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The Use of Preoperative Prophylactic Systemic Antibiotics for the Prevention of Endopthalmitis in Open Globe Injuries

A Meta-Analysis

Tim J. Patterson, MB,[1] David McKinney, MB,[1] Jonathan Ritson, FRCEM,[2,3] Chris McLean, FRCS,[4] Weidong Gu, MD,[5] Marcus Colyer, MD,[6] Scott F. McClellan, MD,[5] Sarah C. Miller, BA,[7] Grant A. Justin, MD,[6,8] Annette K. Hoskin, FRANZCO,[9,10] Kara Cavuoto, MD,[11] James Leong, FRANZCO,[9,12] Andrés Rousselot Ascarza, MD,[13] Fasika A. Woreta, MD,[7] Kyle E. Miller, MD,[6,14] Matthew C. Caldwell, MD,[15] William G. Gensheimer, MD,[16,17] Tom Williamson, FRCOphth,[18] Felipe Dhawahir-Scala, FRCOphth,[19] Peter Shah, FRCOphth,[20,21] Andrew Coombes, FRCOphth,[22] Gangadhara Sundar, FRCSEd,[23] Robert A. Mazzoli, MD,[6] Malcolm Woodcock, FRCOphth,[24] Ferenc Kuhn, MD,[25] Stephanie L. Watson, FRANZCO,[12] Renata S. M. Gomes, PhD,[26,27] Rupesh Agrawal, MD,[28,29,30,31] Richard J. Blanch, FRCOphth[21,32,33,34]

Topic: This study reports the effect of systemic prophylactic antibiotics (and their route) on the risk of endophthalmitis after open globe injury (OGI).

Clinical Relevance: Endophthalmitis is a major complication of OGI; it can lead to rapid sight loss in the affected eye. The administration of systemic antibiotic prophylaxis is common practice in some health care systems, although there is no consensus on their use.

Methods: PubMed, CENTRAL, Web of Science, CINAHL, and Embase were searched. This was completed July 6, 2021 and updated December 10, 2022. We included randomized and nonrandomized prospective studies which reported the rate of post-OGI endophthalmitis when systemic preoperative antibiotic prophylaxis (via the oral or IV route) was given. The Cochrane Risk of Bias tool and ROBINS-I tool were used for assessing the risk of bias. Where meta-analysis was performed, results were reported as an odds ratio. PROSPERO registration: CRD42021271271.

Results: Three studies were included. One prospective observational study compared outcomes of patients who had received systemic or no systemic preoperative antibiotics. The endophthalmitis rates reported were 3.75% and 4.91% in the systemic and no systemic preoperative antibiotics groups, a nonsignificant difference ($P = 0.68$). Two randomized controlled trials were included (1555 patients). The rates of endophthalmitis were 17 events in 751 patients (2.26%) and 17 events in 804 patients (2.11%) in the oral antibiotics and IV (± oral) antibiotics groups, respectively. Meta-analysis demonstrated no significant differences between groups (odds ratio, 1.07; 95% confidence interval, 0.54−2.12).

Conclusions: The incidences of endophthalmitis after OGI were low with and without systemic antibiotic prophylaxis, although high-risk cases were excluded in the included studies. When antibiotic prophylaxis is considered, there is moderate evidence that oral antibiotic administration is noninferior to IV.

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Open globe injury (OGI) is defined as any injury with a full-thickness wound of the external layers of the eye.[1] It is an ophthalmic emergency and a common cause of preventable unilateral blindness worldwide, especially in the young, with an estimated yearly incidence of 4.49 per 100 000 people in the United States population.[2] Management of this sight-threatening condition aims to restore globe integrity and conserve vision. One of the major and potentially severe complications of OGI is endophthalmitis, defined as intraocular infection, with a reported incidence between 0% and 16.5% in prior observational studies.[3]

Causative agents of this exogenous infection include ocular surface and eyelid margin commensal organisms and pathogenic bacteria and fungi from penetrating wounds and

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intraocular foreign bodies. Multiple observational studies have reported both gram-positive, negative, and fungal species.[3,4] Increased endophthalmitis risk is associated with the presence of retained intraocular foreign bodies (IOFB), injuries sustained in rural environments (containing soil or vegetation matter), lens capsule violation, and delayed wound closure.[5] In the developing world, with a proportionally higher prevalence of heavy industry and agricultural sector employment, these risk factors are increased.[6]

The management of endophthalmitis after OGI depends on diagnostic aqueous and vitreous tap, and intravitreal antibiotic administration with or without therapeutic vitrectomy.[2] Even with appropriate management, post-OGI endophthalmitis is associated with poor visual outcomes.[3]

Systemic antibiotic prophylaxis has been associated with a low rate of post-OGI endophthalmitis in several retrospective observational studies. For example, in a military setting with delayed (median, 21 days) IOFB removal, systemic antibiotics (fluroquinolones) in a 79 military patient case series had a 0% endophthalmitis rate reported.[7]

Various routes of antibiotic administration have been trialed, including systemic, topical, subconjunctival, and intravitreal routes.[3] Intraocular and subconjunctival/periocular administrations of medication are ophthalmic surgical skills, not routinely taught outside of ophthalmology specialist training and only administered after primary repair, and so administration may be delayed in environments with limited medical capacity such as the developing world or military deployments.

Systemic antibiotic prophylaxis is likely to reduce the growth and survival of organisms contaminating OGI and therefore reduce the rate of posttraumatic endophthalmitis.

Preoperative systemic antibiotic prophylaxis is a potentially important intervention to reduce the rate of endophthalmitis after OGI, but is routinely administered by only 76% of international eye trauma centers.[8] A systemic review and meta-analysis will support guidelines to reduce unnecessary variation in practice.

