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Intraoperative cefuroxime administration to prevent endophthalmitis in cataract surgery: a Polish perspective

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ABSTRACT

Cataract surgery is among the most common procedures performed in Europe and worldwide. Significant progress has been observed over the recent years, with improvements in the safety and health-related outcomes of the intervention. Nevertheless, cataract surgery is associated with complications, with endophthalmitis being one of the most severe. Cefuroxime, a second-generation cephalosporin, was the first antibiotic applied intraoperatively into the anterior chamber, to prevent endophthalmitis. In contrast to antibiotics administered in drops, the injection of an antibiotic into the anterior chamber of the eye at the end of the operation allows to achieve the drug concentration necessary for effective eradication of microorganisms.

The article discusses the epidemiology of endophthalmitis and the current Polish guidelines for endophthalmitis prophylaxis during cataract surgery. Key results for cefuroxime efficacy from a randomized controlled clinical trial and observational studies about the effectiveness of the antibiotic in real-world clinical practice are cited. Recent data from the National Health Fund of Poland on active monitoring of cataract operations in Poland, including their quality, are presented. The paper also reports the cost-effectiveness of the use of cefuroxime (Aprokam®) for anterior chamber injections in Poland in the prophylaxis of endophthalmitis after cataract surgery.

KEY WORDS: postoperative endophthalmitis; cefuroxime; cataract surgery; cost-effectiveness; Aprokam

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INTRODUCTION

Postoperative endophthalmitis (POE) constitutes a rare but severe complication of cataract surgery. It is an inflammation of the eyeball arising as a consequence of an infection with bacteria or, less frequently, fungi. The causative agent of the infection is usually bacteria that are the own bacterial flora of the eye appendages. The most frequently isolated pathogens responsible for POE include Gram-positive bacteria: coagulase-negative staphylococci, e.g. *Staphylococcus epidermidis* (33–77% of cases), *Staphylococcus aureus* (including methicillin-resistant) (10–21%), β- and ∂-haemolytic streptococci, *Streprococcus pneumoniae* (9–19%) [1]. Gram-negative bacteria are responsible for about 6% of POE cases [2]. Acute POE occurs within 6

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weeks after surgery, with most patients experiencing POE within the first 2 weeks [3, 4]. In acute POE, the first symptoms appear as early as 1–4 days after surgery and progress rapidly. Patients suffer from severe eye pain and significant deterioration of visual acuity. Usually, inflammation of the vitreous body is observed, and it is difficult to inspect the fundus. Approximately 72–85% of patients present with anterior chamber exudate and hypopyon [1, 5]. The prognosis depends on the causative pathogen and the time to treatment. According to 2005–2010 data from a Swedish registry, approximately 33% of patients with a history of POE have visual acuity > 20/40, while 38% experience severe visual impairment (visual acuity below 20/200) [2]. In most studies, the percentage of patients with final visual acuity of ≥ 0.5 after acute POE equals approximately 50–59% [6–8]. Prompt treatment improves the prognosis and allows significant visual acuity loss to be avoided. POE caused by exotoxin-producing streptococci and Gram-negative bacteria, such as *Pseudomonas aeruginosa*, is associated with poor prognosis, even after early antibiotic treatment [1]. Older age, diabetes, ruptured posterior capsule, corneal infiltration, and elevated intraocular pressure are additional factors that worsen the prognosis [9].

ENDOPHTHALMITIS EPIDEMIOLOGY

According to studies performed in Europe, the risk of POE after cataract surgery when no antibiotic is applied to the anterior chamber of the eye ranges from 0.055% [7] to 1.238% [10]. In turn, in a clinical study conducted by the European Society of Cataract & Refractive Surgeons (ESCRS), which also included Polish patients, the incidence of POE in the group without anterior chamber antibiotic application equalled 0.210% (17 cases of confirmed POE out of approximately 8000 cataract operations) (Tab. 1) [4]. The incidence of POE after cataract surgery in Poland has been scarcely investigated. Szaflik and Zaraś, on the basis of data from 53 ophthalmological centres in Poland, estimated the incidence of POE at the level of 0.293% after cataract surgery and of 0.937% after simultaneous cataract and glaucoma surgery [11]. In turn, Wylęgała et al., with evidence from one centre, determined POE incidence after complicated cataract surgery to be 0.376% [12].

