

Infectious endophthalmitis in Boston keratoprosthesis: incidence and prevention

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ABSTRACT.

Purpose: To determine the cumulative worldwide incidence of infectious endophthalmitis and associated vision loss after Boston keratoprosthesis (B-KPro) Type I/II implantation and to propose both safe and inexpensive prophylactic antibiotic regimens.

Methods: Two retrospective methods were used to determine the incidence, visual outcomes and aetiologies of infectious endophthalmitis associated with the B-KPro divided per decade: (i) systematic review of the literature from 1990 through January 2013 and (ii) a surveillance survey sent to all surgeons who implanted B-KPros through 2010 with 1-year minimum follow-up. In addition, a single-Boston surgeon 20-year experience was examined.

Results: From 1990 through 2010, there were 4729 B-KPros implanted worldwide by 209 U.S. surgeons and 159 international surgeons. The endophthalmitis cumulative mean incidence declined from 12% during its first decade of use to about 3% during its second decade in the United States and about 5% internationally during the second decade. There remains a large incidence range both in the United States (1–12.5%) and internationally (up to 17%). Poor compliance with daily topical antibiotics is an important risk factor. While Gram-positive organisms remained dominant, fungal infections emerged during the second decade.

Conclusions: Daily prophylactic topical antibiotics have dramatically reduced the endophthalmitis incidence. Although Gram-positive organisms are the most common aetiology, antimicrobials must be inclusive of Gram-negative organisms. Selection of prophylactic regimens should be tailored to local antibiotic susceptibility patterns, be cost-effective, and should not promote the emergence of antimicrobial resistance. An example of a broad-spectrum, low-cost prophylactic option for non-autoimmune patients includes trimethoprim/polymyxinB once daily.

Key words: Boston keratoprosthesis – endophthalmitis – ocular infections – ocular prophylaxis

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Introduction

For the 4–8 million persons who are blind from corneal disease worldwide (Smith & Taylor 1999; Mariotti 2010; Silva et al. 2006) and who cannot be helped by standard corneal transplantation (Garg et al. 2005), an artificial cornea is an obvious concept (Pellier de Quengsy 1789), yet only a small number of devices have been implanted over its history prior to 1990 (Dohlman et al. 1974; Cardona & DeVoe 1977; Barnham & Roper-Hall 1983). The reason for this slow progress has primarily been the risk of infectious endophthalmitis that can destroy the eye virtually overnight. Thus, artificial cornea surgery has been viewed as being extremely risky and rarely successful over time, but there has been substantial progress in reducing the infection rate over the past few decades (Dohlman & Doane 1994; Alvarez de Toledo et al. 1999; Mannis & Dohlman 1999; Falcinelli et al. 2005).

The Boston keratoprosthesis (B-KPro; FDA approved, 1992) is an artificial cornea of collar button design composed of medical grade poly (methyl methacrylate) (PMMA) with the optical stem implanted through a corneal graft transplanted into the patient's eye similar to a penetrating keratoplasty

(Doane et al. 1996). It can restore sight in eyes that are not candidates for corneal transplantation. Type I design is most frequently used for non-autoimmune graft failure patients with good tear and lid function (Fig. 1). Type II is indicated for patients with cicatrizing corneal diseases with very poor or absent tear function such as Stevens–Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP), severe chemical burns; it has an additional 2-mm-long anterior optical nub attached to the collar button enabling it to protrude through the upper lid.

As with any indwelling or implantable medical device that traverses from the normal microbial flora on the ocular (or skin) surface into a sterile site (anterior chamber, blood), any keratoprosthesis is at high risk for infection (Fig. 2; Behlau & Gilmore 2008), with autoimmune patients at the greatest risk (Nouri et al. 2001; Yaghoobi et al. 2001). Most indwelling or implantable device infections involve biofilms that are naturally resistant to antimicrobials. Their role in chronic inflammation is only beginning to be recognized (Behlau & Gilmore 2008; Behlau et al. 2011a,b; de la Cruz et al.

2011). During the 1990s and later, it was realized that low-dose prophylactic topical antibiotic regimens, given daily for life, were markedly effective in reducing the risk of endophthalmitis in B-KPros patients (Dohlman 1993; Nouri et al. 2001). During 1999, several changes in postoperative management were introduced including (i) large soft contact lenses to be worn around the clock to protect the underlying corneal tissue from dehydration and epithelium defects (Dohlman et al. 2002) and (ii) topical vancomycin in combination with broad-spectrum fluoroquinolones, particularly for patients with autoimmune diseases, resulting in a dramatic decline in bacterial endophthalmitis rates (Durand & Dohlman 2009). With these developments, fungal keratitis and endophthalmitis have been reported (Barnes et al. 2007). Sterile vitritis post-B-KPro implantation has also been identified (Nouri et al. 2005).

The main aims of this study are to assess the true risk of vision-threatening endophthalmitis following B-KPro implantations (Robert et al. 2012b) and to recommend antibiotic prophylaxis combinations and frequencies that are safe, efficacious, and cost-effective (Behlau 2012; Behlau et al. 2012).