The object of this meta-analysis is to report the incidence of posttraumatic endophthalmitis when preoperative systemic prophylactic antibiotics are administered. Subgroup review focused on endophthalmitis rate depending on route of systemic administration and choice of antibiotic.

Methods

This systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] A review protocol was registered with the PROSPERO systematic review database (registration number CRD42021271271).[10] The research was evidence synthesis only with no human subject involvement.

Two modifications to the registered protocol (edit: September 2021) have been actioned. The first is the inclusion of prospective observational studies along with randomized controlled trials (RCTs). Second, data extraction and bias assessment have been carried out by 3 reviewers, as opposed to 2, as proposed in the original protocol.

Inclusion Criteria

Studies on patients who had sustained an OGI (as defined by Kuhn et al[1]) were eligible. Prospective studies that reported the rate of post-OGI endophthalmitis, when systemic antibiotic prophylaxis was and was not given, were included. Only papers published in indexed medical journals were included (conference abstracts were excluded). There was no limitation placed on language, geographical area of origin, or year of publication. Exclusion criteria were the administration of intraocular or subconjunctival prophylactic antibiotics at time of primary procedure so as to isolate the effect of preoperative systemic antibiotics on endophthalmitis rate. This was completed July 6, 2021 and updated December 10, 2022; there were no limitations on years searched.

Search Strategy

Five databases: PubMed, CENTRAL, Web of Science, CINAHL, and Embase were searched together with handsearching of reference lists to identify additional studies. Search strings are contained in the Annex A (available at www.ophthalmologyretina.org).

Risk of Bias Assessment

Three authors (T.J.P., D.M., J.R.) independently assessed the potential bias in RCTs using the Cochrane Collaboration bias (RoB2) tool.[11] Risk of bias in non-RCTs was analyzed using the ROBINS-I tool.[12]

Statistical Methods

The primary outcome was incidence of endophthalmitis, presented as crude rate. Secondary outcome measures included subgroup analysis of endophthalmitis rate depending on route of systemic administration, with crude rates being reported, and, after meta-analysis, odds ratio.

Three independent reviewers (T.J.P., D.M., R.J.B.) individually each reviewed all titles retrieved from the initial search. Duplicates were eliminated, and, if possible, using the abstracts available, each reviewer made a decision on its inclusion. If the paper could not be included or excluded with certainty on the basis of the abstract, then the full text was read. Any disagreements between reviewers on papers' eligibility were resolved by discussion, or, if necessary, arbitration by a senior author (R.J.B.). If a study had been reported by >1 publication, the last publication was used as the reference publication in this review. The included study's reference and citation lists were examined for additional studies which may have met inclusion criteria.

Data were extracted by 3 reviewers working independently, with disagreements resolved by discussion. The following variables were recorded: study information (first author, publication year, study design, and country of origin), participant information (total patients, sex, age range, and median age), intervention information (antibiotic administered, route of administration) and follow-up information (mean and median follow-up duration, planned follow-up period, and how many study participants completed follow-up).

The following outcome data were sought: number of cases of endophthalmitis per total sample. If unpublished information was required then individual study authors were contacted with a maximum return contact period of 30 days.

Meta-analysis was performed for rates of endophthalmitis and for each subgroup analysis when there were ≥ 2 RCTs which examined the same antibiotic route of administration.

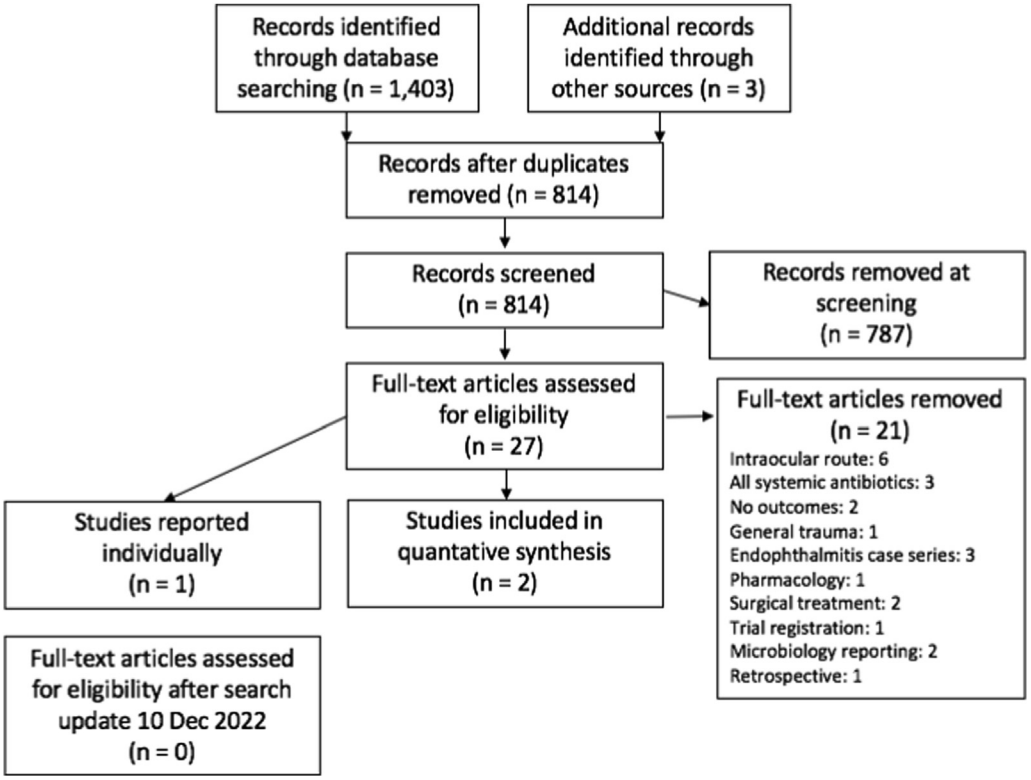

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. A total of 2 studies were included in the end quantitative synthesis and 1 study was individually reported.

