Title: **The Royal College of Ophthalmologists' National Ophthalmology Database Study of Cataract Surgery: Report 13, monitoring post-cataract surgery endophthalmitis rates - the Rule of X**

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Running Title: **Monitoring Post-Cataract Endophthalmitis - the Rule of X**

Abstract (248 words)

Background

Cataract surgical safety has improved over recent decades, with endophthalmitis rates before 2006 typically 0.13%-0.15% compared with the most recent UK national estimate of 0.02%. There remains, however, substantial variation in reported rates from different centres. Due to the low event rate, this disparity may not be noticed and opportunities to improve therefore be missed. We propose a method of monitoring post-cataract endophthalmitis rates that would help centres with higher rates identify this.

Methods

A statistical tool, available to download or use online, permits comparison of local endophthalmitis rate with the estimated UK rate of 0.02%. Centres are encouraged to maintain a register of endophthalmitis cases, and when the number reaches a threshold (X cases), either in a certain time period or in a fixed number of procedures, then the centre can consider itself as an outlier and trigger local investigations to improve infection control.

Results

Example outputs are offered, such as for a unit doing 5 000 cataracts annually, a value of X is suggested such that the third case of endophthalmitis (X=3) in a 12-month period would give 85% confidence, the fourth case 90% confidence and the fifth case 95% confidence that the true endophthalmitis rate for that unit was higher than the national average.

Conclusions

This statistical tool provides a basis for units to set a threshold number of cases of endophthalmitis within a given period that would trigger local processes, thus helping inform local monitoring processes for this rare but potentially catastrophic complication of cataract surgery.

What was known before:

- Post-cataract endophthalmitis rates have fallen since the introduction of routine intracameral antibiotics
- Variation in endophthalmitis rates between centres is still seen in published series and cataract surgical registry data
- Routine monitoring of endophthalmitis rates is not consistently practiced

What this study adds:

- A statistical tool is available that permits users to identify a threshold number of cases (X) which, if reached within a given time frame or within a certain number of cataract procedures, should trigger local investigations into infection control practices

Introduction

Cataract surgery has progressed in safety and quality of outcomes over recent decades, becoming the most frequently undertaken surgical intervention in high income countries. This has arisen from a combination of an ageing demographic and surgery occurring at progressively earlier stages of the disease process (1). Confidence in the quality of outcomes underpins the reducing threshold for surgery. This confidence may be partly due to the very low rate of the potentially blinding post-operative complication of presumed infectious endophthalmitis (PIE).

Whilst PIE has always been a rare event, national surveillance systems, systematic reviews and meta-analyses prior to 2006 reported rates of 0.13% - 0.15% (2-4). The landmark randomised control trial (RCT) investigating the effectiveness of intracameral cefuroxime as a prophylaxis against post-phacoemulsification PIE showed a reduction in rates from 0.34% (23/6 862) in the control arm to 0.07% (5/6 836) when intracameral cefuroxime was used, causing the trial to end early (5). This RCT evidence has been corroborated by observational real-world data; PIE rates for phacoemulsification from Aravind Eye Care systems in India fell from 0.07% (75/104 894) to 0.01% (11/89 358) with the introduction of intra-cameral moxifloxacin prophylaxis ($P < 0.001$) (6). With RCT and observational evidence of this strength, widespread uptake of the use of intracameral antibiotics has been seen and PIE rates have reduced. Large case series of phacoemulsification now report PIE rates of <0.1%, such as 0.08% (131/163 503) from the Malaysian Ministry of Health Cataract Surgery Registry (2018)(7), or 0.00% with no endophthalmitis from the 25 920 patients who received intracameral cefuroxime in an Iranian series (2016),(8) and 0.064% (884/1 383 867) from a nationwide Korean study (2019) (9).

A Cochrane Collaboration systematic literature review on the subject of antibiotic use in cataract surgery concluded that the size of sample needed with rates as low as now reported will probably prevent any further RCT being undertaken. Hence, observational data will be depended upon to guide future policy and practice (10).

Despite this success, variation in rates is still reported, and it is therefore possible that the opportunity exists to further protect patients from this potentially catastrophic complication of cataract surgery.

Outbreaks

The base rate of PIE in a unit is not to be confused with outbreaks of PIE which need to be identified and managed appropriately. A systematic review identified 27 reports of PIE outbreaks following cataract surgery between 1985 and 2011; the most common causes associated with the outbreaks were contaminated solutions and contaminated phacoemulsification machines (11). Differentiating between an outbreak and the natural clustering seen with any random event due to chance is not easy.

