

MAŁGORZATA BADEŁEK-IZDEBSKA, *LIDIA ZAWADZKA-GŁOS

Increase in middle ear infections of *Streptococcus pyogenes* etiology among patients of the Department of Pediatric Otolaryngology of the Medical University of Warsaw in correlation with world reports

Wzrost liczby zakażeń ucha środkowego o etiologii *Streptococcus pyogenes* wśród pacjentów Kliniki Otolaryngologii Dziecięcej Warszawskiego Uniwersytetu Medycznego w korelacji ze światowymi doniesieniami

Department of Pediatric Otolaryngology, Medical University of Warsaw, Poland

Head of Department: Associate Professor Lidia Zawadzka-Głós, MD, PhD

KEYWORDS

Streptococcus pyogenes (GAS), invasive *Streptococcus pyogenes* (iGAS), acute otitis media (AOM), acute mastoiditis

SUMMARY

Introduction. Beta-hemolytic streptococcus is one of the most common causes of out-of-hospital infections. It can cause local or general infections of varying severity, most commonly in the throat, paranasal sinuses, ear and skin. Some infections are invasive in nature. In the last months of 2022, an alarming increase in infections caused by *Streptococcus pyogenes*, including invasive infections, has been observed in many countries in Europe and around the world compared to previous years.

Aim. The purpose of this study was to compare the number of hospitalized patients with acute otitis media and acute mastoiditis of *S. pyogenes* etiology in the first six months of 2023 with hospitalizations for the same reason in the previous 5 years, and to assess the correlation with the observed worldwide trend of an increase in the number of observed beta-hemolytic streptococcus type A infections.

Material and methods. A retrospective analysis of the data of patients diagnosed with acute otitis media and acute mastoiditis of *S. pyogenes* etiology hospitalized in the Department of Pediatric Otolaryngology in the first six months of 2023 was carried out, and their number was compared with patients hospitalized for the same reason in the previous 5 years.

Results. Between January 2023 and the end of June 2023, 15 patients with acute otitis media were hospitalized in the Department of Pediatric Otolaryngology, in which *S. pyogenes* was isolated by bacteriological examination. Purulent leakage from the ear was observed in 10 patients. Isolated otitis media was diagnosed in 4 patients. In 10 children, AOM was complicated by acute mastoiditis, which was confirmed by CT scan. The most severe complication was sepsis of GAS etiology. Intravenous antibiotic therapy and surgical treatment were implemented in all patients, achieving a cure. From 2018 to 2022, the number of patients hospitalized for the same reason was significantly lower each year.

Conclusions. The number of patients hospitalized in the Department of Otolaryngology in the last two months of 2022 and in the first six months of 2023 due to AOM, as well as AOM complicated by mastoiditis, in which the etiologic agent turned out to be *S. pyo-*

genes confirmed the observed worldwide trend towards an increase in the incidence of GAS. GAS-induced AOM is characterized by greater local aggressiveness, manifested by a higher incidence of tympanic membrane perforation, as well as mastoiditis with bone destruction. The primary antibiotic used to treat GAS infections is penicillin, with sensitivity to penicillin also implying sensitivity to all beta-lactam antibiotics. The treatment of GAS with intratemporal complications in the form of acute mastoiditis caused by *S. pyogenes*, especially progressing with bone destruction, requires combined antimicrobial therapy with surgical treatment.

SŁOWA KLUCZOWE

Streptococcus pyogenes (GAS), inwazyjny *Streptococcus pyogenes* (iGAS), ostre zapalenie ucha środkowego (OZUŚ), ostre zapalenie wyrostka sutkowego

STRESZCZENIE

Wstęp. Paciorkowiec beta-hemolizujący jest jedną z najczęstszych przyczyn zakażeń pozaszpitalnych. Może on wywoływać infekcje o charakterze miejscowym lub ogólnym o różnym stopniu ciężkości, najczęściej w obrębie gardła, zatok przynosowych, ucha i skóry. Niektóre zakażenia mają charakter inwazyjny. W ostatnich miesiącach 2022 roku zaobserwowano w wielu krajach Europy i świata niepokojący wzrost zakażeń spowodowanych *Streptococcus pyogenes*, w tym również zakażeń inwazyjnych, w porównaniu do lat poprzednich.