The Review Manager 5 (The Nordic Cochrane Centre) software was used for results synthesis.[12] The primary summary measure (rates of endophthalmitis) of the meta-analysis was given as the odds ratio, with 95% confidence intervals (CIs). Statistical heterogeneity between studies was checked and reported using the I^2 measure of study heterogeneity. If heterogeneity (I^2) was $>$ 50%, a random effects model was used. Studies in which meta-analysis displayed a heterogeneity of $>$ 75% were excluded.[13,14]

In the case of a zero-cell count for any given event, Review Manager 5 software automatically added a 0.5 continuity correction. Only studies in which the majority (4 or more) of areas of potential bias were low risk were analyzed.

Confidence intervals for the difference in proportions were estimated in in R Core Team (2021; R: A language and environment for statistical computing, R Foundation for Statistical Computing), by generating 5000 bootstrap samples.[15]

The strength of evidence presented was assessed using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.[16]

Results

Results of Searches

Two randomized prospective studies (both RCTs), with unique populations, met inclusion criteria.[17,18] One nonrandomized prospective study additionally met inclusion criteria.[19] A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search results is presented in Figure 1.

The included prospective studies contributed 1805 patients, of which 1798 patients were included in this analysis. Seven patients from Essex's 2004 study did not have systemic treatment data recorded. Lengths of follow-up were 1 week,[17] 6 weeks,[18] and a median of 51 weeks.[19] Study details are included in Table 1.

The search was updated on December 10, 2022; no additional studies were added.

Characteristics of Included Studies

Patient characteristics are presented in Table 2. When the 3 studies were pooled, 1356 (75.2%) of patients were male. Mean age ranged from 36.3 (standard deviation, 12.6) to 46 (standard deviation, 19.9) years. Du Toit et al[17] used the Birmingham Eye Trauma Terminology and the Ocular Trauma Score in the description of patient injuries.[1] Tabatabaei et al[18] described injuries using both zones of injury, and through subdivision into blunt versus sharp and IOFB versus non-IOFB injuries.[1] Essex et al[19] separated mechanism of injury from presence of IOFB.

Du Toit et al[17] excluded patients assessed to be at high risk of developing exogenous endophthalmitis after OGI by exclusion of patients with IOFBs, those with wounds caused by a contaminated object, or those injured in a rural setting with organic matter. Tabatabaei et al[18] excluded patients with prior ophthalmic surgery, immunosuppression (including diabetes mellitus), and time between index injury and primary surgery of $>$ 24 hours. Essex et al[19] excluded patients who underwent primary enucleation within 24 hours of index injury, and those

Table 1. Study and Patient Characteristics of Included Studies

Author, yr	Country	Males / Females	Study Inclusion Criteria	Study Exclusion Criteria	Number of Patients Included in this Analysis	Length of Follow-Up	Study Design
Essex et al,[19] 2004	Australia	203/46	All patients admitted with OGI between 1st January 1998 and 31st December 2000 to RVEEH.	Primary enucleation within 24 hrs of injury. Posterior globe rupture or rupture at the rectus muscles without conjunctival breach.	243	Median 51 wks	RCT
Tabatabaei et al[18] 2016	Iran	923/332	Consecutive patients admitted with OGI between January 2011 and May 2013 to FEH. 18 yrs or older. 1 injured eye only.	Prior ophthalmic surgery. Immunosuppression. Time from index injury to primary surgery > 24hrs.	1255	1 wk	RCT
Du Toit et al[17] 2017	South Africa	230/70	Consecutive patients admitted with OGI between April 2012 and October 2014 to GSH. Adult patients.	IOFB. Injury in rural setting. Contaminated causative object.	300	6 wk	Prospective, nonrandomized

FEH = Farabi Eye Hospital (Tehran, Iran); GSH = Groote Schuur Hospital (Cape Town, South Africa); IOFB = intraocular foreign body, NA = not applicable; OGI = open globe injury; RCT = randomized controlled trial; RVEEH = Royal Victoria Eye and Ear Hospital (Melbourne, Australia).

OGIs without direct communication with the environment (posterior ruptures or ruptures at rectus muscle insertions without breach of the conjunctiva).

Risk of Bias in Included Studies

An individual risk of bias analysis, using the Cochrane RoB2 tool, for each RCT is in Table 3. Tabatabaei et al[18] did not report the randomization process, and none of the studies reported masking (blinding). Some concerns were highlighted regarding Tabatabaei's outcome data, as a total of 1255 patients were reported to have completed follow-up, yet the sum of trauma subtypes reported was 1254.[18] The sum of patients' sex, presence or absence of IOFB, and presence or absence of relative afferent pupillary defect was reported as 1255.

An individual risk of bias analysis, using the Robins-I tool, for the included non-RCT, is also presented in Table 3. Risk of bias due to confounding was assessed as moderate risk as preoperative topical antibiotics were also used.[19] Bias in classification of interventions was assessed as moderate risk, as we are unable to tell from the presented data if a patient receiving preoperative antibiotics or not was determined by the mechanism of injury or perceived injury severity.[19] Bias due to deviations from intended interventions was assessed as moderate risk, as we do not know the balance of patients who also received topical preoperative antibiotics between the 2 groups assessed in this study.[19]

Endophthalmitis Rates

In the nonrandomized study, which reported endophthalmitis rates when systemic and no systemic antibiotics were given, the rates reported were 3.75% (3/80 patients; 95% CI, 0.78−10.6%) and 4.91% (8/163 patients; 95% CI, 2.14−9.44%) respectively, a nonsignificant difference ($P = 0.68$; chi-square, 0.166; degrees of freedom, 1; 95% CI, −6.1%−4.4%).[19]