In addition to epidemiological studies, qualitative registries monitoring, among others, cataract surgeries are a source of data on the incidence of POE after cataract removal. The registers enable comparisons of operation results between centres or countries. At the same time, they are intended to encourage clinicians to refine their techniques and improve the results. ESCRS maintains the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO). In 2019, 15 countries (13 from the European Union, including Poland, and two from outside the European Union) reported a total of around 330,000 cataract operations. According to data from clinics contributing data to the registry, the percentage of POE cases equalled 0.013% in 2019 (23 cases out of approximately 170,000 surgeries covered by complete follow-up) [13]. Similar data are provided by the British National Ophthalmology Database (NOD), which serves to perform a qualitative assessment of cataract surgery in England and Wales. As per the data for the latest available period, i.e. from September 2018 to August 2019, the percentage of cataract surgeries complicated by POE was approximately 0.01% [14]. Endophthalmitis, along with the deterioration of visual acuity and posterior capsule rupture, is an indicator of cataract surgery quality also monitored by the National Health Fund of Poland. The percentage of POE cases in the third and fourth quarters of 2018 amounted to 0.2% and 0.3%, respectively. In years 2019–2020, the percentage decreased to 0.1% [15]. Despite the reported decline, the incidence of POE in Poland is still 10 times higher as compared with the data from the European EUREQUO register [13].

ENDOPHTHALMITIS PREVENTION GUIDELINES

The guidelines for cataract surgery developed by the Society of Polish Ophthalmologic Surgeons and the Polish Ophthalmological Society include recommendations for POE prophylaxis [16, 17]. Reducing the incidence of POE requires appropriate prevention. Only patients without inflammatory conditions of the eye surface and appendages should be qualified for surgery. During surgery, it is necessary to reduce the risk of infection by disinfecting the skin with 10% povidone iodide, abundant rinsing the conjunctival sac with 5% povidone iodide, and ensuring that the surgical incisions are tight. Furthermore, the procedure should be performed without such complications as posterior capsule rupture or vitreous leakage into the anterior cham-

Table 1. Risk of postoperative endophthalmitis after cataract surgery depending on intraoperative cefuroxime administration in European studies (own elaboration)

Study	Country	Observation period	Study design; data source	Number of cataract surgeries	Number of POEs	Risk of POE after cataract surgery		
						Whole population	With cefuroxime IC	Without cefuroxime IC
ESCRS 2007 [4]	Europe*	2003–2005	Randomized, controlled, factorial clinical trial; international multicentre study	16,211	20**	0.123%	0.037%	0.210%
Friling et al. 2013 [2]	Sweden	2005–2010	Prospective; national register of cataract surgery	464,996	135	0.029%	0.027%‡	0.392%
Creuzot-Garcher et al. 2016 [27]	France	2005–2014	Retrospective cohort study; national medical administrative database	6,371,242	6668	From 0.145% in 2005 to 0.053% in 2014	From 0.1% in 2005 to 0.046% in 2014	From 0.145% in 2005 to 0.082% in 2014
Daien et al. 2016 [28]	France	2010–2014	Prospective cohort study; national medical administrative database	2,434,008	1941	0.080%	0.057%	0.094%
Rodríguez-Caravaca et al. 2013 [29]	Spain	1998–2012	Prospective observational study; 1 centre	19,463	44	0.226%	0.039%	0.591%
Beselga et al. 2014 [30]	Portugal	2005–2011	Retrospective observational study; 1 centre	15,689	6	0.038%	0%	0.261%
Myneni et al. 2013 [31]	United Kingdom	2004–2012	Retrospective observational study; 1 centre	21,664	16	0.074%	0.022%	0.11%
Röck et al. 2014 [32]	Germany	2002–2009	Retrospective observational study; 1 centre	31,386	31	0.099%	0.044%	0.138%

*Austria, Belgium, Germany, Poland, Portugal, Turkey, United Kingdom, Italy; **confirmed POE cases, i.e., with a positive result with at least one of the laboratory methods: Gram stain, culture, molecular method; ‡ in 99% of cataract surgeries, prophylaxis with cefuroxime was administered, while in the remaining cases moxifloxacin was applied; IC — intracameral; POE — postoperative endophthalmitis

ber. As the efficacy of preoperative antibiotic drops has not been confirmed, their use is being abandoned [16]. Following the European ESCRS guidelines [1], the standard is the aseptic administration of cefuroxime into the anterior chamber of the eye at a dose of 1 mg in 0.1 ml solution [16, 17]. These recommendations are based on the results of a clinical trial conducted by ESCRS on intraoperative antibiotic prophylaxis during cataract surgery [4].