Methods

The Human Studies Committee at the Massachusetts Eye and Ear Infirmary (MEEI), Boston, MA approved this study.

Literature review study design

Search methods

A systematic review of the literature was performed through the Howe

Library at the MEEI to identify all published reports pertaining to endophthalmitis associated with the Boston keratoprosthesis. International databases (PubMed (National Library of Medicine), EMBASE, Web of Science, BIOSIS Previews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systemic Reviews, Clinicaltrials.gov, Guidelines.gov, Latin American and Caribbean Center on Health Sciences Information (LILACS), African Index Medicus, WHO Library and Information Networks for Knowledge Database (WHOLIS), Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Western Pacific Region Index Medicus, NLM Gateway, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform) were searched on 17 February 2012 and updated 24–29 January 2013 without language restrictions. Additional studies were identified by a manual search of the bibliographies and reference lists of original relevant articles and published proceedings.

Selection criteria

Inclusion criteria included (i) human cases, (ii) Boston keratoprosthesis and (iii) endophthalmitis occurrence and/or infection of the aqueous humour and/or vitreous fluid, even if zero. Articles examined included clinically diagnosed culture-positive and culture-negative cases. We did not exclude (i) cases that had other implantable devices (glaucoma shunts) or other surgical procedures (filtering blebs; Taban et al. 2005), even if those devices might be the source of infection and (ii) reports that we disagreed with their clinical and/or microbiological diagnosis of endophthalmitis. On the other hand, investigator reports of suspected ‘sterile vitritis’ without vision loss were excluded in the calculation of infectious endophthalmitis rates.

Worldwide endophthalmitis surveillance survey

The first part of a two-step surveillance survey sent to 368 surgeons who implanted Boston KPros from 1990 through December 2010 contained the following queries: (i) B-KPro surgery start year, (ii) number of keratoprostheses implanted and (iii) number of

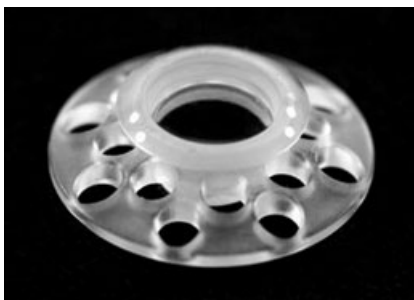


Fig. 1. Photograph of the modern Boston keratoprosthesis (B-KPro) type I composed of poly (methyl methacrylate) (PMMA).

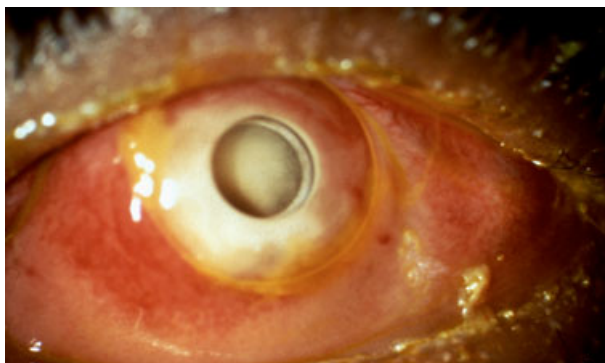


Fig. 2. Acute bacterial endophthalmitis (*Streptococcus pneumoniae*) in a B-KPro type I patient with Stevens–Johnson syndrome.

deidentified endophthalmitis cases, if any. Surveys were sent via email, fax, postal mail, telephone calls and online survey repeatedly to all surgeons that had been shipped a B-KPro until a response was obtained during 2011 through 2012. The number of implanted B-KPros through 31 December 2010 was determined by invoice records and confirmed for accuracy by the reporting surgeon. Implanted B-KPros prior to 1990 and after 31 December 2010 were excluded.

Single-surgeon endophthalmitis-associated B-KPro experience

This is a retrospective single surgeon (Claes H. Dohlman) reporting of endophthalmitis cases associated with B-KPro implantation from a continuous surgical case log maintained over a 20-year period (March 1990 through January 2010) at the Massachusetts Eye and Ear Infirmary, Boston, MA. Prior literature reports (Dohlman & Doane 1994; Dohlman & Terada 1998; Nouri et al. 2001, 2005; Yaghouiti et al. 2001; Dohlman et al. 2002, 2010; Ray et al. 2002; Barnes et al. 2007; Sayegh et al. 2008; Durand & Dohlman 2009; Rivier et al. 2009; Cade et al. 2011) and new endophthalmitis cases were assessed.