Two prospective trials were included (1555 patients). Both these trials reported rates of endophthalmitis in randomized groups comparing patients administered oral versus IV (± oral) prophylactic antibiotics. There was an overall rate of 34 events in 1555 patients (2.19%; 95% CI, 1.52%−3.04%).[17,18] When the data for patients receiving systemic preoperative antibiotics from the nonrandomized study were added, then a rate of 51 events in 1798 patients (2.84%; 95% CI, 2.12%−3.71%) was observed.[17−19]

Subgroup Analysis of Antibiotic Delivery Route

The rates of endophthalmitis were 17 events in 751 patients (2.26%) and 17 events in 804 patients (2.11%) in the oral antibiotics and IV (± oral) antibiotics groups, respectively.[17,18] Meta-analysis found no evidence of a difference between groups. A forest plot of this analysis is presented in Figure 2.

The antibiotic regimens in the studies varied. Du Toit et al[17] employed IV cefazolin and oral ciprofloxacin in the mixed-route group and oral cefuroxime and ciprofloxacin in the oral group. Tabatabaei et al[18] used ceftazidime and vancomycin in the IV-administration group and ciprofloxacin as the oral-administration routine.[18] Essex et al[19] did not report the antibiotics used in preoperative prophylaxis.

Table 2. Patient and Injury Characteristics in Included Studies

Author and yr	Age (yrs), Mean / Median ± SD	Injury Classification (n = Number of Eyes)	Antibiotics Used	Microbiology Cultured in Endophthalmitis Cases
Du Toit et al[17] 2017	38.2 (IV and PO group) ± 12.6 and 36.3 (PO route) ± 14.8	BETT terminology was recorded for all patients: Rupture: 69 Penetrating: 228 Perforating: 2 Mixed groups: 1 OTS Score Min: 27 Max: 100 Mean: 63.0	IV and PO group: Cefazolin (1g, IV, 8 hourly for 3 days) and Ciprofloxacin (750mg, PO, 12 hourly, for 3 days). PO group: Cefuroxime (250mg, PO, 12 hourly, for 3 days) + Ciprofloxacin (750mg, PO, 12 hourly, for 3 days).	Total endophthalmitis cases: 7 Culture negative: 6 Not available: 1
Tabatabaei et al[18] 2016	46 ± 19.9	1254 of 1255 patients had trauma type recorded: Blunt: 984 Sharp: 270 1255 of 1255 patients had IOFB status recorded: IOFB: 284 No IOFB: 971	IV group: Ceftazidime (1g, IV, 8 hourly, for 3 days) and Vancomycin (1g, IV, 12 hourly, for 3 days). PO group: Ciprofloxacin (750mg, PO, 12 hourly, for 3 days).	Total endophthalmitis cases: 27 Staphylococcus epidermidis: 12 Bacilus cereus: 2 Streptococcus pneumoniae: 1 Pseudomonas spp.: 1 Enterococcus faecali: 1 Proteus mirabilis: 1
Essex et al[19] 2004	41.5 ± 19 (endophthalmitis group) and 36.6 ± 21 (non-endophthalmitis group)	249 of 251 OGIs (in 250 patients) had BETTS terminology recorded*: Rupture: 36 Penetrating: 199 Perforating: 14 249 of 251 OGIs had IOFB status recorded: IOFB: 69 No IOFB: 180	Not available	Total endophthalmitis cases: 11 Culture negative: 4 Bacillus cereus: 3 Propionibacterium acnes: 2 Staphylococcus aureus: 1 Streptococcus viridans: 1 Streptococcus oralis: 1 Micrococcus spp.: 1 Corynbacterium: 1 Pseudomonas fluorescens: 1 *Polymicrobial patients:* Propionibacterieum acnes, coagulase-negative staphylococcus, bacillus spp.: 1 Chryseobacterium, meningosepticum, Stenotrophomonas maltophilia: 1

BETT = Birmingham Eye Trauma Terminology; IOFB = intraocular foreign body; IV = intravenous route; OGI = open globe injury; OTS = ocular trauma score; PO = oral route; SD = standard deviation.
*Seven patients in this study did not have systemic treatment data recorded and were excluded from our analysis.

Table 3. Cochrane Risk of Bias 2 Tool Assessment and Robins-I tool Assessment for Bias

Cochrane Risk of Bias 2 Tool			Robins - I Tool	
Source of Potential Bias	*Du Toit et al*[17]	*Tabatabaei et al*[18]	*Source of Potential Bias*	*Essex et al*[19]
Randomization process (selection bias)	Good	Some concerns	Risk of bias due to confounding	*Moderate risk*
Deviation from intended interventions (reporting bias)	Good	Good	Bias in selection of participants into study	*Low risk*
Blinding (selection bias)	High risk	High risk	Bias in classification of interventions	*Moderate risk*
Missing outcome data (attrition bias)	Good	Some concerns	Bias due to deviations from intended interventions	*Low risk*
Outcome measurement (selection bias)	Good	Good	Bias due to missing data	*Low risk*
Selection of reported results (reporting bias)	Low	Low	Bias in measurement of outcomes	*Low risk*
			Bias in selection of the reported result	*Low risk*
			Overall bias judgment	*Low risk*

GRADE Assessment

Regarding the assessment of risk of endophthalmitis when preoperative systemic antibiotics are given or are not given, the GRADE assessment for the level of this evidence was low. This was downgraded due to imprecision, as CIs indicated possible benefits as well as harms, and due to risk of bias from confounding, as preoperative topical antibiotics were also used.