PHARMACOPOEIA REQUIREMENTS FOR OPHTHALMIC DRUGS

According to Pharmacopoeia, ophthalmic medicines prepared in the pharmacy are subject to strict requirements. They should be formulated under precisely specified conditions to ensure that they are sterile and meet class I microbiological purity. Pharmacopoeia defines sterility as the absence of viable microorganisms in a drug. To be able to prepare drugs with this microbiological purity class, it is necessary to follow the principles of asepsis, aimed at ensuring sterility at each stage of drug preparation: from the provision of a workstation and personnel, through the use of appropriate equipment, to the application of substances of a specified quality. To this end, all work surfaces should be disinfected prior to drug preparation, and the drug preparation should be carried out under laminar flow conditions with the use of high-efficiency HEPA filters. The staff must wear sterile protective clothing, disinfect hands, and use sterile gloves. The rooms where

sterile medicines are prepared should be separated from the rest of the pharmacy by an airlock to limit the inflow of polluted air. The sterility of the final product is achieved by final sterilization with the use of mechanical (trickling) or physical (thermal, radiation) methods [18].

CEFUROXIME IN ENDOPHTHALMITIS PROPHYLAXIS

Cefuroxime is a second-generation cephalosporin belonging to the beta-lactam subgroup. Antibiotics of this group are characterized by variable activity against staphylococci and are more active against certain Gram-negative bacteria than the first-generation cephalosporins [19]. Cefuroxime administered into the anterior chamber of the eye is ineffective against methicillin-resistant staphylococci and enterococci [20]. Until 2012, a cefuroxime solution of the desired concentration had to be prepared under aseptic conditions by ophthalmic centres themselves. In 2012, cefuroxime for anterior chamber injections (the Aprokam® formulation) was registered in Europe. The availability of this drug form has significantly influenced its widespread use during cataract surgery. The vials contain the amount of drug and solvent necessary to prepare the medication directly in the operating theatre. After reconstitution, a solution of cefuroxime concentration 50 mg/5 mL ready for injection is obtained. The recommended dose of cefuroxime in POE prophylaxis is 1 mg/0.1 mL. Each vial is labelled as single-use and intended for one patient [21]. Repeated drug withdrawal from the same container for administration to several patients poses a risk of vial leakage and, thus, contamination of the solution with microorganisms [22].

The efficacy of cefuroxime in preventing POE has been confirmed in an ESCRS multicentre randomized clinical trial [4]. The study involved approximately 16,600 patients with an indication for phacoemulsification cataract surgery with intraocular lens implantation. Patients were recruited in nine European countries, including Poland. All groups received standard povidone-iodine before the surgery and levofloxacin up to six days after the intervention.

The interventions compared in the ESCRS study were as follows:

1. No intraoperative antibiotic use.
2. Cefuroxime was injected into the anterior chamber of the eye at the end of cataract surgery.
3. Intraoperative administration of levofloxacin drops only.
4. Intraoperative administration of levofloxacin drops plus cefuroxime applied to the anterior chamber.

For ethical reasons, placebo was not administered into the anterior chamber of the eye, and masking involved levofloxacin exclusively. The primary endpoint was the occurrence of POE, whether proven or presumed. After the cataract surgery, there were 29 cases of POE: 24 in the groups without cefuroxime and 5 in the groups receiving cefuroxime. About 70% of POEs (20 cases) were confirmed by laboratory testing [4]. The median time to the onset of signs and symptoms equalled 4.5 days in confirmed POEs and 9.0 days in unconfirmed cases [23]. Cefuroxime administration was associated with an almost 5-fold lower probability of POE occurrence compared with no such prophylaxis [odds ratio (OR) = 4.92; 95% confidence interval (CI): 1.87–12.9]. The likelihood of the occurrence of exclusively proven POE cases was almost 6-fold lower after cefuroxime application (OR = 5.86; 95% CI: 1.72–20.0). Although perioperative use of levofloxacin drops was also associated with a reduction in POE incidence, the therapeutic effect was smaller and statistically insignificant (regardless of whether all cases of POE or only those confirmed by laboratory testing were considered) [4]. The decrease in POE incidence observed in the ESCRS study after cefuroxime administration is consistent with the results of earlier long-term uncontrolled studies (a retrospective and a prospective one) conducted in Sweden [8, 24]. The retrospective study analysed over 32,000 cataract operations after introducing routine intraoperative use of cefuroxime and over 34,000 surgeries in which the drug was not applied. Prophylaxis with cefuroxime was associated with a significant reduction in POE incidence: from 0.06% to 0.26% ($p < 0.001$) [8]. Cefuroxime injected into the anterior chamber of the eye was well tolerated. The Swedish prospective observational study demonstrated that it did not cause deterioration of visual acuity, the appearance of opacities in the anterior chamber, or loss of corneal endothelial cells [24]. In patients with known penicillin allergy, hypersensitivity to other beta-lactam antibiotics, including cefuroxime, should be considered. Anaphylactic reactions to cefuroxime are rare in POE prophylaxis and can be excluded by taking a reliable history before the drug application [25, 26]. Other adverse events observed in the past resulted from