Cel pracy. Celem pracy było porównanie liczby hospitalizowanych pacjentów z ostrym zapaleniem ucha środkowego oraz ostrym zapaleniem wyrostka sutkowego o etiologii *S. pyogenes* w pierwszym półroczu 2023 roku z hospitalizacjami z tego samego powodu w poprzednich 5 latach oraz ocena korelacji z obserwowanym ogólnosiwiatowym trendem wzrostu ilości obserwowanych zakażeń paciorkowcem beta-hemolizującym typu A.

Materiał i metody. Przeprowadzono retrospektywną analizę danych pacjentów z rozpoznaniem ostrym zapaleniem ucha środkowego oraz ostrym zapaleniem wyrostka sutkowego o etiologii *S. pyogenes* hospitalizowanych w Klinice Otolaryngologii Dziecięcej w pierwszym półroczu 2023 roku oraz porównano ich liczbę z pacjentami hospitalizowanymi z tego samego powodu w poprzednich 5 latach.

Wyniki. W okresie od stycznia 2023 roku do końca czerwca 2023 roku w Klinice Otolaryngologii Dziecięcej WUM hospitalizowano 15 pacjentów z ostrym zapaleniem ucha środkowego, u których w badaniu bakteriologicznym wyizolowano *S. pyogenes*. Wyciek ropny z ucha obserwowano u 10 pacjentów. Izolowane zapalenie ucha środkowego rozpoznano u 4 pacjentów. U 10 dzieci OZUŚ było powikłane ostrym zapaleniem wyrostka sutkowego, co potwierdzono w badaniu TK. Najcięższym powikłaniem była posocznica o etiologii GAS. U wszystkich pacjentów wdrożono antybiotykoterapię dożylną i leczenie zabiegowe, uzyskując wyleczenie. W latach 2018-2022 liczba pacjentów hospitalizowanych z tego samego powodu była rokrocznie znacząco niższa.

Wnioski. Liczba pacjentów hospitalizowanych w Klinice Otolaryngologii WUM w ostatnich dwóch miesiącach 2022 roku oraz w pierwszym półroczu 2023 roku z powodu OZUŚ, a także OZUŚ powikłanym zapaleniem wyrostka sutkowego, u których czynnikiem etiologicznym okazał się *S. pyogenes* potwierdziła obserwowany ogólnosiwiatowy trend do wzrostu zachorowań wywołanych przez GAS. OZUŚ wywołane przez GAS charakteryzuje się większą miejscową agresywnością, objawiającą się częstszym występowaniem perforacji błony bębenkowej, a także zapalenia wyrostka sutkowego z destrukcją kostną. Podstawowym antybiotykiem stosowanym w leczeniu zakażeń GAS jest penicylina, przy czym wrażliwość na penicylinę oznacza również wrażliwość na wszystkie antybiotyki beta-laktamowe. Leczenie OZUŚ z powikłaniami wewnątrzskroniowymi w postaci ostrego zapalenia wyrostka sutkowego wywołanego przez *S. pyogenes*, zwłaszcza przebiegającego z destrukcją kostną, wymaga zastosowania antybiotykoterapii skojarzonej z leczeniem zabiegowym.

INTRODUCTION

Streptococcus pyogenes (group A beta-hemolytic *Streptococcus*, GAS) is a Gram-positive bacteria belonging to the group of closely related pyogenic streptococci. *S. pyogenes* has the ability to colonize the human body, form a biofilm and induce inflammatory processes. This is enabled by the enzymes and toxins it produces, which include M protein (adhesin), variants of which are responsible for the formation of various GAS serotypes, fibronectin and

collagen binding proteins, hyaluronidase, streptokinase, streptolysins S and O, as well as pyrogenic exotoxins (superantigens). *S. pyogenes* can cause local or general infections of varying severity. For the most part, these infections are non-invasive in nature. The most common infections include acute pharyngitis and palatine tonsillitis, i.e. streptococcal tonsillitis and its complications: peritonsillar abscess, peritonsillar tissue inflammation, in addition to scarlet fever (scarlet fever), sinusitis, acute

otitis media, mastoiditis, infectious impetigo. GAS can also cause infections of an invasive nature, such as roseola (erysipelas), cellulitis, streptococcal toxic shock syndrome (STSS), necrotizing fasciitis (NF), sepsis, pneumonia and pleuritis, peritonitis, meningitis, arthritis, osteomyelitis, and perinatal infections. GAS can also cause disease in the form of post-infectious “non-pyogenic” (not associated with local bacterial multiplication and pus formation) syndromes such as acute rheumatic fever resulting in myocarditis and arthritis, and acute glomerulonephritis.

