PERSPECTIVE

Bacillus cereus endophthalmitis

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Endophthalmitis, of any aetiology, is a potentially devastating ocular infection. Few patients are able to maintain good visual acuity. Many retain only navigational vision and a significant number require evisceration or enucleation.^{1,2} The incidence of endophthalmitis after trauma has been estimated to occur in 2–7% of cases.³ Various organisms have been implicated but, in recent years, *Bacillus cereus* has emerged as a particularly virulent organism. Its significance, however, has not always been appreciated. Part of the problem has been related to difficulties in subclassification within the genus *Bacillus*. During the first half of this century bacilli isolated from cases of endophthalmitis were often not subclassified beyond *Bacillus* species and many were grouped as *Bacillus subtilis* by default. In 1948, Bergey set out new criteria to distinguish *Bacillus cereus* from *Bacillus subtilis*. Four years later, in 1952, Davenport and Smith reported the case of a man who lost his eye subsequent to culture proved *B cereus* endophthalmitis. The clinical course described was malignant. Similarities could be drawn between Davenport's case and series reported as early as 1891 by Poplawska, and later by François in 1934. The isolate in those series was thought to be *B subtilis*, but this may have been an error of taxonomy.⁴

A further confounding factor to the recognition of *B cereus* as a destructive ocular pathogen is that it is often found as a contaminant in culture. In 1981, O'Day and his colleagues highlighted the importance of *B cereus* in post-traumatic endophthalmitis which, if grown on culture, should be considered as the primary infectious agent. They suggested that suspicions should be raised if there was a history of soil contamination involving a metallic foreign body.⁵

Whereas *B cereus* was being increasingly recognised in exogenous, post-traumatic endophthalmitis, numerous cases of endogenous endophthalmitis relating to *B cereus* had already been reported in the literature.^{6–13} The infections were linked with the transfusion of contaminated blood products and the use of illicit intravenously administered drugs. Shamsuddin *et al*, in 1982, found that the source of the organism was either the illicit drug itself or the paraphernalia used to inject the substance.¹¹ The bacteraemia associated with the use of contaminated drugs and instruments has also been reported to be the cause of other serious forms of infection including endocarditis, osteomyelitis, meningitis, and necrotising fasciitis.¹⁴

B cereus is well established as a pathogen in the food industry. It is a spore forming bacterium and therefore resistant to temperatures attained during many cooking methods.¹⁵ The spores germinate when heated food – for example, rice, is left unrefrigerated. Brief rewarming is not adequate to destroy the preformed, heat stable toxin. There are two recognised patterns of food poisoning. The first has an incubation period of 8 to 16 hours before the onset of abdominal cramps and profuse, watery, diarrhoea. The second became recognised in the 1970s and was associated with rice purchased from Chinese 'take aways'. The rice would often be prepared in advance and kept at a relatively high temperature. This allowed the bacteria to thrive and

counts in the region of 10⁶ to 10⁹ per gram of rice have been isolated in proved cases. Typically, nausea and vomiting would develop 1 to 5 hours after consumption.¹⁶

In this paper we describe the clinical and bacteriological features of *B cereus* endophthalmitis and discuss management controversies in current clinical practice.

Clinical features

O'Day and colleagues outlined three features common to cases of exogenous *B cereus* endophthalmitis. Firstly, there was a penetrating injury with vitreous involvement. Secondly, perforation was caused by a low velocity metallic fragment. Finally, there was the possibility of soil contamination. The interval between injury and deterioration of vision was typically less than 48 hours.⁵ Severe pain often develops within 24 hours. This occurs in conjunction with a drastic reduction in visual acuity, chemosis, periorbital swelling, and proptosis. Classically, a corneal ring abscess develops in association with the reduction of vision. Some authors have indicated that this is pathognomonic; however, it has been described in other cases of endophthalmitis including those caused by *Pseudomonas* and *Proteus* species.⁵ The other important distinguishing feature is that *B cereus* endophthalmitis often produces associated systemic symptoms. The patient developing fever, leucocytosis, and malaise.