Definition of endophthalmitis

Acute endophthalmitis is easily defined by a sudden onset of eye pain, abrupt decreased vision and intraocular inflammation. Acute endophthalmitis in the setting of a KPro can be clinically divided into two visual outcome groups: one with disastrous outcome and the other, benign with the original vision restored. This study focuses on endophthalmitis associated with vision loss. The authors recognize the challenges of distinguishing chronic endophthalmitis with low-virulent, slow-growing micro-organisms versus sterile inflammation. Any clinically suspected infectious endophthalmitis reported case (even coagulase-negative staphylococci (CNS), uncultured, or culture-negative) was included. 'Sterile vitritis' with a sudden decrease in vision with little erythema or pain, with restoration of pre-event vision with the use of corticosteroids alone (Nouri et al. 2005), was not included in the calculation of incidence.

Statistical analysis

Literature review

We provide a descriptive analysis of endophthalmitis with associated prophylactic antibiotic regimens, aetiologies and susceptibilities when available. Due to limited information, we were unable to reliably perform a meta-analysis study at this time.

Global surveillance survey

We calculated a cumulative incidence of endophthalmitis by counting the number of reported cases of endophthalmitis divided by the total number of implanted B-KPro per each decade.

Single-surgeon experience

Herein, we report both new cases of endophthalmitis and previously reported cases divided per decade. Additionally, selective prophylactic antibiotics and dosing frequency from forty consecutive B-KPro patients (non-autoimmune, non-burn) receiving implantations between 2007 and 2010, with 3-year follow-up, were reviewed. Duration on particular antibiotics with their respective cumulative time periods was recorded.

Results

Yield from literature search

The combined electronic database identified 135 unique citations. Manual search of bibliographies resulted in 11 additional unique citations for a total 146 articles. From these, 46 met our criteria for review. Two articles required translation. The literature (Dohlman & Doane 1994; Dohlman & Terada 1998; Nouri et al. 2001; Yaghouiti et al. 2001; Dohlman et al. 2002; Ray et al. 2002; Aquavella et al. 2005, 2006, 2007; Nouri et al. 2005; Javadi et al. 2006; Zerbe et al. 2006; Akpek et al. 2007; Barnes et al. 2007; Sayegh et al. 2008; Stolz et al. 2008; Aldave et al. 2009; Bradley et al. 2009; Fintelmann et al. 2009; Chew et al. 2009; de la Cruz & McMahon 2009; Durand & Dohlman 2009; Truax et al. 2009; Rivier et al. 2009; Dohlman et al. 2010; Dunlap et al. 2010; Georgalas et al. 2010; Tsui et al. 2010; Cade et al. 2011; Greiner et al. 2011; Gevorgyan et al. 2011; Guell et al. 2011; Li et al. 2011; Verdejo-Gomez et al. 2011; Utine et al. 2011a,b; Aldave et al. 2012; Baj-

racharya et al. 2012; Chan & Holland 2012; Iyer et al. 2012; Kamyar et al. 2012; Kang et al. 2012; Kiang et al. 2012; Patel et al. 2012; Ramchandran et al. 2012; Robert et al. 2012b; Magalhaes et al. 2013) was predominantly retrospective, institutional chart reviews. There were four case reports, several case series restricted to a specific patient population and one quasi-prospective/retrospective multicenter volunteer series. There was only one prospective (non-randomized, non-blinded) case-control study in the Boston keratoprosthesis literature comparing corneal carrier grafts (Robert et al. 2012a). There were no prospective studies with randomization methods.

The United States had the highest number of studies reported (36), while international studies comprised twelve. There were 19 U.S. B-KPro surgeons reporting, accounting for 9.1% of all U.S. B-KPro surgeons, and 12 international surgeons (including two U.S. surgeons operating internationally), accounting for 6.9% of 159 international B-KPro surgeons. Overall, this represents 8.1% of B-KPro surgeons. One surgeon had 13 reports and the largest case series (255; Durand & Dohlman 2009). Two surgeons reported five times either singularly or in combination representing sequential, longitudinal retrospective studies. Determination of the true cumulative endophthalmitis incidence has been complicated by the lack of referencing previously reported patients (Robert et al. 2012b).

The number of B-KPros implanted in eyes reflects 35% of the total United States and 24% of the total international implanted B-KPros. The incidence of endophthalmitis associated with B-KPro implanted prior to 2000 was 13.9% (15/108) in the United States and 100% international (4/4; Javadi et al. 2006). Notably, the cumulative incidence with design and post-operative management changes for B-KPros implanted after 2000 through 2010 (few reports extending into 2011) was 4.8% (53/1211) in the United States, while the international incidence (with a shorter follow-up time) was also 4.8% (14/289). There was a large incidence range with the maximum up to 12.5% in the United States (Chew et al. 2009; Fintelmann et al. 2009; Greiner et al. 2011; Li et al. 2011) and up to 17% (Gevorgyan et al. 2011; Aldave et al. 2012) internationally in

the second decade. Four total case reports without patient denominators were included in these calculations (Georgalas et al. 2010; Tsui et al. 2010; Bajracharya et al. 2012; Robert et al. 2012b).

