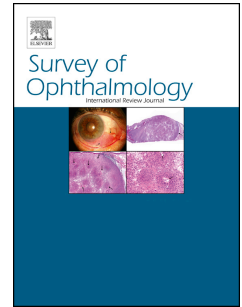


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Antibiotic Prophylaxis in Cataract Surgery in The Setting of Penicillin Allergy: A Decision Making Algorithm

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ANTIBIOTIC PROPHYLAXIS IN CATARACT SURGERY IN THE SETTING OF PENICILLIN ALLERGY:
A DECISION MAKING ALGORITHM

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ABSTRACT

Cataract surgery is the most commonly performed surgical procedure in many developed countries. Post-operative endophthalmitis is a rare complication with potentially devastating visual outcomes. Currently, there is no global consensus regarding antibiotic prophylaxis in cataract surgery despite growing evidence of the benefits of prophylactic intracameral cefuroxime at the conclusion of surgery. The decision about which antibiotic regimen to use is further complicated in patients reporting penicillin allergy. Historic statistics suggesting cross-reactivity of penicillins and cephalosporins have persisted into modern surgery. It is important for ophthalmologists to consider all available antibiotic options and have an up-to-date knowledge of antibiotic cross-reactivity when faced with the dilemma of choosing appropriate antibiotic prophylaxis for patients undergoing cataract surgery with a history of penicillin allergy. Each option carries risks and the choice may have medico-legal implications in the event of an adverse outcome. We assess the options for antibiotic prophylaxis in cataract surgery in the setting of penicillin allergy and provide an algorithm to assist decision making for individual patients.

1. INTRODUCTION

Ophthalmologists are often faced with the dilemma of choosing appropriate antibiotic prophylaxis for patients undergoing cataract surgery who report a history of penicillin allergy. Their choice may be based on antiquated practice patterns and personal experience, rather than an understanding of current evidence and available options. The decision of whether to withhold intracameral antibiotics, give an intracameral cephalosporin, or to give a non-beta-lactam antibiotic is an area of uncertainty. Each option carries risks and the choice may have medico-legal implications in the event of an adverse outcome. The optimum approach requires the ophthalmologist to evaluate the risks associated with each of the available therapeutic options for their individual patient. Recent findings that impact on this decision include an increasing body of evidence supporting the use of intracameral antibiotic prophylaxis at the time of cataract surgery, the discovery that cross-reactivity between penicillins and cephalosporins is side-chain dependent, emerging safety concerns for intracameral vancomycin, and mounting pressure on all health practitioners to control the development of antibiotic-resistant organisms. We assess the options for antibiotic prophylaxis in cataract surgery in the setting of penicillin allergy and provide an algorithm to assist decision making in this area.

2. BACKGROUND

Cataract surgery is the most commonly performed surgical procedure in many developed countries.⁹ Although post-operative endophthalmitis has become a rare complication of phacoemulsification cataract surgery, with reported incidence rates of 0.02% to 0.04%,^{45, 57} poor functional outcomes can be devastating. In a recent review of 99 cases of acute endophthalmitis post cataract surgery, the final visual acuity was worse than 20/40 in 55%, worse than 20/100 in 30%, and only light perception in 10%.²⁴

Risk factors for post-operative endophthalmitis include withholding intracameral antibiotics, clear corneal incisions, posterior capsule rupture, the use of silicone intraocular lenses, prolonged surgery time, lid margin disease and post-operative wound leak.¹⁴ Preoperative preparation of the periocular region with povidone-iodine and adequate lid draping has been shown to be beneficial to clinical outcome in cataract surgery.²¹ Consequently the use of povidone-iodine or chlorhexidine has been widely adopted. Unfortunately, reaching a similar consensus on antibiotic prophylaxis has not been achieved. Several large studies have helped shape best practice guidelines for perioperative antibiotic prophylaxis,^{31, 37, 45} yet significant variation in antibiotic use persists. Reasons include regional antibiotic availability, commercial availability vs compounding pharmacy preparations, surgeon preference, accepted local standards of care, and an unclear risk-benefit profile in the setting of antibiotic allergy.