S. pyogenes is the exclusive human pathogen, which in health conditions is the so-called endogenous bacterial flora of the nasopharynx. GAS carriers are most often school-aged children, i.e. between 5 and 15 years of age. The development of infection may occur as a result of activation of a strain living in the nasopharynx or by droplets and through contact with mucous secretions of a sick person or carrier (exogenous infection). GAS can also be transmitted through infected wounds or by contact with inflamed skin. Confirmation of *S. pyogenes* infection is provided by a positive result of a rapid antigen test, classical bacteriological culture on a special medium, molecular testing (PCR) or a serological test detecting antibodies – antistreptolysin O (ASO). Beta-hemolytic streptococcus is one of the most common causes of out-of-hospital infections.

In the first half of the 20th century, GAS was the most commonly isolated pathogen in patients with acute otitis media, but since the 1950s, cultures have begun to be dominated by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Currently, *Streptococcus pyogenes* is the fourth most common pathogen isolated from cultures from the tympanic cavity. In Poland, a register of invasive infections of *S. pyogenes* etiology is maintained. Notifications are sent to Provincial Sanitary and Epidemiological Stations, and in turn to the National Institute of Public Health – National Institute of Hygiene. Laboratory-confirmed cases are registered with the National Reference Center for Infections of the Nervous System (KOROUN).

Non-invasive GAS infections are easily treated. The primary antibiotic used to treat these infections is penicillin. Sensitivity to penicillin also means sensitivity to other beta-lactam antibiotics. Patients cease to be contagious to the environment after 24 hours from the start of antibiotic therapy. So far, no resistance of *S. pyogenes* to penicillin has been observed, while it tends to increase with macrolides, which are an alternative for treating patients with penicillin hypersensitivity (1). For invasive GAS infections developing deep in the tissues, penicillin alone is not fully effective therefore it is often associated with clindamycin.

AIM

The aim of this study was to compare the number of hospitalized patients infected with *S. pyogenes* in 2023 with hospitalizations for the same reason in the previous 5 years,

and to assess the correlation with the observed global trend of an increase in the number of observed beta-hemolytic streptococcus type A infections. Due to the specifics of our clinical department, we focused only on patients requiring hospitalization for isolated acute otitis media and AOM with acute mastoiditis.

MATERIAL AND METHODS

A retrospective data analysis of patients diagnosed with acute otitis media and acute mastoiditis of *S. pyogenes* etiology hospitalized in the Department of Pediatric Otolaryngology in the first six months of 2023 was carried out, and their numbers were compared with patients hospitalized for the same reason in the previous five years.

RESULTS

Between January 2023 and the end of June 2023, 15 patients with acute otitis media were hospitalized in the Department of Pediatric Otolaryngology of the Medical University of Warsaw, in which *Streptococcus pyogenes* was isolated by bacteriological examination. The youngest patient at the time of onset was 8 months old, the oldest patient was 12 years old, the mean age was 4.3 years. There were 10 boys and 4 girls among the patients. Among the general symptoms, ear pain and fever predominated, and on physical examination, most patients had protrusion of pinna and retroauricular swelling and redness. Purulent leakage from the ear on admission to the hospital was observed in 10 patients. Isolated acute otitis media was diagnosed in 3 patients. Chronic otitis with otorrhea presented 1 patient, who was congenital HIV infection. In 10 children, otitis media was complicated by acute mastoiditis. One patient presented with facial nerve paresis on the side of the affected ear. One patient was diagnosed with influenza B infection before admission. In the most severely ill patient, sepsis of *S. pyogenes* etiology was confirmed, as well as thrombophlebitis of the sigmoid and transverse sinus. In all 10 patients with suspected mastoiditis, a head CT scan was performed confirming the suspected complication.

All 14 patients received empirical intravenous antibiotic therapy in the form of ceftriaxone with clindamycin (9 patients with AOM and mastoiditis), crystalline penicillin with clindamycin (1 patient with AOM complicated by mastoiditis, sepsis and cerebral venous sinus thrombosis), biotraxone (2 patients), amoxicillin with clavulanic acid (2 patients). Due to the coexistence of intracranial complications and the presence of bone destruction in most patients, as well as the observed clinical improvement and resolution of symptoms, we did not deescalate antibiotic therapy. Only in 3 patients, due to persistent purulent leakage from the ear, we changed ceftriaxone to crystalline penicillin during treatment.