Comparison of endophthalmitis to ocular diseases

During the first decade, the dominant ocular diseases in the United States (Nouri et al. 2001) and internationally (Javadi et al. 2006) were autoimmune in 37% and 34% and chemical burn in 26% and 59%, respectively. After 2000, the predominant patient population in the United States had shifted dramatically to non-autoimmune, non-chemical burn patients (Nouri et al. 2005; Durand & Dohlman 2009), while in some developing countries chemical burn remained a dominant clinical diagnosis (Stolz et al. 2008).

Comparison of endophthalmitis to prophylactic antibiotics

During the first decade, there were several antibiotic regimens in use (often in rotation), with trimethoprim-polymyxinB (TMP-PMB) or ofloxacin the most commonly prescribed antibiotics. Of note, there were no reports of fungal endophthalmitis or ‘sterile vitritis’ during this first decade. As of late 1999s through the second decade, with the introduction of bandage contact lenses, broad-spectrum fourth-generation fluoroquinolone either as single agent or in combination with vancomycin, (while TMP-PMB fell out of favour), cases of fungal endophthalmitis were reported (Barnes et al. 2007; Rivier et al. 2009; Utine et al. 2011a; Chan & Holland 2012).

Global surveillance survey

This retrospective self-reporting survey was sent to all surgeons who implanted B-KPros between 1990 through December 2010 as shown in Table 1. In the United States, there was a dramatic decline in the incidence of endophthalmitis from the first decade of use (12%) compared to the second decade (2.9%). The international incidence of endophthalmitis from the first decade was not calculated due to the absence of reliable reports. In the second decade, a higher cumulative incidence of endophthalmitis was seen internationally (5%) compared to U.S. surgeons (2.9%).

Surgeons by geographical locations are not shown due to confidentiality and anonymity.

Single-surgeon experience

Table 2 reports the largest retrospective single-surgeon case series spanning over two decades with a minimum 2-year follow-up. In the first decade, the incidence of severe bacterial endophthalmitis was high, particularly in autoimmune patients (Nouri et al. 2001), while no fungal infections were seen. In the second decade, there was a dramatic decline to 1.7% in severe bacterial endophthalmitis cases, however, a rise in fungal endophthalmitis to 2.4%. Of the seven reported cases of fungal infection, four were cured with minimal visual loss. Two cases (0.7%) of atypical mycobacterial endophthalmitis also emerged.

The mean (average) time from B-KPro implantation to all types of endophthalmitis cases was 20 months, while the median was 14.3 months. This large difference was due to late onset bacterial endophthalmitis often related to non-compliance. Frequent early bacterial endophthalmitis events

skewed the overall distribution to the left with the lower quartile (Q₂₅) at 5.5 and the upper quartile (Q₇₅) at 30.3 months. The median time for bacterial endophthalmitis was 13 months with Q₂₅ = 4.8 and Q₇₅ = 34, while for fungal endophthalmitis the median time was 18.5 months with Q₂₅ = 14.5 and Q₇₅ = 26 months. The percentages of cases that occurred within the first 12 months were 47.8% and 28%, respectively, within the first 24 months 60.9% and 71.4%, respectively, and only within 36 months did 82.6% bacterial cases and 100% of fungal cases occur.

Glaucoma drainage devices (GDD) were present in 20 of 30 patients with B-KPros at the time of endophthalmitis. A trabeculectomy-associated blebitis was the source of infection in one B-KPro patient (Dohlman et al. 2002). Similar to others’ (Al-Torbak et al. 2005; Zerbe et al. 2006; Bradley et al. 2009; Kim & Chen 2011; Li et al. 2011), conjunctival dehiscence over the tube or erosion over the trabeculectomy leading to infection was implicated or contributory in 40% of GDD/BKPro-associated endophthalmitis cases.

Antibiotic non-compliance occurred in one-fourth of the patients in the first

Table 1. Boston keratoprosthesis-associated endophthalmitis worldwide surveillance survey. Reports are for Boston keratoprostheses implanted from 1990 through 31 December 2010, with a minimum 1-year follow-up. Endophthalmitis incidence includes both bacterial and fungal aetiologies.

	United States 1990–2010	International 2002–2010
Total B-KPro surgeons	209	159
B-KPro surgeons response rate	95.2%	66.7%
Number of implanted B-KPros	3501	1228
% Implanted B-KPros accounted	99.5%	86.2%
Number of endophthalmitis cases	111	65
Cumulative incidence of endophthalmitis	3.2%	5.0%
Incidence of endophthalmitis per decade (1990–2000)	12.0%	NA
Incidence of endophthalmitis per decade (2001–2010)	2.9%	5.0%

Table 2. Single-surgeon experience in Boston of B-KPro-associated endophthalmitis over a 20-year period. The total period is divided into a first decade (March 1990–Dec 1999) and second decade (Jan 2000–Jan 2010). The second decade coincides with design changes, bandage contact lens and vancomycin use; minimum 2-year follow-up.