The European Society of Cataract & Refractive Surgeons (ESCRS) randomized controlled trial of antibiotic prophylaxis in cataract surgery found that intracameral cefuroxime was associated with a five-fold decrease in the incidence of post-operative culture-positive endophthalmitis compared with no antibiotic prophylaxis on the day of surgery.⁸ This study

served as the basis for the ESCRS practice guidelines that recommended systematic use of intracameral cefuroxime at the time of cataract surgery.⁷ Despite this guideline, antibiotic prophylaxis practice patterns in many European countries diverge from the ESCRS recommendation.⁹ Similarly in North America, a 2014 survey of members of the American Society of Cataract and Refractive Surgery (ASCRS) found that only 26% of respondents gave intracameral cefuroxime at the conclusion of surgery.¹⁷ Surveys in the Asia Pacific region reveal intracameral cephalosporins are routinely given by 28% of ophthalmologists in Singapore,³⁹ 33% of ophthalmologists in New Zealand⁵⁶ and approximately 80% of ophthalmologists in Australia.⁴⁹ It should be noted that both the American Academy of Ophthalmology and the Royal College of Ophthalmologists hold the view that antibiotic use is left to the surgeon's discretion.

Controversy exists not only about the optimal use of intracameral antibiotics, but also whether they should be routinely administered at all. A recent review of nearly 500,000 cataract procedures found an absolute risk reduction for post-operative endophthalmitis of just 0.025%, indicating that 4000 patients would need to receive intracameral cefuroxime to prevent a single case of post-operative endophthalmitis.³⁹ The risk reduction would be expected to be more significant in cases at increased risk of endophthalmitis such as posterior capsule rupture.³⁷ A 2014 editorial suggests that since modern cataract surgery is becoming faster and safer, previous studies on antibiotic prophylaxis struggle to remain relevant with these improving techniques.⁷⁵ Currently, there is no global consensus regarding antibiotic prophylaxis in cataract surgery, but with the growing popularity of intracameral cefuroxime, whether due to medicolegal concerns or the adoption of guidelines, it is important for surgeons to consider available options in the setting of penicillin allergy.

3. PENICILLIN AND CEPHALOSPORIN ALLERGY

Penicillin is the most frequently reported cause of drug allergy, with 5-10% of the general population describing an allergic reaction.^{38, 44, 78} Of relevance to cataract surgeons, this rate of self-reported allergy increases with age.⁵³ Penicillin allergy can include any of the four hypersensitivity reactions described by Gell and Coombs,³² but Type 1 (immediate, IgE-mediated) and Type 4 (delayed, cell-mediated) reactions are most common. Reactions can also be non-immune such as diarrhea and vomiting and superinfections such as candidiasis. Type 4 hypersensitivity reactions to penicillin manifest as a maculopapular skin eruption occurring more than 2 days after exposure.¹⁶ Type I hypersensitivity reactions usually occur within one hour of drug administration. Clinical signs include hypotension, laryngeal edema, wheeze, angioedema, urticaria and anaphylaxis. Despite such frequent self-reporting of penicillin allergy, the number of patients who have a true immune-mediated hypersensitivity reaction is actually only 5-10% of those reporting it.⁸⁴ True anaphylaxis to penicillin occurs in just 0.01% to 0.04% of patients.⁸⁴

Historically, the recommended management of an individual with penicillin allergy has been to avoid the use of cephalosporins completely. This was based on the widespread belief that there was approximately 10% cross-reactivity between penicillins and cephalosporins. Recent studies indicate that the true rate of cross-reactivity between penicillins and

cephalosporins is less than 5%.⁸⁴ One review found that cross-reactivity between penicillins and cephalosporins in individuals who self-reported a penicillin allergy was approximately 1%. In those with confirmed type 1 penicillin hypersensitivity, this figure rose to 2.55%.¹³ The 10% rate of cross reactivity found in early studies is likely attributable to contamination of the study drugs (cephalosporins) with penicillin during manufacturing. An implication of this is that patients reporting cephalosporin reactions occurring over 15 years ago, unless life-threatening, are unlikely to react to the cephalosporins of today.

The rate of cross-reactivity between penicillins and cephalosporins also varies with the type of cephalosporin given. The structural similarities shared by penicillins and cephalosporins include a beta-lactam ring and various side chains. The antibiotics differ in structure of their side chains as well as their degradation pathways.¹ Current opinion is that immunologic cross-reactivity is not incited by the beta-lactam ring, but by similarities between the side chains of cephalosporins and penicillins. This means that patients with documented type 1 hypersensitivity to penicillin may receive cephalosporins with a low risk of having an allergic reaction, provided that the cephalosporin used has a different side chain to that of the penicillin responsible for the allergic reaction.⁶⁵