Regarding the assessment of risk of endophthalmitis with preoperative systemic antibiotics via the oral or IV (± oral) routes, the GRADE assessment for the level of this evidence was moderate. This was downgraded due to downgraded imprecision as CIs indicated possible benefits as well as harms.

Discussion

This systematic review of 1798 patients from 1 prospective study and 2 RCTs found a rate of endophthalmitis of 2.84% after OGI, although both RCTs specifically excluded some patients at high risk (as outlined in the Characteristics of Included Studies section). High-risk OGIs were defined as those with IOFB or after agricultural trauma.[6] There was no evidence that the administration of systemic antibiotic prophylaxis affected this rate, although the CIs are consistent with a clinically significant benefit, suggesting that the study was underpowered. Similarly, there was no evidence of a difference in rates of endophthalmitis between IV and oral routes of antibiotic prophylaxis administration.

Both RCTs in this review used ciprofloxacin in the oral therapy arms, which has equivalent bioavailability between oral and IV routes, in addition to excellent vitreous penetration; this suggests that, if antibiotic prophylaxis prevented endophthalmitis after OGI, no difference between oral and IV routes should be expected. Tabatabaei et al[18] administered vancomycin and ceftazidime in the IV arm, compared with ciprofloxacin in the oral arm, consistent with an equivalent effect on endophthalmitis prophylaxis of these antibiotic regimens.

Large (up to 675 patients), retrospective studies examining the rate of post-OGI endophthalmitis when prophylactic systemic antibiotics are administered had reported rates of between 0.9% and 4.3%, consistent with the 2.84% in this review of prospective studies.[20,21] No RCTs assessing the efficacy of systemic antibiotics for endophthalmitis prophylaxis were found. Older, retrospective studies of endophthalmitis reported higher rates of up to 16.5%, more than in the prospective or retrospective studies examining antibiotic prophylaxis reported here.[3] Differences may reflect changes in injury patterns over time, such as the proportion of IOFB, changes to management practices such as the timing of primary repair, and study inclusion criteria, as much as an effect of antibiotic prophylaxis.

Single doses of ciprofloxacin (second-generation fluoroquinolone) and moxifloxacin (fourth-generation fluoroquinolone) have demonstrated the ability to generate a 90% minimum inhibitory concentration in vitreous humor against common endophthalmitis causative bacteria.[22,23] Vancomycin (glycopeptide) and ceftazidime (third-generation cephalosporin) penetrate vitreous less effectively after systemic administration in studies on phakic and uninflamed eyes, although OGI is likely to

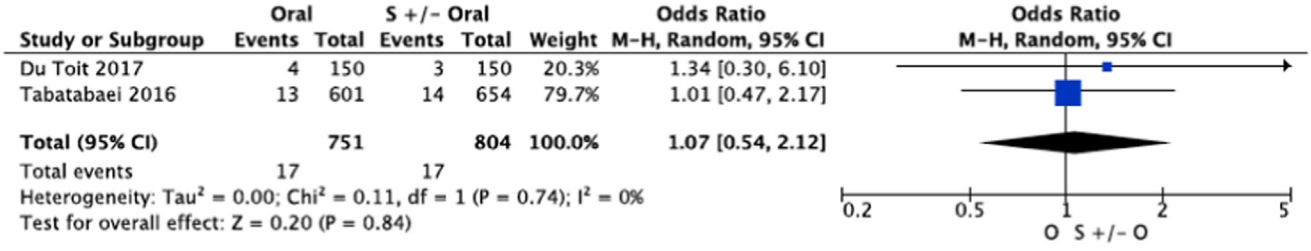

Figure 2. Forest plot analysis of oral versus IV (± oral) antibiotics as prophylaxis for post-open globe injury endophthalmitis. There was no evidence for a difference between groups, odds ratio 1.07 (95% confidence interval [CI], 0.54–2.12).

affect the integrity of the blood-eye barrier and alter pharmacokinetics.[24,25] As gram-positive bacteria are the most commonly cultured from intravitreal samples after traumatic endophthalmitis, the addition of a glycopeptide is a pragmatic choice for prophylaxis.[3] This was reflected by this analysis which reported that 25 of 29 culture positive cases of endophthalmitis (84.0%) cultured gram-positive bacteria.

The review did not find evidence to support or refute the use of systemic antibiotic prophylaxis to prevent endophthalmitis after OGI, but the results of the single prospective study included were consistent with an absolute risk reduction of up to 6.1%.

Systemic antibiotic prophylaxis must be considered in context, with other interventions potentially reducing the rate of endophthalmitis after OGI. These other practices include shielding of the injured eye before repair, reducing time to primary repair, preparation and cleaning of the operative field (i.e., ocular surface and eyelid margins), intraocular foreign body removal, and administration of intraocular and post-operative antibiotics, each of which may also improve outcomes and be targets for future work, in addition to preoperative systemic antibiotic prophylaxis.[26–28] The 2 RCTs included in this analysis excluded patients at increased risk of endophthalmitis through delayed surgery or wound contamination.[17,18] These studies reported a lower overall rate (2.19%) of endophthalmitis than the rate reported by Essex et al[19] (3.75%) in the sample of patients who had systemic antibiotic prophylaxis, which did not exclude any patients for being at a higher risk of endophthalmitis.[17,18] The authors note that Essex et al[19] modified Kuhn et al's criteria for OGI and excluded patients at a lower risk of endophthalmitis after OGI by not including those with posterior ruptures or ruptures at the rectus muscle insertions where the conjunctiva was not breached.[1] Other factors that may influence decision making based on the risk of endophthalmitis include the occurrence of bilateral OGI, more common in the military environment, where wound contamination may also be higher.[29]