	1990–1999	2000–2010
Total number of B-KPro implantations	113	291
Autoimmune %	42	32
Chemical or thermal burn %	29	12
Graft failure or other (non-autoimmune, non-burn) %	29	56
Severe endophthalmitis		
Bacterial %	10.1	1.7
Atypical mycobacteria %	0	0.7
Fungal %	0	2.4

Table 3. Boston area community-based hospitals antibiotic susceptibilities–2012. Numbers are percent susceptible based on Clinical & Laboratory Standards Institute (CLSI) guidelines.

Organisms	B-lactams											
	Penicillin or Ampicillin	Oxacillin	Cefazolin, Ceftriaxone*, or Cefazidime	Erythromycin or Azithromycin	Vancomycin	Ciprofloxacin-Levoflox-4FQ	Clindamycin	Chloramphenicol	Tetracycline or Doxycycline	Trimethoprim/Sulphamethoxazole	Polymyxin B [†]	Gentamicin or Tobramycin
Gram-positives	17		71%	43	100	69–72	64	99	96	99	R	98
<i>Staphylococcus aureus</i> -total												
MSSA	24		100	57	100	87–90	74	99	95	99	R	99
MRSA	R	R	R	10	100	26–28	38	94	98	98	R	97
Coag-negative staphylococci	22		66%	43	100	66–68	61	98	90	77	R	91
<i>Streptococcus pneumoniae</i>	66	ND	88	60	100	100	88	95*	84	82	R	ND
Gram-negatives	51	R	89–97	R	R	86	R	S	75	89	>99	90
<i>Escherichia coli</i>												
<i>Serratia marcescans</i>	R	R	95–98	R	R	95	R	92 [†]	9	100	>98	95
<i>Proteus mirabilis</i>	79	R	100	R	R	95	R	S	R	95	R	89
<i>Pseudomonas aeruginosa</i>	R	R	99	R	R	87–86	R	R	R	R	>99	87–92

MSSA = methicillin-sensitive *S. aureus*, MRSA = methicillin-resistant *S. aureus*. R = naturally resistant or susceptibility is 0%, 4-FQ = moxifloxacin and gatifloxacin, ND = not done. Sources are from the Porter Bacteriology Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA, with the exception of chloramphenicol susceptibilities (Clinical Microbiology, Newton-Wellesley Hospital, Newton, MA (2010)).

* *Streptococcus pneumoniae* MA State median susceptibilities reported (2011), MA Dept of Public Health, Jamaica Plain, MA).

[†] Data are derived from the literature.

decade. In the second decade, antibiotic non-compliance in two of five patients precipitated severe bacterial endophthalmitis with complete vision loss – remarkably in a brief 3–5 days. In the other three patients, partial non-compliance (not taking one of the two antibiotics) appeared to lead to destructive endophthalmitis in just a few days.

Information on antibiotic susceptibility was limited because two-thirds of the endophthalmitis events occurred in patients who lived or travelled to areas distant from our site. Antibiotic resistance (all fluoroquinolone resistance) was identified in five cases involving CNS and *Streptococcus pneumoniae* infection; both organisms are associated with a 30–40% resistance (Table 3). Both cases of atypical mycobacteria (*M. abscessus*) were fluoroquinolone resistant (de la Cruz et al. 2007). All seven fungal and the two atypical mycobacterial cases were on both vancomycin and 4-FQ at the time of the endophthalmitis, and 50% of these infections were in non-autoimmune, non-burn patients (Fig. 3).

To offer insight into safe and cost-effective antibiotic regimens, we reviewed sequential medical records for non-burn/non-autoimmune patients who received a B-KPro from 2007 through January 2010 and calculated the number of years on a prophylactic antibiotic regimen. Since 2007, there has been a deliberate shift back to TMP-PMB use in this non-inflammatory group. We report 30 cumulative years of TMP-PMB alone use without adverse events except due to non-compliance in one patient (Fig. 3). One patient while on fluoroquinolone alone (Fig. 3) experienced CNS vitritis 1-week post-Ahmed shunt placement and 5 months post-B-KPro implantation (2009); he regained full vision. Of note, no patients have developed fungal keratitis or endophthalmitis while on TMP-PMB.

Discussion

The present study is a descriptive synthesis of three reporting methodologies to assess the cumulative incidence of endophthalmitis and to assess the efficacy of different antibiotic prophylactic regimens for prevention of endophthalmitis associated with the Boston keratoprosthesis. The challenges in this study are those inherent in retrospective