incorrect solution preparation with too high antibiotic concentration. The most commonly reported events arising from incorrect dosing were macular oedema, haemorrhagic retinopathy, serous corneal detachment, and corneal oedema [26]. The risk of such complications is now marginal due to the availability of cefuroxime in sterile, single-use packs with the correct dose of the drug.

CEFUROXIME IN CLINICAL PRACTICE

The efficacy of cefuroxime for POE prophylaxis, proven in the ESCRS study, has been confirmed in real-world clinical practice settings. Numerous observational and epidemiological studies have demonstrated significantly lower rates of POE since the introduction of routine cefuroxime use after cataract surgery (Tab. 1). Swedish ophthalmologists pioneered cefuroxime-based POE antibiotic prophylaxis. In Sweden, antibiotic administration into the anterior chamber of the eye has been routinely practised for many years [8, 24]. Data from the Swedish cataract registry for the years 2005–2010 revealed that lack of cefuroxime prophylaxis was associated with an almost 3-fold increased probability of acute POE (OR = 2.6; 95% CI: 7.1–25.4) [2]. During this period, the incidence of POE was 14 times lower in patients given cefuroxime prophylaxis than in the group without cefuroxime therapy. Simultaneously, the incidence of POE in the general population was significantly lower than that observed in the years 2002–2004 (0.029% vs. 0.048%; $p < 0.001$) [2]. In turn, according to the French cataract registry, the proportion of operations with cefuroxime prophylaxis has varied over the recent years. One year before cefuroxime was registered for POE prophylaxis, it had been used in a mere of 14% of surgeries. Since 2012, over the following 3 years, its application in France increased to approximately 80%. During the same period, the incidence of POE in the general population declined almost 3-fold (Fig. 1) [27]. Cefuroxime has been demonstrated to reduce the risk of POE both in patients with and without posterior capsule rupture. Antibiotic administration to the anterior chamber of the eye did not increase the incidence of cystoid macular oedema [28]. Benefits of cefuroxime applied during cataract surgery have also been reported in smaller, single-centre observational studies conducted in Europe [29–32]. Cefuroxime prophylaxis has reduced POE incidence by 2–15 times as compared with no prophylaxis (Tab. 1). No case of POE was observed in a Portuguese centre over a 5-year period during which cefuroxime was