Owing to the fulminant nature of this infection, O'Day and others have emphasised the importance of maintaining a high degree of suspicion coupled with early intervention in order to attempt to salvage vision.^{5 17–20} Unfortunately, in one series the mean time from injury to intervention was 30 hours.¹⁷

The incidence of *Bacillus* species as a causative organism in penetrating ocular trauma has been estimated to be between 27–46%.^{18 20} The patient was more likely to have *Bacillus* species as the causative organism if there was an associated retained intraocular foreign body or if the injury had occurred in a rural or agricultural setting.^{23 26 27 29} It has been suggested that the bacilli may colonise the ocular surface and the foreign body is contaminated as it penetrates the globe. Another possibility is that the projectile is of a low velocity, and hence does not self sterilise before penetrating the globe.²⁶

Reported series over the period of 1981–91 are consistent in that the prognosis for vision is dismal. Indeed, many patients ultimately required evisceration or enucleation. If we consider the culture positive cases from these series, *Bacillus* species have been identified in 82. Final visual acuities are outlined in Table 1. In some cases the final visual acuity was not recorded but rather the final outcome. The majority were left with either perception of light or no perception of light. *B cereus* has been identified in 38/82 cases (46.3%). The final outcome in 22 of these cases was either evisceration or enucleation.^{3 5 19 20 27 31–34} Recovery of useful vision (better than 20/100) in *B cereus* endophthalmitis is rare. We know of only three cases following trauma^{20 30 35} and one secondary to a bacteraemia.³²

The largest single reported series of *B cereus* endoph-

Table 1 Summary of reported series 1981-91

Author	Year	Organism	No	Results				
				PL	NPL	Evisceration	Enucleation	Other
Diamond ²²	1981	<i>Bacillus</i> spp	1	0	0	0	0	20/40
Rowsey <i>et al</i> ³¹	1982	<i>Bacillus</i> spp	5	2	0	0	2	CF
		<i>B. cereus</i>	2	2	0	0	0	0
		<i>B. cereus</i>	6	0	2	0	4	0
O'Day <i>et al</i> ⁵	1982	<i>B. cereus</i>	4	0	0	4	0	0
Ho <i>et al</i> ³³	1982	<i>B. cereus</i>	4	0	2	0	1	20/70
Puliafito <i>et al</i> ³²	1982	<i>Bacillus</i> spp	4	0	1	0	2	0
Brinton <i>et al</i> ⁵	1984	<i>Bacillus</i> spp	4	1	1	0	1	0
		<i>B. cereus</i>	1	0	0	0	1	0
		<i>B. cereus</i>	4	1	0	1	1	20/300
Schemmer and Driebe ²⁰	1987	<i>B. cereus</i>	2	0	1	0	0	20/60
		<i>Bacillus</i> spp	3	0	3	0	0	0
Affeldt <i>et al</i> ¹⁸	1987	<i>Bacillus</i> spp	5	2	2	0	0	20/200
		<i>B. cereus</i>	9	1	4	3	1	0
		<i>Bacillus</i> spp	2	0	1	1	0	0
Boldt <i>et al</i> ²⁷	1989	<i>B. cereus</i>	6	0	1	0	2	20/30, 20/50
		<i>Bacillus</i> spp	4	1	0	0	3	20/400
		<i>B. cereus</i>	2	0	0	0	0	0
Hemady <i>et al</i> ¹⁹	1990	<i>Bacillus</i> spp	12	1	0	0	3	20/40, 20/30
		<i>B. cereus</i>	2	0	0	0	0	20/20
		<i>Bacillus</i> spp	6	1	0	1	3	20/200
Mieler <i>et al</i> ²³	1990	<i>B. cereus</i>	4	1	0	0	3	0
Vahey and Flynn ³⁴	1991	<i>Bacillus</i> spp	2	0	0	0	0	20/40, 20/30
		<i>Bacillus</i> spp	6	1	0	1	3	20/20
		<i>B. cereus</i>	12	1	1	4	5	20/200