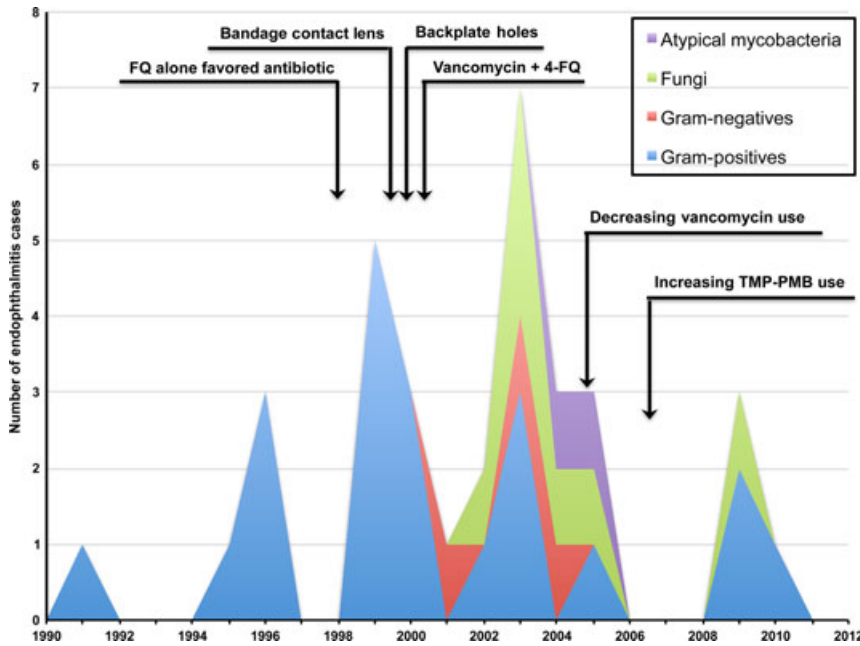


Fig. 3. Boston keratoprosthesis-associated endophthalmitis microbial spectrum timeline. This single-surgeon timeline over 20-year period reflects device interventions, introduction of bandage contact lens and changes in prophylactic antibiotic usage.

literature reviews and surveillance surveys in which criteria and diagnostic methods to diagnose endophthalmitis are not predefined and could be potentially subjects for recall bias. Incomplete reporting of prophylactic antimicrobial regimens and microbiologic details further limits this study.

For the purpose of this study, the definition of endophthalmitis is involvement of the posterior (vitreous) of the eye – not keratitis alone or anterior chamber reaction alone. A sudden infection with redness, severe pain and positive culture, leading to a dramatic reduction of final vision is the main focus of this study. However, in other cases, the vision loss may be sudden and drastic, but the subsequent course mild and with little pain, tenderness or redness and with a final recovery to most or all of the pre-existing visual acuity. The latter presentation can represent a sterile (possibly immune-mediated) vitritis (Nouri et al. 2005), or it can result from infection with a low-virulent organism (e.g. CNS) – the distinction may be clinically difficult; cultures can be ambiguous (Ormerod et al. 1993a, b; Bannerman et al. 1997), and therefore, exact aetiology can remain in doubt. The first severe group with poor visual outcome is the subject of this study.

To assess accurately the cumulative global incidence of endophthalmitis, we used two methodologies. The first was a systematic literature review, inclusive of case reports, in which we found the cumulative incidence to be no more than 4.8% in both the United States and internationally during the second decade of B-KPro implantation. The discrepancy from other literature reviews (Robert et al. 2012b) reflect that we evaluated (i) the incidence by implantation study years and not by publication year, (ii) later publications by the same surgeon(s) to avoid duplicate reporting and (iii) all electronic databases without language restrictions. The second method we employed was the ‘door-to-door’ global surveillance survey (Table 1) often viewed as the most accurate, albeit labour intensive. Herein, we report that the overall cumulative incidence in the United States of Boston keratoprosthesis-associated endophthalmitis was 3.2% spanning over two decades of use. The international incidence was higher at 5% during the second decade despite shorter follow-up periods. As might be expected, countries with greater economic and medical resources have lower endophthalmitis rates than less developed countries, where most of the corneal blind dwell. The challenges these latter countries

continue to face are microbiologically unsafe water, medical access and compliance. We suspect that the difference between the literature review and the surveillance survey in the United States is a reporting bias that favours publication of ‘positive’ findings (endophthalmitis).

The paradigm shift in endophthalmitis incidence is best exemplified from one surgeon’s long-term practice in Boston where the overall severe bacterial endophthalmitis incidence fell from 10% in the 1990s to less than 2% in 2000–2010 period (Table 2), with a similar number of autoimmune patients represented in the two decades. Similar results in the literature and by unpublished surgeons’ reports during the surveillance survey have been achieved (Table 1). Several postulates for this drastic improvement include design changes improving nutrition to the corneal graft, therapeutic contact lens to minimize drying-associated epithelial damage and the systematic introduction of vancomycin to the prophylactic repertoire (especially in the vulnerable autoimmune patients), all in the late 1990s (Fig. 3; Nouri et al. 2001; Durand & Dohlman 2009). The efficacy of vancomycin in combination with a fluoroquinolone was compared to a fluoroquinolone alone concluding that combination therapy was superior to single fluoroquinolone therapy (Durand & Dohlman 2009). Of note, vancomycin was neither combined with another non-fluoroquinolone antibiotic nor was a comparison made to another antibiotic combination regimen such as TMP-PMB. Importantly, reports of fungal infections (keratitis and endophthalmitis) and uncommon organisms (Barnes et al. 2007; Chan & Holland 2012) only occurred after introduction of these changes (Fig. 3).