Meta-analysis of pooled data from 23 studies confirmed that cross-reactivity to cephalosporins is related to side chain similarity. The rates of cephalosporin allergy were assessed in 2400 patients reporting penicillin allergy and a control group of 39,000 patients with no such history. First-generation cephalosporins conferred the highest risk of cross-reactivity. However, the attributable risk was only 0.5%, meaning that the allergy rate was only 0.5% higher in the group with penicillin allergy than in the control group. Second and third generation cephalosporins generally have different side chains to the penicillins, and these agents were not associated with an increased risk of cross-reactivity in patients with penicillin allergy.⁶⁹

Cefuroxime and cephazolin, the most commonly administered intracameral cephalosporins, both have low rates of cross-reactivity to penicillin as a result of their unique side chains.^{13, 70} One prospective study exposed 41 patients with confirmed penicillin allergy to cephazolin, cefuroxime, or ceftriaxone. No patients had an allergic reaction. This study concluded that cross-reactivity is low, provided that the side chain is different to that of the penicillin responsible for the initial allergic reaction.⁶⁵

Unfortunately, ascertaining an accurate past history of penicillin allergy can be difficult. Patients often provide a vague recollection of the type of reaction they suffered, sometimes decades ago. Even in those patients with a documented penicillin allergy, often little detail is recorded about the symptomatology and onset.⁶⁸ One review evaluating how best to determine if a patient is allergic to penicillin found that neither clinical history nor skin prick testing can reliably determine which patients with penicillin allergy will react to a cephalosporin.⁷³ They recommend taking a detailed allergy history, and if this does not indicate a type 1 reaction, then proceed with giving a cephalosporin. A history of a maculopapular rash with penicillin is of no prognostic value as this reaction does not increase the risk of anaphylaxis with repeat exposure and has not been associated with cross-reactivity to cephalosporins.⁸⁴ If clinical history raises concerns about a type 1 hypersensitivity reaction then skin prick testing is recommended. In a standard

ophthalmology clinic without ready access to skin prick testing, this would translate to taking a detailed allergy history focusing on symptom type and speed of onset. Depending on the likelihood of the reported reaction being type 1 hypersensitivity, either a cephalosporin could be given under close supervision or an alternative drug class chosen.

Reported cases of anaphylaxis following intracameral cefuroxime injection are extremely rare;^{60, 85} however, the use of cefuroxime in patients with penicillin allergy remains highly controversial. A survey of ophthalmologists in the United Kingdom indicated that 67% did not consider penicillin allergy a contraindication to intracameral cefuroxime use, while the remaining 33% opted for alternative antibiotic prophylaxis.³⁵ A later study of smaller ophthalmology units in the United Kingdom found that only 37% of surgeons would continue using cefuroxime in the setting of reported penicillin allergy.⁶⁴ This difference in opinion may reflect that ophthalmologists working in smaller centers with reduced access to personnel skilled in resuscitation may be more likely to assess the perceived risk of anaphylaxis as being more problematic than the increased risk of endophthalmitis from withholding intracameral cefuroxime.

4. ANTIBIOTIC OPTIONS

4.1 INTRACAMERAL CEPHALOSPORINS

There is reasonable evidence to state that the current gold standard for antibiotic prophylaxis in cataract surgery is to inject intracameral cefuroxime at the end of the procedure, although the absolute risk reduction in routine cases is small. Legitimate concerns exist about toxicity from preparation error when cefuroxime is prepared by methods other than commercial preparation.²⁵ In the vast majority of surgical cases where intracameral cefuroxime is used, preparation of the injection is performed manually on the day of surgery. This multi-step process has the potential for dilution errors and breaches of sterility that could affect an entire operating list. To the best of our knowledge there is only one commercially available preparation of cefuroxime (Aprokam®, Laboratoires Thea, France). This requires only a single reconstitution and can be used for single cases. Aprokam has been approved for use in over 20 European countries with no reported adverse events in over 1.3 million doses.¹⁷ Intracameral cephazolin also appears to be an effective prophylactic agent, with one study showing a risk reduction of 88.7% to give an endophthalmitis incidence rate of 0.047% with a good safety profile.²⁹

Given the above discussion about the benefits and risks of using cephalosporins in patients reporting penicillin allergy, a reasonable option may be to proceed with using an intracameral cephalosporin. We first need, however, to consider what other options are available and how they compare. In an ideal scenario, patients would have already had blood and skin testing to assess for immunological evidence of hypersensitivity to particular antibiotics. It is more relevant to consider real world scenarios where access to such tests is not feasible or when the patient only states their allergy in the final check of details immediately prior to surgery.