Royal College of Ophthalmologists (RCOphth) guidelines on outbreaks suggest that "*even one or two extra events during a short time frame may have arisen from a preventable and recurring cause*" and should therefore raise concern, but no clear definition of an outbreak is offered (https://www.rcophth.ac.uk/wp-content/uploads/2016/07/Managing-an-outbreak-of-postoperative-endophthalmitis-Final-2022.pdf accessed December 2022). A published simulation based on a true PIE rate of 0.14% showed that if an "outbreak" is defined as three cases per 1 000 operations, 60% of centres providing cataract surgery will report an "outbreak" annually purely by random chance and clustering; if the definition is relaxed to four cases per 1 000, then around 30% of centres will report an outbreak annually (12). With lower PIE rates in the age of intravitreal antibiotics, the frequency of false positive reporting of outbreaks due to chance has reduced, but nonetheless the opportunity-costs of investigating spurious outbreaks of PIE are potentially substantial.

Monitoring

Whilst guidelines exist to identify PIE outbreaks, there is no systematic means by which individual hospitals providing cataract surgery in the UK experiencing higher PIE rates in their routine service could be detected.

The aim of this study is to provide a statistical framework for units to use for monitoring their PIE rates, allowing them to identify where they may be running a rate that is higher than the national average with an acceptable level of confidence, and thereby prompting review of the measures taken to minimise rates.

Methods

The RCOphth National Ophthalmology Database (NOD) has reported a risk factor analysis of PIE (13). Within the data utilised for that risk factor analysis, the overall PIE rate was 0.02% (308 cases) in a sample of 1 351 415 cataract operations performed between 01/04/2010 and 31/03/2021 in 76 centres by 3 570 surgeons (13).

Variation in the rates between centres was observed in our sample, and whilst it could be accounted for by random chance, it is also possible that there could be centres which are, year after year, experiencing significantly higher PIE rates, without their status as national outliers becoming apparent to the hospital or its surgeons.

The Rule of X

Taking the RCOphth NOD national estimated rate of 0.02% as a true representation of the PIE rate in UK departments, we calculated the number of cases that a centre should experience to declare themselves as having a PIE rate which is statistically significantly higher than the national overall rate.

Research papers traditionally accept a 95% confidence interval (CI) in results to declare statistical significance; National Audits in England routinely utilise 3 standard deviations from the mean as their threshold for declaring a surgeon an outlier for particular outcomes or complications of surgery (14).

However, a hospital wishing to monitor its PIE rates may not wish to wait until they have a rate high enough to represent such high levels of statistical significance before undertaking an internal review of policies and practices. When the data starts to suggest that there may be a problem in the underlying PIE rate, many surgeons or centres might opt to revisit their infection control practices, and look for opportunities to improve.

We present threshold case numbers that would trigger investigation using the Fleiss Quadratic Adjustment. This was used to formulate confidence intervals to identify cases with statistically significantly higher rates of PIE than the overall national estimate. The appropriate z values were selected from the percentage points of the normal distribution for a one-tailed test.

Due to the instability in the estimates with a small number of cases due to the very low event rate, the estimates are valid for a number of operations above 1 000 eyes, 2 000 eyes and 3 000 eyes for the 85%, 90% and 95% CI, respectively.