PL=perception of light; NPL=no perception of light; CF=counting fingers.

thlmitis was from the Bascom Palmer Eye Institute in Florida. Over a 16 year period, 18 cases of *Bacillus* species endophthalmitis were identified. Of those *B. cereus* was found to be the causative organism in 12. Nine cases were as a result of trauma, two were secondary to intravenous drug abuse, and one subsequent to a corneal ulcer. Of the post-traumatic cases there was a retained metallic intraocular foreign body in five. The final visual acuities were no perception of light in 10/12 (83%), 1/12 (8.3%) had perception of light, and 1/12 (8.3%) achieved visual acuity of 6/60; nine of the eyes were either eviscerated or enucleated, and two others had complicated vitreoretinal procedures.³⁴

Bacteriology

B. cereus is a Gram positive rod which is motile, non-encapsulated, and grows both aerobically and anaerobically. These rods measure 1-1.2 by 3-5 µm and have squared off ends. It is capable of spore formation. The spores form under aerobic conditions, they measure 1-1.5 µm, are ellipsoidal in shape, and do not extend beyond the cell outline. They may be central or subterminal. On nutrient agar the colonies are large, white, flat, and irregular in appearance. On blood agar there is a large area of β haemolysis to be noted.^{4 14 36-38}

These pathogenic organisms, which had previously been regarded as part of the *B. subtilis* group, were reclassified as *B. cereus* based on the following three distinguishing features. Firstly, *B. cereus* was found to be larger than the *B. subtilis* species (which measure 0.7 by 2-3 µm). Secondly, the colonies formed by this species were not rhizoid. Finally, when *B. cereus* was grown on a glucose medium vacuolation could be demonstrated on Gram stain.^{4 14 36-38}

In 1949, Chu postulated that the virulence due to *B. cereus* was as a result of its lecithinase activity.⁴ Forty five years later the exact mechanisms for the aggressive nature of these infections is still being investigated. Initially, the search had been for a single toxin, like the α toxin produced by *Clostridium perfringens*. α Toxin has lecithinase activity, haemolytic activity, and lethality. Turnbull and others surmised that, in the case of *B. cereus*, there was not one single toxin responsible for this but three.^{39 40} It would appear that the most likely toxin to account for the lecithinase activity of *B. cereus* is phospholipase C. It is thought that there are three different forms of this toxin. Phosphatidylcholine hydrolase, one of three enzymes, has been extensively studied, yet unequivocal evidence linking this particular enzyme to the invasiveness of *B. cereus* infections is lacking.²⁶ Turnbull suggested that its role may be to cause disruption of phospholipid membranes exposed by other toxins. It is also

thought to cause the release of lysosomal enzymes from neutrophils.²⁶ Loop fluid inducing/skin test/necrotic toxin along with its counterpart cereolysin are believed to account for the lethality. Loop fluid inducing/skin test/necrotic toxin is an exotoxin that has been linked to the diarrhoea caused by *B. cereus* food poisoning. In addition to lethality, cereolysin is thought to have the ability to cause haemolysis. A causal relation between the in vitro activities of these toxins and serious ocular and systemic infections is still under investigation.^{26 33 39 40}

Irrespective of which toxin is responsible for the aggressiveness of *B. cereus*, the various enzymatic activities have been used to help identify the organism in culture. To aid in the identification of *B. cereus*, egg yolk enriched agar can be used in addition to standard culture media.^{36 37}

Egg yolks contain the lipoprotein lecithovitellin. The use of egg yolk agar to identify bacterial organisms is based on their lecithinase activity. The agar itself is prepared by diluting egg yolk with saline to produce a clear yellow medium. When organisms with lecithinase activity are grown on this medium some of the enzyme diffuses into the agar forming areas of opalescence surrounding the colonies. *B. cereus* has a marked lecithinase activity which can help to distinguish it from other organisms which grow on egg yolk agar, - for instance, *Staphylococcus aureus*, which causes a zone of clearing rather than opalescence.^{33 34 38}