4.2 ORAL PERI-OPERATIVE ANTIBIOTICS

There is currently insufficient evidence to recommend routine use of peri-operative oral antibiotics in standard cataract surgery. A large survey of over 300,000 cataract surgeries showed that the addition of systemic antibiotics did not significantly lower the rate of post-operative endophthalmitis.⁷⁶ Oral fluoroquinolones have been shown to penetrate the anterior chamber of the eye.³⁰ They are often given as initial endophthalmitis prophylaxis following penetrating ocular trauma, and they may therefore have a role in complicated cases of cataract surgery. There are no studies which have looked at bacterial load in human eyes following oral administration of these antibiotics. In general, the use of oral or systemic antibiotics as prophylaxis for endophthalmitis is controversial and not recommended.⁷⁹

4.3 TOPICAL PERI-OPERATIVE ANTIBIOTICS ONLY

Most cases of post-operative endophthalmitis are thought to be from the patient's own conjunctival flora, and therefore many of the prophylactic measures routinely used are aimed at reducing ocular surface bacteria.⁶⁷ Topical peri-operative antibiotics in the form of chloramphenicol, ofloxacin or gatifloxacin eye drops do not appear to provide additional risk reduction in preventing endophthalmitis when patients have received intracameral antibiotics.⁷¹ This is helpful in reducing cost and additional tasks for the patient, but what about for patients who have not received intracameral antibiotics? There is certainly evidence that post-operative endophthalmitis rates with topical treatment alone are low. Using fourth generation topical fluoroquinolones immediately pre-operatively along with routine post-operative use resulted in an incidence rate of endophthalmitis of 0.07% in over 20,000 cases in one retrospective review.⁶² This rate compares favourably to those described in the landmark ESCRS study where the incidence of endophthalmitis without any antibiotic prophylaxis was 0.345%, and the group receiving 5 drops of topical levofloxacin (third generation fluoroquinolone) on the day of surgery had an endophthalmitis rate of 0.247%.⁸ The use of topical antibiotic in the days prior to surgery remains controversial as it has been shown that one drop of 5% povidone-iodine is equivalent to topical antibiotic (Neosporin®) used three times a day for 3 days in reducing ocular surface flora.²

A large database review of over 300,000 cataract procedures found that topical gatifloxacin (fourth generation fluoroquinolone), ofloxacin (second generation fluoroquinolone), and polymyxin/ trimethoprim were all more effective than giving no antibiotic prophylaxis, with endophthalmitis incidence reduced by approximately half. Topical aminoglycosides, however, were no better than using no antibiotic at all.⁴² Fluoroquinolones provide slightly better coverage against both Gram-positive and Gram-negative bacteria than chloramphenicol, and fourth generation fluoroquinolones have excellent ocular penetration, although overall, chloramphenicol exhibits similar resistance patterns as first and second generation fluoroquinolones.⁸¹

If topical antibiotic drops are going to be used as monotherapy, a retrospective cohort study of 1525 eyes indicates that they should be given frequently (every one to two hours on the day of surgery), starting after four hours of patching rather than waiting until the first post-operative day.⁸⁶ This same study indicated that ciprofloxacin (second generation fluoroquinolone) was inferior to ofloxacin in preventing endophthalmitis, which is consistent

with the ability of ofloxacin to penetrate the anterior chamber four times more readily than ciprofloxacin.¹⁵ In a recent editorial, Olsen proposes that the known and expected increased risk of endophthalmitis with wound leak⁸⁶ may be due to high intracameral antibiotic concentration preventing infection immediately after surgery, but dropping to sub-therapeutic levels by day one when a leaking wound may allow influx of bacteria.⁶⁶ Whether this rate of endophthalmitis with a leaking wound would be lower with frequent topical drops compared to intracameral antibiotics has not been answered, but is logical if organisms are entering from the conjunctival sac.

It would appear from this evidence that the optimal use of topical antibiotic drops alone would be to use a fourth generation fluoroquinolone frequently, beginning on the day of surgery. The downside of this management technique would be very real concerns about creating resistant organisms;²⁸ however, judicious use only in patients with a reliable history of penicillin anaphylaxis would mean that few patients were exposed to this regimen and the risk of creating resistant organisms could be minimized.

4.4 SUBCONJUNCTIVAL ANTIBIOTIC

The use of subconjunctival antibiotic has declined since the release of the ESCRS guidelines, but it continues to be used by many surgeons, especially in the United Kingdom.³⁵ There is plenty of retrospective evidence of endophthalmitis rates being reduced by administration of subconjunctival antibiotics.⁵² A large review of 50,177 cataract surgeries showed the incidence rate of endophthalmitis to be 0.064% when subconjunctival cephazolin was used. This seems impressive; however, that rate was further decreased to just 0.01% following a change to intracameral cephazolin.⁸³ Similarly, a non-randomized retrospective cohort study found a threefold decrease in the rate of endophthalmitis with cefuroxime injected intracamerally instead of subconjunctivally.⁹⁰ Clearly the intracameral route provides additional prophylaxis against endophthalmitis when compared to subconjunctival administration of the same drug.