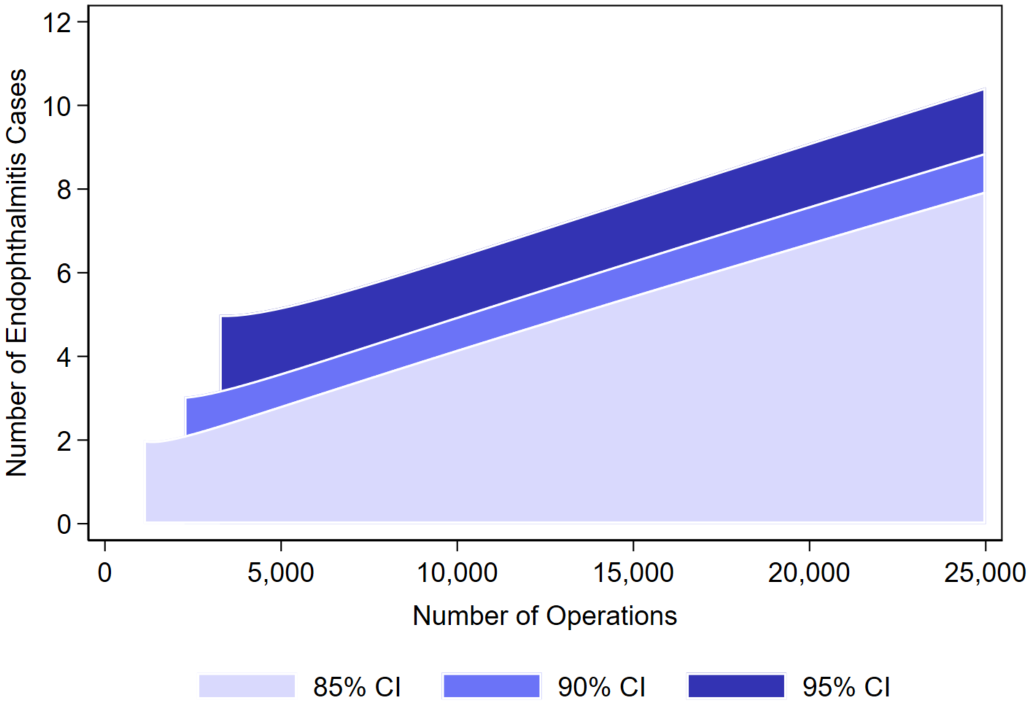
We present calculations for the number of cases that centres of varying surgical activity would need to experience in any given 12-month period in order to be identified as outliers with various levels of confidence, 85%, 90% and 95%. With the number of cases needed to trigger this identification as a potential outlier changing over time and between centres, we have created an online tool that allows the user to enter an annual surgical activity rate and select whichever confidence level they prefer.

The tool also allows variation of the underlying mean PIE rate which informs the estimate of the acceptable number of cases. This is important as we expect our medical data capture systems to improve with developments in electronic medical records and greater facility to link data for the same patient presenting at different centres, so it may be that the estimated PIE rate in the UK is found to be higher than was identified by the RCOphth NOD national minimum estimated PIE rate. Alternatively, this rate may drop over time as new infection control strategies are identified.

Results

The rule of X is a guideline for operating centres to utilise in their clinical practice. When the number of PIE cases reaches the threshold of X cases, either within the last 12 months (or within a fixed number of procedures), then the centre can consider itself as an outlier and trigger local investigations into improved infection control options. The values of X for acceptable levels of endophthalmitis at differing levels of confidence are illustrated, Figure 1.

Figure 1: Thresholds for acceptable endophthalmitis rates based on the number of operations performed by a centre per year



At the 95% level of confidence, the *rule of six* could be utilised for centres doing between 3 000 and 8 000 cases per annum. The 6th case would indicate, with 95% confidence, that this centre has a PIE rate which is statistically significantly higher than overall national minimum rate estimate for PIE of 0.02%. For a centre performing 3 000 operations, this would give an event rate of 0.2% to trigger an investigation.

Due to the serious nature of PIE, many centres will not wish to delay initiating investigation into opportunities to improve infection control strategies until they are 95% confident that they are outliers. The 90% CI can be used, and the *rule of 4* can be utilised for centres with a number of operations between 2 000 and 7 000 eyes, providing a statistically significantly high rate of endophthalmitis. For centres with 2 000 eyes, the fourth case of endophthalmitis would trigger an investigation with a centre rate of 0.2%.

Suitable for a centre with a smaller number of cases per annum, or for triggering an investigation at a lower rate, the 85% CI can be selected with the *rule of 3* implemented. This can be used for centres with 1 000 to 5 000 operations annually, giving a rate of 0.3% as a threshold for centres operating on 1 000 eyes a year, Table 1.

Table 1: Thresholds for outlying number of cases of endophthalmitis for different levels of confidence intervals based on the number of operations per year.