Over the past two decades, there have been widely different management patterns and outcomes from different institutions both in the United States and internationally, and they offer valuable clues that may lead to improved and standardized postoperative prophylaxis. The use of vancomycin mono-prophylaxis by Mannis and coworkers (Bradley et al. 2009; Greiner et al. 2011; Li et al. 2011) dramatically shifted infections to Gram-negatives and yeast (even in non-autoimmune, non-burn eyes) and demonstrated that

even high-dose vancomycin was insufficient to ward off *Staphylococcus aureus* infections in exposed situations. Thus, their report provides supportive evidence that coverage of Gram-negative bacteria is important in prophylaxis and that the effects of vancomycin on commensal ocular microflora is profound. Additionally, there has been concern that high-dose vancomycin may lead to epithelial cytotoxicity (Yu & Huang 2011).

Fluoroquinolones, particularly the fourth generation, have also been used as a single agent for prophylaxis. The longitudinal experience of Aquavella and coworkers provides the most insight. Combined vancomycin and fluoroquinolones resulted in no infections in their early reports (Aquavella et al. 2005, 2006; Aquavella et al. 2007; Akpek et al. 2007; Dunlap et al. 2010). As he and others changed to fluoroquinolone use alone (Chew et al. 2009; Fintelmann et al. 2009; Robert et al. 2012a,b; Ramchandran et al. 2012), vitritis with CNS emerged with greater than 50% CNS documented to be resistant to fluoroquinolones (FQ-R), along with two other FQ-R species (Ramchandran et al. 2012). Fluoroquinolone resistance has been well documented even in ocular isolates over the past two decades (Table 4; Ocular Microbiology, Bascom Palmer Eye Institute (2012); Schimel et al. 2012).

Reports have been accumulating that vancomycin as a single agent, frequent dosing of broad-spectrum

fourth-generation fluoroquinolones, or vancomycin in combination with a fluoroquinolone (FQ) heavily selects for colonizing yeast, fungi and uncommon FQ-resistant bacteria (including atypical mycobacteria; Chew et al. 2009; Fintelmann et al. 2009; Utine et al. 2011a; Chan & Holland 2012; Patel et al. 2012). In our single-surgeon experience (Fig. 3), we see the effect of vancomycin for selection of these same uncommon pathogens. Evidently, our prophylactic choices do appear to have a profound effect on the ocular surface's protective indigenous microbiota.

It may seem counter-intuitive that such a small dose of antibiotics, if given daily, can protect an eye with a penetrating device from infection. The result of prophylaxis cannot be the total elimination of the indigenous microbiota, but prevention of infection by opportunistic pathogenic bacteria, while not promoting antibiotic resistance and maintaining some protective commensal microflora.

With judicious prophylactic antibiotic usage, we have seen no cases of marked adverse reaction, on the surface or inside the eye. On the other hand, we would caution against using combinations of powerful antibacterials in too frequent doses such as four times a daily. Such a high concentration and frequent prophylactic dosing over long times can lead to ocular toxicity (Bezwada et al. 2008; Etminan et al. 2012), is challenging and costly

for patients and can invite fungal or other opportunistic infections. Given that *S. pneumoniae* infections of the eye almost always leads to devastating loss of vision, we also recommend prevention with the newer pneumococcal vaccines. Cultures at the time of surgery to screen for resistant organisms or when there is a clinical change are encouraged.

An additional factor in achieving success with endophthalmitis prophylaxis is the patient's compliance with the regimen – for life. As we and others have witnessed, even after years of KPro stability, the patient must understand that a lapse over a few days can result in the devastating loss of the eye, and this message deserves to be repeated at every patient visit. Under any circumstances, it seems that the greatest threat to long-term safety of the operated eye lies in laxity of steady, daily compliance with the antibiotic prophylaxis.

Tied into the compliance issue are the cost of antibiotics and the complexity of purchase. Expensive drugs requiring compounding in a pharmacy and also shipment can be discouraging to the point of non-compliance. Difficulties of medication access may be playing a significant role in the higher endophthalmitis rates seen internationally (Table 1; Gevorgyan et al. 2011). Table 4 illustrates the cost aspect of antibiotic combinations in the Boston area that will have to be put into the context of what is available on the

Table 4. Topical ophthalmic antibiotic retail cost in the United States 2012. Prices are retail prices per Massachusetts Eye and Ear Infirmary (MEEI) suppliers unless noted.