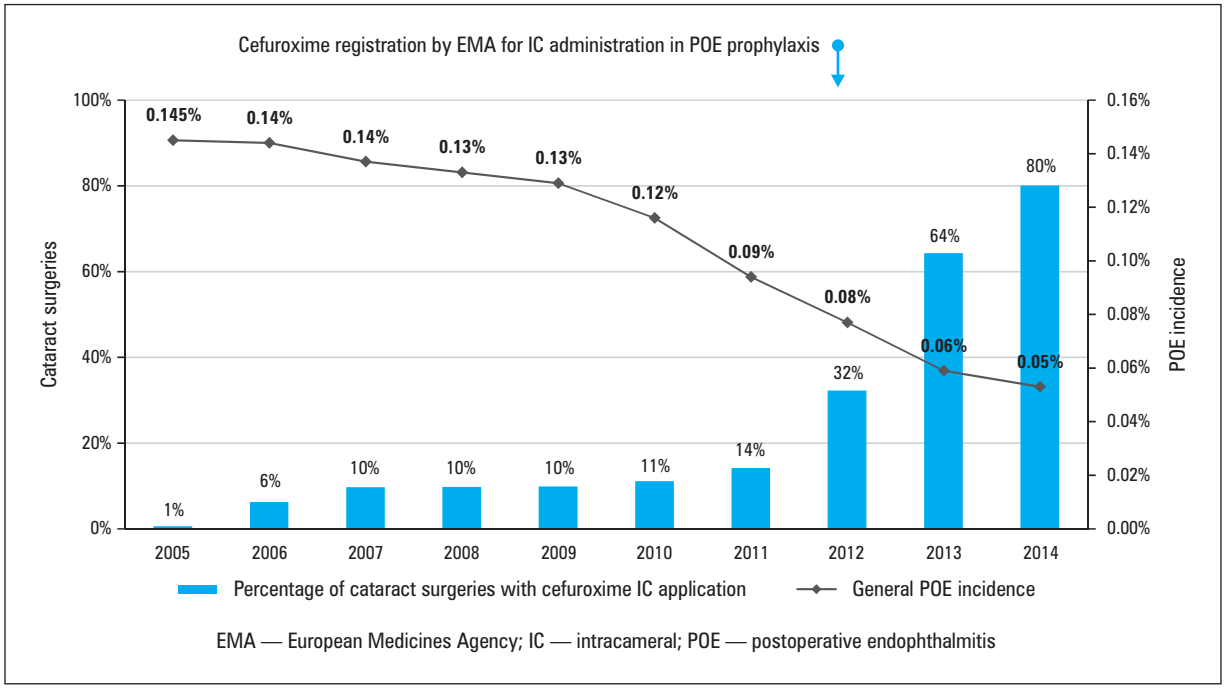

FIGURE 1. Cataract surgery with cefuroxime and the frequency of postoperative endophthalmitis (POE) in France in 2005–2014 [27]. EMA — European Medicines Agency; IC — intracameral

routinely administered [30] (Tab. 1). There are also reports of a reduced POE incidence after the implementation of cefuroxime prophylaxis from regions outside Europe [33–35].

Observational studies concerning the prevention of POE have been the subject of published systematic reviews. Bowen et al. [36], on the basis of a systematic review of medical databases, identified one randomized clinical trial (ESCRS) and nine observational studies with a control group addressing the efficacy of cefuroxime administration into the anterior chamber. The studies were carried out in Europe, Canada, the United States, and India. A meta-analysis of the observational studies results revealed that the use of cefuroxime injections reduced the probability of POE as compared with no such prophylaxis (OR = 0.26; 95% CI: 0.15–0.45; $p < 0.00001$). At the same time, these results were consistent with the efficacy of cefuroxime observed in the ESCRS randomized clinical trial (OR = 0.21; 95% CI: 0.08–0.54; $p = 0.001$) [36]. In turn, Kessel et al. [37], on the basis of the results of 10 observational studies, demonstrated that cefuroxime reduced the incidence of POE after cataract surgery by 91% as compared with the baseline risk without its use (relative risk [RR] = 0.09; 95% CI: 0.05–0.15; $p < 0.001$) [37]. A Cochrane Collaboration review evaluated the effectiveness of intraoperative endophthalmitis prophylaxis during cataract surgery [38]. Of the five randomized clinical trials published up to 2016, only the study on cefuroxime in POE prophylaxis (ESCRS) provided evidence with the highest level of certainty. The authors of the review indicate that owing to the rare occurrence of POE and the need to include large patient populations, it is unlikely that many more clinical trials regarding the prevention of POE will be conducted. In view of the above, many single-centre observational studies have been performed on the effectiveness of POE prophylaxis with cefuroxime. All these studies unanimously confirm the efficacy of cefuroxime, demonstrated in the ESCRS study [38].

CATARACT SURGERY IN POLAND

Cataract surgery is an example of a medical service that — except for very limited cases requiring general anaesthesia — should not require hospitalization. Access to less invasive surgical techniques and better anaesthetics has increased in recent years. These innovations have, on the one hand, improved the safety and health-related outcomes of surgery and, on the other, reduced costs and increased access to surgery. During the decade of 2004–2014, there was a gradual increase in the proportion of individuals aged ≥ 65 years undergoing cataract surgery and in the number of cataract operations per 100,000 inhabitants in most European countries. The most notable trend was the increase in the percentage of cataract surgeries performed as same-day interventions [39].

These trends have also been noted in Poland in recent years. According to the data of the National Health Fund of Poland, in 2017, the proportion of operations performed as same-day interventions amounted to about 50%. The changes to cataract surgery funding introduced in 2018 have provided an impetus to move away from multiple-day hospitalization of patients. Consequently, since the second half of 2019, the percentage of same-day surgeries in Poland has remained at the level exceeding 95%. This change was accompanied by a simultaneous reduction in the number of patients waiting for cataract surgery (from about 500,000 in 2017 to about 100,000 at the end of 2020) and a shortening of the average time to wait for surgery (from about 480 days in 2017 to about 120 days at the end of 2020) [15]. The above improvements are a major success in cataract surgery in Poland, which has significantly increased the procedure availability to patients while making better use of medical resources.