Limitations

A limitation of the reviewed studies is that they did not mask patients or assessments. The studies were heterogenous in their length of follow-up, with the shortest being 1 week;[17] however, as endophthalmitis is most commonly an early complication (within days of trauma), the development of endophthalmitis, secondary to OGI, would likely be captured within this timeframe. The inclusion criteria varied significantly between the 2 RCTs, with the smaller study by Du Toit et al[17] specifically excluding patients at high risk of endophthalmitis from IOFB or contamination, while Tabatabaei et al[18] excluded patients at high risk of endophthalmitis from delayed surgery, so the estimated rate of endophthalmitis from these studies may not be representative of a general population sample of OGI, although the larger of the 2 studies (Tabatabaei et al[18]) did include patients with IOFB and high-risk wounds.[17,18] Other factors that influence the rate of post-OGI endophthalmitis such as timing of primary closure, zone of injury, and mechanism were not recorded and with the potential of epidemiological and practice variability, the external validity of these reported data may be limited.

The loss to follow-up rate was also heterogenous between meta-analyzed studies, varying between 0% and 10.3% (in the systemically treated, oral route group) which is reflected in the risk of bias assessment under attrition bias and all of which make direct comparisons difficult.[17–19]

Although the prospective evidence for systemic preoperative antibiotic prophylaxis may be equivocal, individual decisions must be based on expert knowledge and experience of the risk of endophthalmitis, assessing OGI across the range of injury severity, wound contamination, and, in the context of local risks and the catastrophic consequences for the patient if endophthalmitis develops, against the relatively low risk of systemic antibiotic administration.

Another limitation of the review design may include the specific inclusion and exclusion criteria. Only prospective studies were included, with the aim of ensuring maximum capture while reducing selection, allocation, and attrition bias. The small number of eligible prospective studies, with sample sizes which may render them underpowered as endophthalmitis rates are generally low, makes the case for future adequately powered trials to form more solid grounds for recommendations.

Additionally, the exclusion of patients who had undergone prophylactic intraocular or subconjunctival antibiotic injection limited study numbers. The authors excluded intraocular and subconjunctival antibiotics to isolate systemic preoperative prophylaxis. The decision to administer (or not) systemic preoperative antibiotics is distinct from the decision to administer intraoperative or perioperative locally injected antibiotics, being administered in different practice settings, often by different professional groups. Preoperative antibiotics may be administered by non-ophthalmologists and administration is not delayed by operating theater or surgical team availability. This is, therefore, often a decision made before the patient sees an ophthalmologist.

In most of the world, primary repair is not performed immediately and may be significantly delayed. In 1 United Kingdom study, the mean delay was 14 hours, while in Brazil routine delays of several days are reported for theater availability.[29,30,31] Delayed surgery is well-evidenced to increase endophthalmitis risk and the extent to which systemic antibiotics reduce endophthalmitis risk is therefore a crucial question in its own right.[26]

Although there is no prospective evidence to support preoperative antibiotic prophylaxis for endophthalmitis after OGI, the single included prospective study was consistent with no benefit up to an absolute risk reduction of 6.1%, meaning that decisions to prescribe should be weighted on a case-by-case risk/benefit assessment that considers possible adverse effects and potential consequences for the patient. When antibiotic prophylaxis is considered, there is moderate evidence that oral ciprofloxacin administration is noninferior to IV.

While 3 studies were included in the review, only 1 nonrandomized study was designed to answer the primary review question, because the 2 RCTs did not include appropriate control groups. Despite international variation

in practice and the catastrophic implications for patients of developing endophthalmitis after OGI, only a single non-randomized, prospective study has examined the benefits of systemic antibiotic prophylaxis after OGI. The 3 included studies demonstrate that RCTs in this area are possible, highlighting the need to generate stronger evidence.

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Annex A. Search Strings

1. **PubMed search string (40):** ((“open globe injur*”[Title/Abstract] OR open globe trauma[Title/Abstract] OR “intraocular foreign bod*”[Title/Abstract]) OR ((eye[Title/Abstract] OR globe[Title/Abstract] OR ocular[Title/Abstract]) AND (laceration [Title/Abstract] OR rupture[Title/Abstract] OR “penetrating”[Title/Abstract] OR perforation[Title/Abstract])) AND (antibiotic [Title/Abstract] OR antimicrobial [Title/Abstract]) AND (endophthalmitis [Title/Abstract] OR infection [Title/Abstract])
2. **CENTRAL search string (5):** (((“open globe injury*”):ti,ab OR (“open globe trauma”):ti,ab OR (“intraocular foreign body*”):ti,ab) OR (((eye):ti,ab OR (“globe”):ti,ab OR (ocular):ti,ab) AND ((laceration):ti,ab OR (rupture):ti,ab OR (“penetrating”):ti,ab OR (perforation):ti,ab)) AND ((antibiotic):ti,ab OR (antimicrobial):ti,ab) AND ((endophthalmitis):ti,ab OR (infection):ti,ab))
3. **Web of Science search string:** ((“open globe injur*” OR open globe trauma OR “intraocular foreign bod*”) OR ((eye OR open globe OR ocular) AND (laceration OR rupture OR penetrating OR perforation))) AND (antibiotic OR antimicrobial) AND (endophthalmitis OR infection)
4. **CINAHL search string:** ((“open globe injur*” OR open globe trauma OR “intraocular foreign bod*”) OR ((eye OR globe OR ocular) AND (laceration OR rupture OR “penetrating” OR perforation))) AND (antibiotic OR antimicrobial) AND (endophthalmitis OR infection)
5. **Embase search string:** (('open globe injur*' OR 'open globe trauma' OR 'intraocular foreign bod*').tw OR (('eye' OR 'globe' OR 'ocular').tw AND ('laceration' OR 'rupture' OR 'penetrating' OR 'perforation').tw) AND (('antibiotic' OR 'antimicrobial').tw) AND ('endophthalmitis' OR infection).tw)

Footnotes and Disclosures

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[1] Northern Ireland Medical and Dental Training Agency (NIMDTA), Belfast.