Microbial spectrum	Antibiotics	Quantity (ml)	Cost per ml (U.S. dollars)
Gram-Positives	Vancomycin 14 mg/ml*	4	8
	Azithromycin 1% (AzaSite)	2.5	41
	Cefazolin 133 mg/ml*	4	8
	Levofloxacin 0.5%	5	16
	Ofloxacin 0.3%	5	3
	Chloramphenicol 0.5% [†]	10	8
	Doxycycline 0.1% [†]	10	5
	Trimethoprim/Polymyxin B (Polytrim)	10	1
	Gatifloxacin 0.5% (Zymaxid)	2.5	49
	Moxifloxacin 0.3% (Vigamox)	3	36
	Ciprofloxacin 0.3%	2.5	10
	Ceftazidime 50 mg/ml*	4	9
	Gentamicin 3 mg/ml*	7	4
	Tobramycin 3 mg/ml*	7	6
Gram-Negatives			

* MEEI compounding patient cost (non-retail).

[†] Leiter's compounding pharmacy (preservative-free formulations).

market in any specific country. Given the increasing fluoroquinolone resistance, a particularly effective broad-spectrum combination antibiotic at low cost seems to be TMP-PMB (Tables 3 and 4); it is now favoured by us in our non-autoimmune patients with relatively normal tear and blink mechanisms with only one drop instilled per day (Table 5). In autoimmune patients, on the other hand, 1.4% vancomycin is added once or twice per day to either TMP-PMB or fluoroquinolone (Table 5). Perhaps an only eye and chemical burn eyes would also fall in this latter category. Since this shift in practice, the emergence of inherently resistant yeast, fungi and atypical organisms in non-autoimmune patients appears to have abated (Behlau I and Dohlman CH, unpublished data; Table 5, Fig. 3).

Compared to aggressive bacteria that can slide along the KPro stem and rapidly infect the anterior chamber, fungal infections are usually slower and can be contained if recognized. They usually start as a keratitis in the graft, manifested as a whitish sheen in the tissue around the stem and progress relatively slowly. Still of the cases of endophthalmitis reported in Table 2, six were ascribed fungal aetiology but of these, only two patients lost vision in the operated eye. With more attention, education and rapid intervention,

fungal keratitis leading to endophthalmitis may be prevented. Often, cure requires longer antifungal treatment and eventual KPro exchange. In countries with warm, humid climates and agricultural exposures, prophylactic antifungals may perhaps be given together with antibacterials after KPro surgery. Also, the benefits of economical 5% povidone-iodine wash at each clinic visit (Table 5) are not yet evidence based but appear promising, especially in high-risk patients and environments (Pineda R and Behlau I, unpublished data; Ament et al. 2009; Magalhaes et al. 2013). Additionally, short ‘bursts’ of antifungals (e.g. amphotericin B drops twice daily for a week every 2–3 months) appear beneficial in some autoimmune or burn patients, especially in those with prior fungal infections or heavy colonization. The cost and the availability of antifungal treatments may be limiting in some locations.

The reported results are clearly important for the proper positioning of the B-KPro in the stepladder of worldwide surgical treatment options of corneal opacities. Our hope is that the global bacterial infection rate post-B-KPro (over the patient’s lifetime) can be reduced to one per cent or less with thoughtful and compulsive management while awaiting newer antimicrobial approaches to

prevent both colonization and infection of the B-KPro itself (Behlau et al. 2011a,b).

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Table 5. Examples of daily prophylactic antibacterial regimens. Double antibiotic regimens are recommended to prevent the emergence of resistance. Antibiotic selection should be based on local susceptibility patterns. Alternative I is currently preferred by us.

	Alternative I	Alternative II	Alternative III
Low risk (low inflammation)	Trimethoprim sulphate 0.1%-Polymyxin B (TMP-PMB) 1× per Day	Vancomycin 1.4% plus Fluoroquinolone 1–2× per Day	Chloramphenicol 1%* plus Fluoroquinolone 1–2× per Day
High risk (autoimmune, chemical burn, only eye, epithelium defects)	Vancomycin 1.4% plus TMP-PMB 1–2× per Day	Vancomycin 1.4% plus Fluoroquinolone OR TMP-PMB plus Fluoroquinolone 1–2× per Day	Chloramphenicol 1%* plus Fluoroquinolone OR TMP-PMB plus Choramphenicol 1%* 1–2× per Day

Additional recommendations to be considered:Preoperative:

- (1) Pneumococcal vaccine (conjugate (PCV-13) or polysaccharide (PPSV-23))
- (2) Baseline cultures: a) MRSA nasal screen and b) conjunctival and/or corneal culture with sensitivities

Routine clinic visit:

- (1) Reinforce antibiotic adherence and availability
- (2) Povidone-iodine 5%; wash per clinic visit
- (3) Consider contact lens exchange or cleaning (if deposits or every 3 months)

* Chloramphenicol is not commercially available in the United States. Vancomycin must be specially prepared. Fluoroquinolones (FQ): ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin.

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Authors Contribution

IB, KVM and JNM have full access to all of the data in the study and take responsibility for the integrity of the data. IB and ENN take responsibility for the data analysis.

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Conflict of Interest

The MEEI B-KPro Fund is supported by sale of the Boston keratoprosthesis. The Boston keratoprosthesis is marketed under the auspices of the Massachusetts Eye and Ear Infirmary, Boston, MA.

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