All patients were qualified for surgical treatment: 10 patients with mastoiditis underwent an anthromastoidectomy with myringotomy and ventilation drainage, the remaining

four patients underwent only myringotomy with ventilation drainage. Bacteriological tests were performed from material taken from the external auditory canal (patients with purulent leakage), from the tympanic cavity (with myringotomy) or from mastoid cells. The antibiogram of cultured *S. pyogenes* in each case confirmed the pathogen's susceptibility to all beta-lactam antibiotics, erythromycin, clindamycin and benzyl penicillin.

The duration of intravenous antibiotic therapy was: 7 days for patients with drainage, 10 days for patients with anthromastoidectomy and 14 days for a patient with complications such as sepsis and thrombosis.

All patients were cured. In the child with facial nerve palsy, nerve function has returned to normal. The patient with thrombosis is under hematological care and requires monitoring of the effects of thrombosis treatment with low-molecular-weight heparin.

The following are data on patients hospitalized in the years 2018-2022 for AOM and AOM with mastoiditis of the etiology of *S. pyogenes*.

In 2022, the Department of Otolaryngology at WUM hospitalized 7 patients with *S. pyogenes* etiology, among whom 1 patient received only intravenous antibiotic therapy, 6 patients also received ventilator drainage, while 3 patients required an anthromastoidectomy. An important note is that 4 of the 7 patients were hospitalized in November and December 2022.

In 2021, AS complicated by mastoiditis of GAS etiology was confirmed in 3 patients, all of whom required surgical treatment-anthromastoidectomy with ventilation drainage.

In 2020, our Clinic treated only 1 patient with AOM complicated by mastoiditis of GAS etiology, in whom an anthromastoidectomy with placement of ventilation drains was performed.

In 2019, 3 patients with AOM and mastoiditis of *S. pyogenes* etiology were hospitalized. Treatment included antibiotic therapy i.v. anthromastoidectomy and drainage of the tympanic cavity.

In 2018, again, only 1 patient with acute otitis media and mastoiditis had GAS as the cause of inflammation.

DISCUSSION

In the first half of the 20th century, GAS was the most commonly isolated pathogen in patients with acute otitis media, but since the 1950s, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* began to dominate bacteriological studies. Currently, *Streptococcus pyogenes* is the fourth most common pathogen isolated from eardrum cavity cultures (2).

In March 2023, KOROUN published information about the increase in *Streptococcus pyogenes* infections in Poland and other countries (3). The information was related to the publication of a report by the UK Health Security Agency (UKHSA) on the sharp increase in the number of cases of diphtheria, but also in the number of iGAS

infections compared to the same period of the year in previous years (4). The increased incidence of iGAS affected all age groups with the largest increase in children under 10 years of age (an increase from 4-12 to 24%). Of particular concern was the increased number of deaths among children under the age of 15 from invasive GAS infections (4). Also in December 2022 World Health Organization (WHO) confirmed information flowing to it (5) from the ECDC (European Centre for Disease Prevention and Control), among others, about the alarming increase in iGAS not only in other European countries such as: Netherlands, France, Ireland (6-8), Great Britain (9), but also in the United States (10).

In the course of studies conducted so far, among others, typing emm (the gene encoding the M protein), no newly emerging types of GAS gene sequences have been identified, which would explain the observed increase in GAS infections. Also, no increase in resistance to previously used antibiotics for treatment has been observed.

Some authors suggest that the reason for the high incidence rate of GAS in 2022/2023 can be attributed primarily to the widespread spread of the pathogen in the non-immunocompetent population. The low exposure to GAS in recent years associated with the implementation of COVID-19-related restrictions – mainly non-pharmacological interventions in the form of social distancing and wearing masks – has likely resulted in lower levels of immunity to GAS at the population level. This is particularly evident among the youngest children, a large proportion of whom have never been exposed to this particular pathogen. Also of great importance is the increased activity of influenza viruses, rhinoviruses or RSV, which, by damaging the epithelium of the respiratory tract, may facilitate mucosal colonization by *S. pyogenes*, which may also explain the increase in the number of iGAS infections recorded in the winter season of 2022/23 in many European countries (11, 12). The increased number of cases of iGAS without or with a complication of acute mastoiditis of *S. pyogenes* etiology observed by our Department confirmed the alarming increase in infections due to GAS observed in many countries. The highest number of middle ear infections of GAS etiology requiring hospitalization was recorded in November 2022, as well as in January and February 2023.

CONCLUSIONS

The number of patients hospitalized in the Department of Otolaryngology at WUM in the last two months of 2022 and in the first six months of 2023 due to AOM, as well as AOM complicated by mastoiditis, in which *S. pyogenes* turned out to be the etiologic agent, confirmed the observed worldwide trend toward an increase in GAS-caused infections.