Compared with the intracameral route, the subconjunctival route is theoretically more likely to trigger a severe allergic reaction in a sensitised patient owing to the abundance of conjunctival associated lymphoid tissue, mast cells, and lymphatic vessels. The magnitude of this increased risk is difficult to quantify for such a rare event as anaphylaxis, but an anaphylactic reaction has been reported after 50mg of cephazolin was injected into the subconjunctival space in a patient with penicillin allergy.¹⁰ One study assessed 36 patients with penicillin allergy and found no adverse effects after subconjunctival cefuroxime injection, consistent with the fact that the rate of immunological cross-reactivity is low.⁵⁹ It should be noted that although the anterior chamber is an immune-privileged site, antigens injected into the anterior chamber also drain to pre-auricular and submandibular lymph nodes, and the phenomenon of anterior chamber-associated immune deviation does not offer protection against a type 1 hypersensitivity reaction since the systemic immunoregulatory response to intracameral antigen takes at least one week to develop.²² Any difference in allergy risk between the intracameral and subconjunctival routes is therefore likely to be small.

When a subconjunctival alternative to a cephalosporin is used, as may be the case in the setting of penicillin allergy, it is frequently gentamicin that is chosen.³⁴ This is despite awareness of its conjunctival toxicity, patient discomfort⁴⁷, toxic myopathy of the extraocular muscles,³⁶ and the potential for intraocular spill-over and retinal toxicity.⁵⁵ One practice made attempts to reduce their baseline endophthalmitis rate from 0.63% using povidone-iodine alone by adding subconjunctival gentamicin. This did not reduce the rate of post-operative endophthalmitis on their service.⁷²

Overall, the subconjunctival route for antibiotics in the setting of penicillin allergy has benefit over not using any antibiotic, and if a cephalosporin is used, the risk of anaphylaxis is similarly small. The additional benefit given by intracameral injection, however, indicates that if the risk is to be taken by giving a cephalosporin, the risk to benefit ratio is in favour of administering it to the anterior chamber. Subconjunctival gentamicin does not compare as a good option because of its side-effect profile.

4.5 INTRACAMERAL VANCOMYCIN

A retrospective, Australian study found an impressive reduction (from 0.43% to 0.049%) in the incidence of post-operative endophthalmitis when intracameral vancomycin was introduced.⁵ Vancomycin has been shown to persist in the anterior chamber at a bactericidal level for over 32 hours after a bolus injection, which may account for this effect.⁶³ In vitro studies show it to be more effective than fourth generation fluoroquinolones against coagulase-negative staphylococci species, which are the most common isolates from endophthalmitis samples.⁴¹ Vancomycin is highly effective against all Gram-positive bacteria including the most common causes of post-cataract surgery endophthalmitis, *Streptococcus* and *Staphylococcus* species. It is also the most effective antibiotic against the increasingly common methicillin resistant staphylococcus aureus (MRSA).¹² It is, however, ineffective against Gram-negative bacteria. This spectrum of action seems acceptable given that the Endophthalmitis Vitrectomy Study found only 6% of post-operative endophthalmitis was caused by Gram-negative organisms.⁴⁰ However, recent reports suggest an increasing incidence of Gram-negative endophthalmitis²⁰ and the most common causative gram negative organism, *Pseudomonas aeruginosa*, is associated with poor visual outcomes.²⁷

Meta-analysis of intracameral antibiotic use in cataract surgery based on non-randomized studies found that the risk of endophthalmitis was significantly lower in patients treated with intracameral cephazolin, cefuroxime and moxifloxacin, whereas no significant effect was found for intracameral vancomycin. The relative risk (RR [95% confidence interval]) of endophthalmitis was reduced to 0.10 (0.06-0.17) in patients receiving cephazolin, 0.09 (0.05-0.15) in patients receiving cefuroxime, 0.22 (0.10-0.50) in patients receiving moxifloxacin and 0.30 (0.02-3.90) in patients receiving vancomycin.⁵⁰ The quality of evidence for vancomycin use was low or very low so these results must be interpreted with caution.