	Number of PIE cases needed to indicate a higher than average rate at different confidence intervals		
Numbers of Operations per year	**85% CI**	**90% CI**	**95% CI**
1 000	2.0	N/A	N/A
2 000	2.1	3.0	N/A
3 000	2.2	3.1	5.0
4 000	2.5	3.4	5.0
5 000	2.8	3.6	5.2
6 000	3.1	3.9	5.4
7 000	3.4	4.1	5.6
8 000	3.6	4.4	5.9

Discussion

Despite the RCOphth NOD representing a successful cataract surgical quality assurance programme monitoring posterior capsule rupture and all-cause vision loss rates, there is no effective system for identifying centres with higher PIE rates. Due to the very low event rate for PIE, monitoring for most individual surgeons in the UK is not possible. With a median cataract annual activity recorded on the RCOphth NOD Cataract Audit being 66 cataract operations per year, even for surgeons with 10 times that national average activity levels, it is improbable that they as individuals will have more than one case in a time frame sufficiently short to raise concerns.

Whilst it is possible, in theory, that where departmental audits of PIE are undertaken regularly, and where sufficiently recent literature review derived benchmarks are utilised in these audits, then centres may be able to detect where their PIE rate is higher than reported elsewhere. However, this is not happening routinely, therefore there is a strong possibility that there is a wide variation in the PIE risk patients are exposed to in the different surgical centres without this ever becoming apparent. The RCOphth NOD data used for the endophthalmitis risk factor analysis included data from 76 centres; 29 centres had no cases of PIE over the time period of data collection, and the range for the remaining centres was 0.01% to 0.10%. Without intentional monitoring, this tenfold variation, if representative of true differences in actual PIE rates, may never become apparent to the centre, and the opportunity that exists for them to improve therefore be missed.

In the absence of any guidelines regarding the rate of PIE that should cause concern, this study presents a statistical tool to permit centres to evaluate their observed PIE rates in the light of national incidence.

The rule of unintended consequences

There are, of course, direct costs and opportunity costs of any monitoring activity – and further costs incurred as random chance will produce some false positives of PIE rate monitoring. Centres might then inappropriately identify themselves as outliers, invest time exploring opportunities to reduce their infection rates, and may initiate practices that are wasteful of resources. As clustering of PIE cases by chance is inevitable, in such instances, whatever intervention is introduced will have the apparent effect of reducing PIE rates in subsequent audits. Centres must, therefore, be very aware of the risk of drawing false conclusions and should be open to concluding that their current practice represents the best evidence-based approach to post-cataract infection control, and choose not to take any action but to continue monitoring rates.

There are, on the other hand, substantial savings on offer where cases of infection can be prevented (estimated at $4 893 per PIE case from the USA (2016)) (15). Cost-effectiveness considerations are paramount in publicly funded health care services, and it is essential that centres avoid implementing measures that are not cost-effective and increase the risk of antimicrobial resistance, such as administering pre-operative prophylactic antibiotics, which has been estimated to only become cost-effective if PIE rates were to rise to over 5.5% (16). With emotive issues such as catastrophic visual loss from PIE, desire to take action can lead to implementation of measures that increase the perception of safety, but actually expose patients to risk by inefficiently utilising finite resources; such desires must be acknowledged and resisted (17).

Conclusion - Using the Rule of X

The rule of X has been developed as a resource to assist centres in identifying when their rate of PIE may be higher than that being achieved elsewhere. In practical terms, it would require a system for logging cases of PIE within a surgical centre, and for periodic review of that log, we would suggest on a quarterly basis.

The cumulative PIE case total for the most recent 12-months could be reviewed in higher volume centres. A centre doing 5 000 cataracts (where X=3) annually could therefore monitor PIE cases, and if a third case is seen in any 12-month period, this would indicate with 85% confidence that this centre had a higher PIE rate than the national average (table 1). For a unit doing 6 000 cases per annum, a fourth case would be needed to reach that threshold.

In lower volume centres where an estimate of the PIE rate based on 12-months surgical activity would have very wide confidence intervals, surgeons could review the number of PIE cases from a longer time period, or set a number of cases, for instance, the most recent 3 000 operations. Using this example, the third case in the last 3 000 operations would indicate (with >85% confidence) that the centre may have a higher rate than should be achievable, Table 1.

Thus, a rolling retrospective audit of PIE cases is permitted, using the national rate estimate as a comparator, such that if the threshold number of PIE cases is reached, an internal conversation to explore options to reduce the risk of PIE may be triggered.

Although we present the value of X for 85%, 90% and 95% confidence levels, we suggest that for many centres, the 85% CI level may seem appropriate, and the risk of mistakenly self-identifying as having a potential problem due to random clustering is probably worth accepting in order to avoid waiting too long before looking into potentially modifiable risk factors for PIE within a cataract service.

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