homology with some equivalent eukaryotic enzymes (98, 99, 173). It is not positioned close to the chromosomal gene cluster encoding the other two secreted phospholipases C (98). The sphingomyelinase gene has also been cloned and sequenced, and the secondary structure has been partially determined (86, 181). With the gene for the phosphatidylcholine-specific enzyme, it forms the gene cluster mentioned above (13, 63, 160). The phosphatidylcholine phospholipase and sphingomyelinase act synergistically to lyse erythrocytes, creating a duplex hemolysin called cereolysin AB (63). It is not related to the thiol-activated cytolysin.

A second factor, described as hemolysin II, is a thermolabile protein of 29 to 34 kDa which is unaffected by cholesterol or antistreptolysin O and does not have an established role in vivo. Nevertheless, a mouse-lethal factor which is claimed to be similar if not identical to hemolysin II has been purified (139). The molecule has a molecular weight of 34,000, is hemolytic, is not affected by cholesterol, and does not cause fluid accumulation in ligated mouse intestinal loops, but is lethal to mice on intravenous injection (139). It is unclear whether it is related to the 45-kDa mouse-lethal toxin described earlier (142, 143).

OTHER NONANTHRAX BACILLI

Bacillus species other than *B. cereus* and *B. anthracis* are believed to have a role in both gastrointestinal and nongastrointestinal disease. Many of the earlier reports of systemic disease caused by "*B. subtilis*" are difficult to interpret because of incorrect species identification, and many of these isolates were probably *B. cereus*. Occasional reports have appeared implicating *B. thuringiensis*, *B. alvei*, *B. circulans*, *B. licheniformis*, *B. macerans*, *B. pumilus*, *B. sphaericus*, and *B. subtilis* in systemic and gastrointestinal disease (171). For example, *B. coagulans*, *B. sphaericus*, *B. macerans*, and *B. subtilis* have caused septicemia, *B. subtilis* and *B. sphaericus* have caused endocarditis, and *B. circulans* and *B. sphaericus* have been implicated in meningitis (9, 15, 42, 43, 96, 121, 123, 129, 134, 162, 169, 171, 176).

For food-borne illness, conclusive proof is often difficult to obtain if the food is not available for analysis or was stored at room temperature rather than under refrigeration. Cases of *B. licheniformis* food poisoning present a clinical picture similar to that of *C. perfringens* food poisoning and the diarrheal syndrome caused by *B. cereus*. *B. subtilis*, in contrast, produces an acute-onset emetic syndrome, although a significant minority also suffer diarrhea (96). If food poisoning by these *Bacillus* species is established, the syndromes may be produced by toxins similar or identical to those produced by *B. cereus*. It is interesting to speculate whether the principal toxins are located on mobile genetic elements and whether intraspecies transfer might confer enterotoxicity within the genus as a whole, explaining the sporadic isolation of different species in apparent cases of food poisoning.

B. thuringiensis, which produces potent protein toxins that target the mid-gut of susceptible insect species (30, 34–36, 40, 74), has not been reported to cause gastrointestinal disease in humans, although culture filtrates of the organism have been shown to cause increased vascular permeability and fluid accumulation in the RIL test (65, 150, 164). It has been associated with two cases, a wound and an ocular infection (171).

CONCLUSION

The ubiquitous presence of *B. cereus* means that contamination from the environment in hospitals and clinics will always occur. When the etiology of infections is unclear, a high index of suspicion of *B. cereus* infection is required for patients who are intravenous drug abusers or immunosuppressed as a consequence of human immunodeficiency virus infection, chemotherapy, or malignancy. Serious nongastrointestinal disease due to *B. cereus* is uncommon. The rare infections seen are associated with trauma or surgery, particularly when these lead to the introduction of foreign bodies, including prosthetic implants, intravascular catheters, or ventricular shunts. Spinal anesthesia accounts for many of the central nervous system infections. Spore-forming gram-positive rods resembling *Bacillus* species isolated from the eye or, when there are clinical signs and symptoms consistent with the presence of organisms, from normally sterile sites such as the blood and cerebrospinal fluid should not be arbitrarily dismissed as contaminants. For preliminary empiric therapy, clinicians should be reminded of the possibility of *B. cereus* infection, since delay in appropriate treatment can lead to significant morbidity and mortality in systemic disease. Direct susceptibility testing should be performed, as *B. cereus* is resistant to most β-lactam antibiotics.

Gastrointestinal disease caused by this organism is more common than was once thought. The incidence is probably higher than reported, because the diarrheal and emetic syndromes are self-limiting and usually cause only moderate morbidity. Contamination of foodstuffs is common, as is asymptomatic fecal carriage, because of the stability of the spores formed. In most cases, expensive reference laboratory biological tests are needed to prove conclusively the presence of toxigenic strains and to establish an epidemiological association between isolates from the implicated food and those from the patient's specimens.

The incidence of gastrointestinal disease can be reduced by good hygiene and food preparation practices, particularly in restaurants, and is discussed in detail elsewhere (61, 96). Although a wide variety of foods are associated with this illness, inadequately cooked rice dishes continue to cause a disproportionately large number of cases.

B. cereus produces several toxins, including a necrotizing enterotoxin, emetic toxin, hemolysins, and phospholipases,

which are important virulence determinants. The enterotoxin and emetic toxins are responsible for the clinical signs and symptoms of the diarrheal and emetic syndromes characteristic of gastrointestinal illness. The in vivo role of the hemolysins and phospholipases is not entirely clear, but they could be significant virulence determinants in ocular and wound infections and other necrotizing lesions.

ACKNOWLEDGMENTS

I thank Anne Uttley, David Dance, John Kramer, and Kate Cheney for their helpful comments on the manuscript.

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