[2] Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom.

[3] Royal Centre for Defence Medicine, Birmingham, United Kingdom.

[4] Epsom and St Helier University Hospitals NHS Trust, Carshalton, United Kingdom.

[5] Vision Center of Excellence, Research & Development Directorate, J-9, Defence Health Agency, Silver Spring, Maryland.

[6] Uniformed Services University of the Health Sciences, Bethesda, Maryland.

[7] Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

[8] Duke Eye Center, Duke University Hospitals, Durham, North Carolina.

[9] The University of Sydney, Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, Sydney, New South Wales, Australia.

[10] Lions Eye Institute, University of Western Australia, Perth, Australia.

[11] Bascom Palmer Eye Institute, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida.

[12] The University of Sydney, Save Sight Institute, Faculty of Medicine and Health, Sydney, NSW, Australia.

[13] Consultorios Oftalmológicos Benisek-Ascarza, Ciudad Autónoma de Buenos Aires, C1115ABB Buenos Aires, Argentina.

[14] Department of Ophthalmology, Navy Medical Center Portsmouth, Portsmouth, Virginia.

[15] Department of Ophthalmology, San Antonio Uniformed Services Health Education Consortium, San Antonio, Texas.

[16] Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

[17] White River Junction Veterans Administration Medical Center, White River Junction, Vermont.

[18] Department of Ophthalmology, St Thomas Hospital, London, United Kingdom.

[19] Manchester Royal Eye Hospital, Manchester, United Kingdom.

[20] Birmingham Institute for Glaucoma Research, Birmingham, United Kingdom.

[21] Ophthalmology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.

[22] Department of Ophthalmology, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, United Kingdom.

[23] Department of Ophthalmology, National University Hospital, Singapore.

[24] Worcestershire Acute Hospitals NHS Trust, Worcester, United Kingdom.

[25] Helen Keller Foundation for Research and Education, Birmingham, Alabama.

[26] BRAVO VICTOR, Research & Innovation, London, United Kingdom.

[27] Northern Hub for Veterans and Military Families Research, Northumbria University, Newcastle, United Kingdom.

[28] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore.

[29] Singapore Eye Research Institute, Singapore.

[30] Lee Kong Chian School of Medicine, Singapore.

[31] Duke NUS Medical School, Singapore.

[32] Neuroscience & Ophthalmology, Institute of Inflammation & Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[33] Ophthalmology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.

[34] Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine, Birmingham, United Kingdom.

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Abbreviations and acronyms:
CI = confidence interval; **IOFB** = intraocular foreign body; **OGI** = open globe injury; **RCT** = randomized controlled trial; **SD** = standard deviation.

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Trauma, Endophthalmitis, Open globe injury, Antibiotics, Prophylaxis.

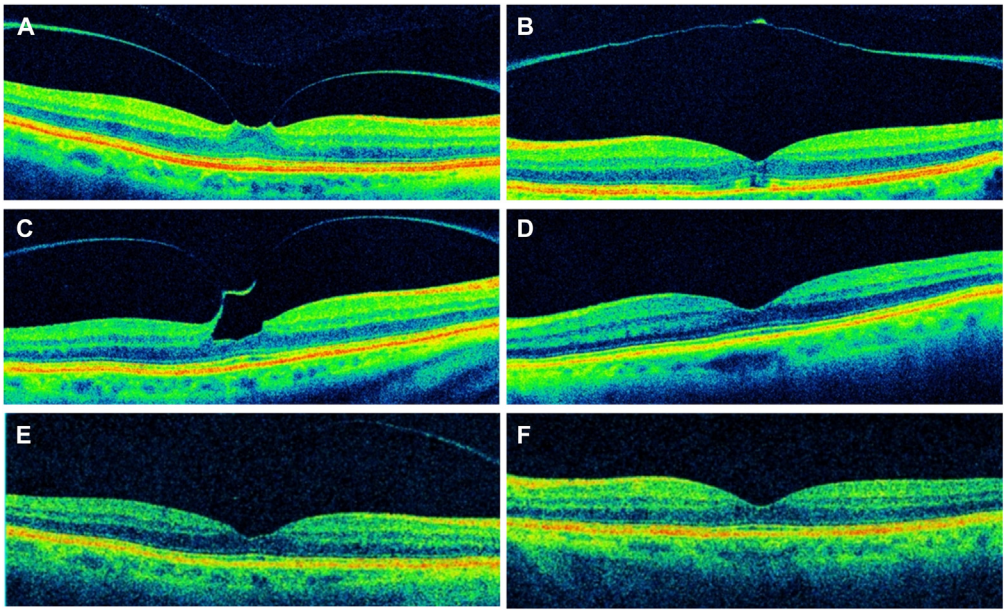
Correspondence:
Richard J. Blanch, FRCOphth, Neuroscience and Ophthalmology, 3rd Floor Robert Aitken Building, off Mindelsohn way, Birmingham, B15 2TH. E-mail: blanchrj@bham.ac.uk.