Endogenous versus exogenous *Bacillus cereus* endophthalmitis

In a review on endogenous endophthalmitis, it has been suggested by Greenwald *et al* that the pathogenesis of endogenous endophthalmitis is different from exogenous endophthalmitis.⁶ They felt that whereas the primary focus of infection in exogenous endophthalmitis was within the vitreous body, the primary ocular focus for endogenous endophthalmitis was the vasculature. They found that, in endogenous endophthalmitis, blood cultures were as good as, or better than intraocular sampling for isolation of the infecting organism. Their findings supported the need for suspicion coupled with early intervention, but they felt that the outcome of therapy was unaffected by the use of intravitreal antibiotics, and as there are potential hazards, intravenous antibiotic therapy was sufficient. This view is also in contrast with the pharmacological studies of Barza and others that demonstrate low intravitreal concentrations of topically, periocular, and systemically administered antibiotics.⁴¹⁻⁴⁷ Not all authors who have published experience with the treatment of endogenous endophthalmitis due to

B. cereus would agree and advocate the use of intraocular antibiotics.^{8 13}

Management and antibiotic therapy

In 1985, Affelt *et al* presented their results of 27 cases of culture positive post-traumatic endophthalmitis. They found that the *Bacillus* species was the most commonly isolated organism.¹⁸ Boldt *et al* were later to confirm this finding especially when the injury occurred in an agricultural setting.²⁷ Vahey and Flynn found that of their cases of endophthalmitis 66% were due to *B. cereus*.³⁴ Indeed, examining the literature over the past 15 years demonstrates that maintaining a high index of suspicion for *B. cereus* infection is of paramount importance.^{3 5 6 17-20 22-24 26 27 31 32 34 48}

With regard to the management, it is well accepted that the appropriate cultures should be acquired before use of antibiotics. Both aqueous and vitreous samples should be obtained. The growth of the same organism from both samples increases the likelihood of it being the infecting organism.⁴⁸⁻⁵² However, Forster's dictum is that the vitreous is more likely to reveal a positive result.^{41 53} The selection of an antibiotic, as well as an appropriate means of administration, has been the subject of much research and controversy. Although topical, periocular, and systemically administered antibiotics are still used by many ophthalmologists in the treatment of endophthalmitis, studies by Barza and others have shown that the intravitreal concentrations achieved by these methods are low.^{42-47 54-59}

The use of intraocular antibiotics was first pioneered by Ludwig von Sallmann in 1944. He and his colleagues studied the effect of intravitreal penicillin on experimentally induced staphylococcal endophthalmitis. Using a standardised inoculum, they found that if the penicillin was injected within 6 to 12 hours the infection was thwarted.⁵⁸ The selection of the appropriate antibiotic for the treatment of *B. cereus* endophthalmitis is based on in vitro trials.^{42-47 54-63}

Many authors have suggested that clindamycin, in combination with gentamicin, has a synergistic effect against *B. cereus*.^{5 17 23 24 26 27 29 31} Gigantelli *et al* examined the in vitro susceptibility of *B. cereus* to a combination of gentamicin and vancomycin compared with gentamicin and clindamycin; their studies suggested that the latter was more effective.⁶² However, in vitro studies by Weber *et al* have suggested that vancomycin is a suitable alternative to clindamycin.⁶⁰ All 54 strains of *B. cereus* tested were found to be susceptible to vancomycin, whereas only 39 were susceptible to clindamycin (by a microdilution technique). Gentamicin and the other aminoglycosides were found to be quite active against *B. cereus*. The semisynthetic penicillins and the cephalosporins were, however, rather ineffective. This is likely to be related to the ability of the organisms to elaborate a β lactamase. They discovered that the minimum bactericidal concentration (MBC) for vancomycin was not much higher than its minimum inhibitory concentration (MIC) (9% higher) whereas for clindamycin the MBC was 46% greater than the MIC.⁶⁰ This may be significant if the intravitreal levels achieved are low.