COST-EFFECTIVENESS OF POE PROPHYLAXIS WITH CEFUROXIME (APROKAM®) IN POLAND

Pharmacoeconomic analyses are conducted to determine which available interventions will produce the most significant health-related effects at the lowest cost in a given indication. Rękas et al. [40] conducted a cost-effectiveness and cost-utility analysis of POE prophylaxis with cefuroxime (Aprokam®) injected into the anterior chamber of the eye under aseptic conditions, i.e. one vial for one patient, as compared with no such prophylaxis. The analysis was based on a model incorporating parameters related to the course of the disease and the costs of its treatment in Poland. The risk of POE in the Polish population of patients not receiving anterior chamber antibiotic prophylaxis was assumed to be 0.337% [11], and the efficacy of cefuroxime was based on the ESCRS study results [4]. The model considers

the quality of life (health utility) for the health states "with POE" and "without POE". POE can result in significant visual impairment; therefore, the model differentiates the quality of life depending on visual acuity after POE. The analysis indicated that the application of cefuroxime (Aprokam®) to the anterior chamber of the eye after cataract surgery allowed to avoid 30 cases of POE per 10,000 patients in Poland. From a lifetime perspective, the benefit of cefuroxime (Aprokam®) allows to achieve 7 quality-adjusted life years (QALY) per 10,000 patients. The total costs of treatment are about 8 PLN higher with the Aprokam® formulation prophylaxis in comparison with the lack of prophylaxis with this antibiotic [40]. According to the National Health Fund of Poland, 380,000 and 290,000 cataract surgeries were performed in 2019 and 2020, respectively [15]. Considering the results of the cost-effectiveness analysis, one can estimate that routine, appropriate administration of Aprokam® would have prevented approximately 1100 and 860 cases of POE in 2019 and 2020, respectively. The authors of the analysis demonstrated that cefuroxime (Aprokam®) was a highly cost-effective intervention. The incremental cost-utility ratio (ICUR), i.e., the cost of obtaining an additional QALY with the use of cefuroxime (Aprokam®) in the Polish conditions, equals approximately 11,000 PLN/QALY. This represents approximately 8% of the cost-effectiveness threshold at the time (139,953 PLN/QALY in years 2018–2019) [40]. Because of the scarce epidemiological data on the incidence of POE in Poland and the associated uncertainty, the authors of the analysis conducted the modelling for extreme values, i.e., the incidence of 0.125% and 3%. Neither the lowest nor the highest POE incidence changed the inference: cefuroxime (Aprokam®) prophylaxis turns out cost-effective in each option. At the lowest POE risk, i.e., 0.125%, ICUR reached a value of 60% of the cost-effectiveness threshold at the time [40]. The results of the Polish analysis of the cost-effectiveness of POE prophylaxis with cefuroxime (Aprokam®) remain in line with those obtained in the United States [41], Spain [29], and France [12]. Both the cost-effectiveness of cefuroxime (Aprokam®) and the potential savings from the prevented POE cases are consistently demonstrated.

CONCLUSIONS

Cefuroxime administered into the anterior chamber of the eye at the end of cataract surgery effectively reduces the risk of POE. This was confirmed in an ESCRS randomized controlled clinical trial and in numerous prospective and retrospective observational studies conducted in Europe. The results of the ESCRS study and the registration by the European Medicines Agency of a cefuroxime solution prepared for use directly in the operating room (Aprokam®) have exerted a major impact on clinical practice. Following the European ESCRS guidelines, cefuroxime prophylaxis is recommended by the Society of Polish Ophthalmologic Surgeons and by the Polish Ophthalmological Society. The active monitoring of the quality of cataract surgery by the National Health Fund of Poland confirms that POE incidence is still higher in Poland than in other European countries. In recent years, cataract treatment in Poland has undergone favourable changes, with an almost complete shift to surgeries performed as same-day interventions. This has resulted in a significant reduction in queues and waiting times. As implied by the experience of other countries, routine intraoperative administration of cefuroxime can significantly reduce the risk of POE as a cataract removal complication. Prophylaxis with the Aprokam® formulation is highly cost-effective, with ICUR constituting a small fraction of the official cost-effectiveness threshold in Poland.

Conflict of interest

MR, KKJ, RR have indicated no conflicts of interest. KJ and DG have declared the financial support from Thea Polska Sp. z o.o.

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