References

1. Kuhn F, Morris R, Witherspoon CD, et al. A standardized classification of ocular trauma. *Opthalmology*. 1996;103:240–243.
2. Mir TA, Canner JK, Zafar S, et al. Characteristics of open globe injuries in the United States from 2006 to 2014. *JAMA Opthalmol*. 2020;138:268–275.
3. Ahmed Y, Schimel AM, Pathengay A, et al. Endophthalmitis following open-globe injuries. *Eye (Lond)*. 2012;26:212–217.
4. Long C, Liu B, Xu C, et al. Causative organisms of post-traumatic endophthalmitis: a 20-year retrospective study. *BMC Opthalmol*. 2014;14:34. https://doi.org/10.1186/1471-2415-14-34.
5. Reynolds DS, Flynn Jr HW. Endophthalmitis after penetrating ocular trauma. *Curr Opin Opthalmol*. 1997;8:32–38.
6. Krishnaiah S, Nirmalan PK, Shamanna BR, et al. Ocular trauma in a rural population of southern India: the Andhra Pradesh Eye Disease Study. *Opthalmology*. 2006;113:1159–1164.
7. Colyer MH, Weber ED, Weichel ED, et al. Delayed intraocular foreign body removal without endophthalmitis during Operations Iraqi Freedom and Enduring Freedom. *Opthalmology*. 2007;114:1439–1447.
8. Miller SC, Fliotsos MJ, Justin GA, et al. Global current practice patterns for the management of open globe injuries. *Am J Opthalmol*. 2022;234:259–273.
9. PRISMA Statement and Checklist. http://www.prisma-statement.org/; 2009. Accessed June 4, 2021.
10. Prospero systematic review database. https://www.crd.york.ac.uk/prospero/. Accessed June 4, 2021, 2020.
11. Cochrane of bias tool (RoB2). https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0; 2019. Accessed June 4, 2021.
12. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
13. Review Manager 5. https://community.cochrane.org/help/tools-and-software/revman-5. Accessed June 4, 2021. Cochrane Collaboration.
14. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11:193–206.
15. Demets DL. Methods for combining randomized clinical trials: strengths and limitations. *Stat Med*. 1987:341–348.
16. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. http://gdt.gradepro.org/app/handbook/handbook.html; 2013. Accessed April 18, 2022.
17. Du Toit N, Mustak S, Cook C. Randomised controlled trial of prophylactic antibiotic treatment for the prevention of endophthalmitis after open globe injury at Groote Schuur Hospital. *Br J Opthalmol*. 2017;101:862–867.
18. Tabatabaei SA, Soleimani M, Behrooz MJ, Sheibani K. Systemic oral antibiotics as a prophylactic measure to prevent endophthalmitis in patients with open globe injuries in comparison with intravenous antibiotics. *Retina*. 2016;36:360–365.
19. Essex RW, Yi Q, Charles PG, Allen PJ. Post-traumatic endophthalmitis. *Opthalmology*. 2004;111:2015–2022.
20. Andreoli CM, Andreoli MT, Kloek CE, et al. Low rate of endophthalmitis in a large series of open globe injuries. *Am J Opthalmol*. 2009;147:601–608.e2.
21. Durrani AF, Zhao PY, Zhou Y, et al. Risk factors for endophthalmitis following open globe injuries: a 17-year analysis. *Clin Opthalmol*. 2021;15:2077–2087.
22. Hariprasad SM, Shah GK, Mieler WF, et al. Vitreous and aqueous penetration of orally administered moxifloxacin in humans. *Arch Opthalmol*. 2006;124:178–182.
23. el Baba FZ, Trousdale MD, Gauderman WJ, et al. Intravitreal penetration of oral ciprofloxacin in humans. *Opthalmology*. 1992;99:483–486.
24. Meredith TA, Aguilar HE, Shaarawy A, et al. Vancomycin levels in the vitreous cavity after intravenous administration. *Am J Opthalmol*. 1995;119:774–778.
25. Aguilar HE, Meredith TA, Shaarawy A, et al. Vitreous cavity penetration of ceftazidime after intravenous administration. *Retina*. 1995;15:154–159.
26. Thompson WS, Rubsamen PE, Flynn Jr HW, et al. Endophthalmitis after penetrating trauma. Risk factors and visual acuity outcomes. *Opthalmology*. 1995;102:1696–1701.
27. Thevi T, Abas AL. Role of intravitreal/intracameral antibiotics to prevent traumatic endophthalmitis - meta-analysis. *Indian J Opthalmol*. 2017;65:920–925.

28. Eye trauma: initial care (CPG ID:03). https://jts.amedd.army.mil/assets/docs/cpgs/Eye_Trauma_Initial_Care_01_Jun_2021_ID03.pdf; 2021. Accessed June 1, 2022.
29. Dhillon A, Ahmad MSZ, Breeze J, Blanch RJ. Prolonged deployed hospital care in the management of military eye injuries. *Eye (Lond)*. 2020;34:2106–2111.
30. Peleja MB, da Cunha FBS, Peleja MB, Rohr JTD. Epidemiology and prognosis factors in open globe injuries in the Federal District of Brazil. *BMC Opthalmol*. 2022;22:111. https://doi.org/10.1186/s12886-021-02183-z.
31. Blanch RJ, Bishop J, Javidi H, Murray PI. Effect of time to primary repair on final visual outcome after open globe injury. *Br J Opthalmol*. 2019;103:1491–1494.

Pictures & Perspectives



Bilateral Spontaneous Release of Vitreomacular Traction

A 78-year-old woman presented with blurry vision. Spectral-domain OCT (Cirrus 5000) showed vitreomacular traction (VMT) in the right eye (OD) (**A**) with visual acuity (VA) of 20/20 and released VMT with partial thickness macular hole in the left eye (OS) (**B**, VA of 20/40). Observation was elected. Thirty-one months later, OCT showed progressive VMT in the OD (**C**, VA of 20/20), and reconstitution of the retinal layers in the OS (**D**, VA of 20/30). Last follow up 12 months later showed VMT release in the OD (**E**, VA of 20/25), and stable findings in the OS (**F**, VA of 20/30). (Magnified version of Figure **A**-**F** is available online at www.ophthalmologyretina.org).

Patrick C. Staropoli, MD
Harry W. Flynn, Jr., MD

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, Florida