After the initial interest in the use of intraocular antibiotics in the 1940s it was not until the mid 1970s when advances in vitrectomy techniques developed that the idea was rejuvenated.⁶³ Animal studies have demonstrated the usefulness of intraocular antibiotic in combination with vitrectomy.⁶⁴ Increasingly, vitrectomy is being considered as part of a therapeutic regimen when dealing with endophthalmitis.⁴⁸ Theoretically, vitrectomy is thought to reduce the size of the inoculum and facilitate circulation of antibiotics within the posterior segment.

The use of intravitreal antibiotics, although accepted by many authors as a cornerstone in the management of

endophthalmitis, is shunned by others for fear of retinal toxicity.^{17 22 24} Their value in controlling intraocular infection has been proved in animal and some human studies,^{3 17 19 22 23 25 32 42 43 45 50} the dosage in humans being calculated from pharmacokinetic data in animals.⁴²

The controversy as to the effect of intraocular antibiotics on the retinal tissues versus the benefits continues.^{48 61} Recently published work suggests that aminoglycosides are associated with macular infarction. Gentamicin is thought to be the most toxic of the aminoglycosides.⁶⁵⁻⁷² Amikacin, another aminoglycoside is thought to be less toxic and was thus chosen for use in the Endophthalmitis Vitrectomy Study. Other reasons for the selection of amikacin included a wide clinical experience and a theoretical synergy between amikacin and vancomycin.⁶¹ Some authors have suggested that ceftazidime would be a suitable alternative to an aminoglycoside in the treatment of endophthalmitis. It has a broad spectrum of activity against both Gram positive and Gram negative organisms, including *Pseudomonas*, and it has been reported to be less toxic to retinal tissues. Donahue *et al*, in their paper on postoperative endophthalmitis, have suggested that provided microscopy rules out Gram negative organisms vancomycin alone would be a suitable agent. If Gram negative organisms are identified or no laboratory support is available an aminoglycoside or a cephalosporin, such as ceftazidime, should also be injected.⁷⁰ Unfortunately, in post-traumatic endophthalmitis where *B. cereus* may be involved, ceftazidime is not suitable owing to documented resistance to cephalosporins.^{26 34 38 48 60}

A recent paper by Lesk and colleagues measuring the levels of ciprofloxacin in the aqueous humour, the vitreous, and the subretinal fluid in patients undergoing ocular surgery suggests that oral ciprofloxacin achieves an intravitreal concentration which exceeds the MIC₉₀ for *B. cereus*.⁷³ Furthermore, rabbit studies suggested that intravitreal ciprofloxacin was well tolerated and exceeded the MIC₁₀₀ for all commonly encountered bacteria.⁷⁴ It would appear that this warrants further investigation.

It is clear from the literature that *B. cereus* endophthalmitis should be considered in two settings. Firstly, in the intravenous drug abuser who develops an endophthalmitis. In this situation it is important to culture body fluids in addition to aqueous and vitreous sampling. The selection of antimicrobials will be influenced by bacteriological results and sensitivities. Parenterally administered antibiotics have a significant role in the therapy of endogenous endophthalmitis.^{6 38} Secondly, in cases of penetrating trauma with a soil contaminated metallic foreign body. Rapid intervention is imperative.^{3 5 17 20 34} Aqueous and vitreous samples should be taken for microscopy and culture. Even if there is no overt evidence of infection, prophylactic intravitreal antibiotics should be considered. Vancomycin 1000 μ g in combination with amikacin 400 μ g are the standard choices.³⁴ The use of antibiotics administered topically, subconjunctivally, and systemically in endophthalmitis remain standard practice. However, in traumatic *B. cereus* endophthalmitis they can be considered as adjunctive therapy.

B. cereus endophthalmitis is a relatively rare event, but has catastrophic results. Preservation of vision is based on clinical suspicion and rapid intervention.

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