Intracameral vancomycin has been shown to increase the risk of cystoid macular edema (CMO) after cataract surgery.⁶ Historically reserved for infections recalcitrant to other

agents, vancomycin has long been considered the first-line treatment of endophthalmitis. This raises questions about its appropriateness as a prophylactic agent in the era of increasing antibiotic resistance. This, along with the lack of definitive evidence for its efficacy in reducing post-operative endophthalmitis, lead to the US Centers for Disease Control and Prevention discouraging its routine use as perioperative prophylaxis in ophthalmic surgery.²³ Despite these potential concerns, intracameral vancomycin is commonly used and is supported by anecdotal evidence from eminent surgeons including Richard Mackool, who has stated that at his institute not a single case of endophthalmitis occurred in 80,000 consecutive cataract surgeries using intracameral vancomycin.⁸⁹

More recently, an emerging association between vancomycin and haemorrhagic occlusive retinal vasculitis (HORV) is expected to discourage its routine use in ophthalmic surgery.^{58, 88} The mechanism of HORV is uncertain but it is suspected to be a delayed-onset type 3 (immune complex) hypersensitivity reaction, analogous to an ophthalmic variant of vancomycin-induced leukocytoclastic vasculitis.¹⁸ HORV can occur on first exposure to vancomycin (it does not require previous sensitisation) and vancomycin skin-prick testing is normal as HORV is not a type 1 or type 4 hypersensitivity reaction.⁸⁸ It presents as a diffuse occlusive retinal vasculitis 1-14 days post-operatively, associated with minimal vitritis and anterior uveitis. This can help to distinguish it from infectious endophthalmitis.⁴³ Visual outcomes are typically poor and episodes are frequently followed by rapid neovascularisation of the iris and angle.⁸⁸ It is suspected that mild variants of HORV may exist and that the condition is under-recognised.⁵⁸

In a patient with penicillin allergy, intracameral vancomycin has many benefits. Evidence about its efficacy is disputed but theoretically and anecdotally, it appears to be highly effective. Emerging concerns about HORV will likely deter its routine use but for the patient with documented penicillin anaphylaxis undergoing unilateral cataract surgery, intracameral vancomycin represents a strong option. If vancomycin is given, it is prudent to defer surgery on the fellow eye by at least two weeks to ensure the patient does not mount a HORV response.

4.6 INTRACAMERAL MOXIFLOXACIN

Moxifloxacin is a fourth-generation fluoroquinolone antibiotic that is rapidly active against a broad spectrum of Gram-positive and Gram-negative bacteria and atypical microorganisms.⁸⁰ This provides broader cover than the previously mentioned agents and accordingly, a large retrospective database review found that intracameral moxifloxacin was as effective as intracameral cefuroxime in preventing endophthalmitis.⁴² No anterior segment toxicity has been found with its intracameral use.²⁶ The results of a smaller retrospective study concluded that the self-preserved ophthalmic formulation of moxifloxacin can be safely injected intracamerally without adverse effects on any patient-oriented outcomes.⁹¹ This removes the concern about toxicity and dosing errors inherent with having to reconstitute other antibiotics.

While there is excellent safety data for intracameral moxifloxacin, there is less information about its efficacy in preventing endophthalmitis. One study from Japan found an incidence

of endophthalmitis of 1 in 6265 cases with use of undiluted intracameral moxifloxacin. The incidence in the group that did not receive intracameral moxifloxacin was one case in 1955 surgeries, indicating a three-fold decrease in the incidence of endophthalmitis.⁵⁴ The endophthalmitis case in the moxifloxacin administration group responded well to a single intravitreal injection of vancomycin and ceftazidime. A much larger, multicenter analysis predominately from North America found an endophthalmitis incidence of just 1 in 35 000 cases who received intracameral moxifloxacin though this was for bilateral sequential surgery, indicating that higher risk cases were probably excluded from analysis.³

Allergy to fluoroquinolones is rare but cross-reactivity between generations does occur, meaning that moxifloxacin should be avoided in the rare instances when a patient is allergic to other fluoroquinolones.³³ In penicillin-allergic patients, moxifloxacin is often the chosen alternative to a cephalosporin. To the best of our knowledge, there have been no reported cases of allergy to intracameral moxifloxacin.

As is the case with vancomycin, there are concerns that routine use of moxifloxacin will lead to resistance and ultimately the loss of efficacy of what is currently considered an excellent, broad spectrum antibiotic. Bacteria are theoretically less likely to develop resistance to fourth generation fluoroquinolones because of the dual targeting of DNA gyrase and topoisomerase IV¹¹ requiring a double mutation to neutralise. One retrospective review of endophthalmitis cases, including post cataract surgery, observed that there was an apparent lack of efficacy of conventionally used antibiotics, including the fourth-generation fluoroquinolones with an emergence of increasingly resistant strains of bacteria.⁴ While this cannot be taken as evidence of developing resistance through overuse of fluoroquinolones, it is concerning for their ongoing efficacy.