GAS-induced AOM is characterized by greater local aggressiveness, manifested by a higher incidence of tympanic membrane perforation (13), as well as mastoiditis with bone destruction (14, 15).

The primary antibiotic used to treat GAS infections is penicillin, and sensitivity to penicillin also means sensitivity to all beta-lactam antibiotics. The treatment of GAS with intratemporal complications in the form of acute mastoiditis caused by *S. pyogenes*, especially progressing with bone

destruction, requires combined antimicrobial therapy with surgical treatment.

The observed increase in GAS infections should oblige healthcare staff to remain vigilant and result in appropriate treatment to minimize the risk of iGAS invasive disease.

CONFLICT OF INTEREST KONFLIKT INTERESÓW

None
Brak konfliktu interesów

CORRESPONDENCE ADRES DO KORESPONDENCJI

*Lidia Zawadzka-Głós
Klinika Otolaryngologii Dziecięcej
Warszawski Uniwersytet Medyczny
ul. Żwirki i Wigury 63A
02-091 Warszawa
tel.: +48 (22) 317-97-21
laryngologia.dsk@uckwum.pl

submitted/nadesłano:

6.10.2022

accepted/zaakceptowano do druku:

27.10.2022

REFERENCES/PIŚMIENNICTWO

1. Hon KL, Chow TC, Cheung TS et al.: Severe Group A and Group B Streptococcus Diseases at a Pediatric ICU: Are they Still Sensitive to the Penicillins? *Curr Clin Pharmacol* 2020; 15(2): 125-131.
2. Hullegie S, Venekamp RP, van Dongen TMA et al.: Prevalence and Antimicrobial Resistance of Bacteria in Children With Acute Otitis Media and Ear Discharge: A Systematic Review. *Pediatr Infect Dis J* 2021; 40(8): 756-762.
3. https://koroun.nil.gov.pl/wp-content/uploads/2023/03/kopia_GAS-10.03.2023.pdf.
4. <https://www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2022-to-2023-season/group-a-streptococcal-infections-report-on-seasonal-activity-in-england-2022-to-2023>.
5. World Health Organization (15 December 2022): Disease Outbreak News; Increased incidence of scarlet fever and invasive Group A Streptococcus infection – multi-country. Available at: <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON429>.
6. <https://www.ecdc.europa.eu/en/news-events/increase-invasive-group-streptococcal-infections-among-children-europe-including>.
7. Health Protection Surveillance Centre (HPSC). Update on group A streptococcus. HPSC, Dublin 2022. Available from: <https://www.hpsc.ie/news/title-22663-en.html>.
8. De Gier B, Marchal N, de Beer-Schuurman I et al.: Members of the GAS study group; members of the ISIS-AR study group. Increase in invasive group A streptococcal (*Streptococcus pyogenes*) infections (iGAS) in young children in the Netherlands, 2022. *Euro Surveill* 2023; 28(1).
9. Guy R, Henderson KL, Coelho J et al.: Increase in invasive group A streptococcal infection notifications, England, 2022. *Euro Surveill* 2023; 28(1): 2200942.
10. Centers for Disease Control and Prevention (CDC). Increase in invasive group A strep infections, 2022. CDC, Atlanta 2022.
11. de Gier B, Vlamincx BJM, Woudt SHS et al.: Associations between common respiratory viruses and invasive group A streptococcal infection: A time-series analysis. *Influenza Other Respir Viruses* 2019; 13(5): 453-458.
12. Herrera AL, Huber VC, Chaussee MS: The Association between Invasive Group A Streptococcal Diseases and Viral Respiratory Tract Infections. *Front Microbiol* 2016; 7: 342.
13. Marchisio P, Esposito S, Picca M et al.; Milan AOM Study Group: Prospective evaluation of the aetiology of acute otitis media with spontaneous tympanic membrane perforation. *Clin Microbiol Infect* 2017; 23(7): 486.e1-486.e6.
14. Segal N, Givon-Lavi N, Leibovitz E et al.: Acute otitis media caused by *Streptococcus pyogenes* in children. *Clin Infect Dis* 2005; 41(1): 35-41.
15. Cohen R, Varon E, Bidet P et al.: Diagnostic Accuracy of Group A Streptococcus Rapid Antigen Detection Test on Middle Ear Fluid in Children With Acute Otitis Media With Spontaneous Perforation: A Prospective Multicenter Evaluation. *Pediatr Infect Dis J* 2023; 42(9): 816-818.