In a patient with penicillin allergy, intracameral moxifloxacin has many appealing features. It can be injected undiluted from a commercial preparation; it is non-toxic to the eye and appears effective in preventing endophthalmitis. The level of evidence is lower compared to that for intracameral cefuroxime but it weighs up as a viable alternative in many respects.

4.7 ANTIBIOTICS IN THE IRRIGATING SOLUTION

As there is no proof of any additional benefit of adding antibiotic to the irrigation solution during cataract surgery, and there appears to be no significant advantage to using antibiotic in the irrigating solution during cataract surgery compared to intracameral injection, the practice is discouraged by the American Academy of Ophthalmology and not recommended by the European Society of Cataract and Refractive Surgeons. Intracameral antibiotic concentrations are much lower when added to the irrigating fluid compared to direct injection. This is important for concentration dependent microbial activity. Retinal toxicity is a potential problem with continuous irrigation of certain antibiotics. It is also difficult to assess how much antibiotic exposure (and antibiotic-microbe contact time) actually occurs during a case with the only steady state that can be achieved being the low concentration of antibiotic remaining in the anterior chamber at the end of the case.

One small, underpowered study did find a reduced rate of post-operative endophthalmitis when they added vancomycin and gentamicin to their irrigating solution and compared this

with cases using balanced salt solution alone. There were no cases of endophthalmitis in 322 surgeries of the treatment group compared to two cases of endophthalmitis in 322 surgeries in the balanced salt solution alone group. The small sample size for a rare outcome produced wide confidence intervals and the result was not statistically significant.⁷⁷ Another study found a significant reduction ($p = 0.0015$) in post-cataract endophthalmitis when they switched from plain balanced salt solution to the balanced salt solution with added vancomycin for hydrating incisions and pressurizing eyes at the end of cases. They did however, maintain their standard of having vancomycin in the irrigating solution during surgery for all cases.⁷⁴

4.8 ANTIBIOTIC INJECTION INTO THE VITREOUS

The anterior chamber is able to clear some post-operative microbial contamination without developing into endophthalmitis. Vitreous, however, may act as a culture medium for microbial growth. Given that there is strong evidence for the benefits of intracameral antibiotic injection at the conclusion of cataract surgery, one potential next step at attempting to reduce the risk of endophthalmitis is to deliver antibiotics more posteriorly, either via a trans-zonular or pars-plana route. Placing drugs in the vitreous would potentially lengthen their half-life and prolong their prophylactic effects.

The trans-zonular route of injection is performed prior to final removal of visco-elastic. One major concern is possible damage to structures including the ciliary body or zonules causing de-stabilization of intraocular lenses. Another is disruption of the anterior hyaloid face with potential for subsequent retinal tears and detachments. The pars-plana route is a more familiar procedure as it is similar to administering intravitreal injections to treat macula degeneration. Similar risks to these injections exist including haemorrhage, retinal tears and detachment.

A recent modification to these techniques has been the use of combination steroid-antibiotic compounds injected at the conclusion of surgery. In addition to potentially reducing endophthalmitis risk, injection could avoid compliance issues with post-operative drops and decrease post-operative inflammation. The downsides of delivery of these combination medications to the vitreous cavity include post-operative floaters with decreased day-one visual acuity as well as concerns about raised pressure with steroid responsive patients.

4.9 FUTURE DIRECTIONS

With the growing popularity of cataract surgery, companies are working on new techniques, IOL properties and innovative drug delivery systems to make surgery safer and more efficient for both the surgeon and the patient. Injectable IOLs have been shown to be associated with a lower incidence of post-operative endophthalmitis compared to folded IOLs inserted using forceps.⁸⁷ Pre-loaded, injectable IOLs have been shown to significantly reduce operating time and lens handling compared to manually loaded, injectable IOLs.⁴⁸

Reduced potential contact with conjunctival flora and reduced operating time should presumably lead to even lower incidence rates of endophthalmitis. Hydrophilic acrylic IOLs soaked in fluoroquinolone have been shown to provide effective and safe levels of intraocular antibiotic for up to 16 hours after implantation.⁵¹ This would protect the eye from endophthalmitis-causing organisms in the initial post-operative period when sutureless corneal wounds may be susceptible to influx.⁸²

Slow release systems eluting levofloxacin or moxifloxacin are in development. Initial studies of a moxifloxacin punctum plug that can be inserted after cataract surgery have shown promise. Preliminary results showed 100% retention through day 10, with maintained tear fluid levels above the minimum inhibitory concentration required to inhibit the growth of 90% of common susceptible pathogens without adverse events.¹⁹

5. DISCUSSION

Given that both post-cataract surgery endophthalmitis and penicillin anaphylaxis are rare, determining a definitive, evidence-based protocol for antibiotic prophylaxis is inherently difficult. The best that a surgeon can do is to keep abreast of available evidence and make an informed decision in the best interest of each individual patient. The decision will be influenced by local antibiotic availability and the reliability of antibiotic preparation methods as well as legal considerations of either withholding intracameral antibiotics or administering new and potentially off-label routes of drug administration. The accompanying algorithm (Figure 1) outlines our current practice for antibiotic prophylaxis.

Given the rarity of penicillin anaphylaxis, and the low rate of cross-reactivity to cefuroxime and cephazolin, we feel that current evidence supports administering intracameral cefuroxime if the history of penicillin allergy is considered to be low risk or in any way questionable. One study group co-administered an oral antihistamine in this scenario and reported no allergic reactions.⁶¹ This could be considered an adjunctive measure although the additional benefit is questionable. Cephazolin could be substituted for cefuroxime according to local availability and compounding methods.

When there is a more definite history of penicillin allergy, it may still be reasonable to administer intracameral cefuroxime, as it still stands that the likelihood of cross-reaction is very small. However, surgeons may consider that even a remote chance of anaphylaxis is unacceptable, especially if cataract surgery is performed without the assistance of an anaesthetist. In considering a next best alternative to cephalosporins, the decision can be broken down according to drug and route of administration.

Despite there being few prospective studies looking at antibiotic prophylaxis in cataract surgery, the volume of evidence in favour of intracameral antibiotics is becoming vast. As one recent editorial stated, published studies representing more than 1.3 million patients in whom topical antibiotics were associated with a 2.66 times greater incidence of post-operative endophthalmitis than were intracameral antibiotics.⁴⁶ The intracameral route is also more convenient and cheaper for the patient.

Vancomycin and moxifloxacin are the most frequently used intracameral antibiotics after cefuroxime. Of these agents, moxifloxacin appears to have a greater benefit-to-risk profile than vancomycin. There are no formulation concerns, it is highly effective and there is no known risk of HORV. For these reasons, intracameral moxifloxacin is our preferred prophylactic agent in patients with a convincing history of penicillin anaphylaxis.

Availability of all of these medications varies worldwide. If cephalosporins are avoided due to penicillin allergy and moxifloxacin (to be used either intracamerally or topically) is not available, intracameral vancomycin could be considered. However, until the risk of HORV is better defined our practice will be to avoid intracameral vancomycin. In this scenario, topical agents should be considered and we recommend the use of ofloxacin drops. Ideally, they should be given frequently following pad removal on the day of surgery. Practically, we recommend waiting to instil topical antibiotics until after return of corneal sensation and an adequate blink reflex to avoid accidental injury to the eye from either the bottle or following replacement of a pad covering an anaesthetic cornea. This would be expected to occur relatively earlier when surgery is performed under topical anaesthesia and may be delayed until the first post-operative day with regional anaesthetic blocks.

6. CONCLUSION

A large number of factors must be considered when choosing antibiotic prophylaxis in patients with penicillin allergy. Evolving safety and efficacy data for many commonly used agents as well as limited numbers of randomised, prospective studies makes this area of decision making both dynamic and complex. Having to make important decisions in the operating theatre can be stressful and therefore we encourage ophthalmologists to develop a protocol that is appropriate for their work environment, local antibiotic availability and accepted standards of care. We hope this review serves as a framework to guide this process and recommend that each surgeon makes their own decision individually about antibiotic prophylaxis in cataract surgery for each of their patients.

7. LITERATURE SEARCH

A literature search was conducted in November 2016 using the MEDLINE and EMBASE databases. The search was performed on all fields using the search terms 'antibiotic', 'prophylaxis', 'cataract', 'phacoemulsification', and 'endophthalmitis'. Reference lists of cited publications were examined to find additional articles of relevance. A few select articles published before 1990 are included for historical purposes, but the review is based mainly on articles published in the past decade. We included case reports in some sections as we were reporting on rare complications without case series or larger studies available.

8. DISCLOSURES

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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