Ekvivalent: Mikrobiološki uzročnici kroničnog rinosinuitisa i njihova antimikrobna osjetljivost - utjecaj na antibiotsku profilaksu i liječenje

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Završni specijalistički rad

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MICROBIAL CAUSATIVE AGENTS AND THEIR ANTIMICROBIAL SUSCEPTIBILITY PATTERNS IN CHRONIC RHINOSINUSITIS – IMPACT ON ANTIBIOTIC PROPHYLAXIS AND TREATMENT

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SUMMARY – Chronic rhinosinusitis (CRS) is debilitating condition comprising inflammation of the mucosa of the nasal and paranasal sinuses, requiring conservative and often surgical treatment. Functional endoscopic sinus surgery (FESS) is a CRS treatment during which a microbiological diagnostic procedure may be conducted. Preoperative antibiotic prophylaxis is administrated before FESS. When indicated, the administered empiric antibiotic therapy must cover most common causing microbial agents. The aims of this study were to identify microbial pathogens isolated from sinonasal cavities in patients undergoing endoscopic sinus surgery, to determine bacterial antibiotic susceptibility patterns and compare them with guidelines for treatment and perioperative prophylactic use of antimicrobial agents. A retrospective cohort study on 456 samples collected between 2016 and 2019 was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery and the Department of Microbiology, Parasitology and Hospital Infections in the Clinical University Centre Sestre milordnice, Zagreb. The most common isolated pathogens were Peptostreptococcus spp., Propionibacterium spp., Staphylococcus aureus, Pseudomonas spp., Fusobacterium spp. and Haemophilus influenzae. According to antibiotic susceptibility patterns, empiric antibiotic treatment with amoxicillin-clavulanic acid was appropriate. Due to high rates of antibiotic resistance of anaerobic bacterial isolates to metronidazole, it cannot be recommended in empirical antibiotic treatment or preoperative surgical antibiotic prophylaxis.

Key words: *chronic rhinosinutis; sinus endoscopic surgery; antibiotic resistance; antibiotic prophylaxis*

Introduction

According to the European Position Paper on Rhinosinusitis and Nasal Polyps, chronic rhinosinusitis (CRS) is defined by two or more major symptoms, one of which must include nasal congestion or frontal or posterior discharge. Other symptoms may include facial pain or pressure and loss of the sense of smell, with duration of symptoms exceeding at least 12 weeks. Chronic rhinosinusitis is a clinical syndrome that comprises a heterogenous group of inflammatory diseases of the sinonasal mucosa, which effects patients' health-related quality of life and presents significant healthcare costs and burden[1-5].

The etiology of CRS has been a topic of constant research and still remains under investigation since it has been associated with diverse causative factors,

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including microbial agents, anatomic variations, genetic disorders of ciliary epithelium, acquired epithelial barrier integrity and mucociliary clearance disorders such as secondary ciliary dyskinesia, as well as immune-mediated causative factors such as hypersensitivities associated with asthma, hormonal imbalance, autoimmune disorders and immunodeficiency. Microbial-based pathogenesis studies include investigation of a single pathogen, intramucosal bacteria, biofilm, and the mucosal dysbiosis hypothesis impact. Despite the diversity of potential causative factors, they all share permanent inflammation as the common mode of pathogenesis. The diagnosis of CRS should be confirmed by demonstrating sinonasal inflammation using anterior rhinoscopy, nasal endoscopy, or computed tomography. There are two major subtypes of chronic rhinosinusitis: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP).

Prevalence studies show that prevalence of CRS in general population varies between 2% and 15%, depending on CRS definition criteria. The highest prevalence was found in the studies using self-assessment questionaries, and the lowest prevalence in studies using MKB-9 code. Prevalence differed in age groups, with the highest proportion in the middle aged, working population[6-10].

CRS treatment options depend on presenting symptoms and potential complications, and include conservative and/or surgical treatment. Conservative treatment includes topical corticosteroids, nasal saline irrigation, and systemic antibiotic therapy for infectious exacerbations. Apart from antibiotic use in infectious exacerbations, there is a lack of high-quality evidence on routine antibiotic use, especially long-term non-macrolide antibiotics. Additionally, prolonged use of antibiotics is associated with the emerging antibiotic resistance rates of common respiratory bacterial pathogens[11]. Endoscopic sinus surgery is undertaken in patients requiring surgical treatment for normal drainage and sinus aeration, to prevent complications, and in complication resolutions[12]. Preoperative antibiotic prophylaxis is administrated before surgical treatment according to guidelines. In addition to prophylaxis, antibiotic treatment of chronic rhinosinusitis is one of the most common reasons for antibiotic prescription. Therefore, it is of great importance to monitor antibiotic susceptibility patterns of bacterial respiratory pathogens isolated in patients undergoing sinus surgery. Surveillance of antibiotic susceptibility patterns serves as an adjustment tool for prophylactic and empiric antibiotic treatment guidelines.

The aims of this study were to identify microbial pathogens isolated from sinonasal cavities in patients undergoing endoscopic sinus surgery, to determine bacterial antibiotic susceptibility patterns and to compare them with guidelines for treatment and perioperative prophylactic use of antimicrobial agents.

Methods

Setting

The study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery and the Department of Microbiology, Parasitology and Hospital Infections in Clinical University Centre Sestre milordnice, Zagreb.

Study design

This was a retrospective cohort study on microbiology reports originating from paranasal sinuses sampling in patients who underwent functional endoscopic sinus surgery. Maxillary, ethmoid, frontal, and sphenoidal sinuses were sampled. Patients included in the study had chronic rhinosinusitis (CRS) with or without complications. Diagnostic criteria for CRS were applied according to EPOS2012 guidelines[13]. The study was conducted from January 1st, 2016 util December 31st, 2019.

Microbiological analysis

Samples were obtained during surgery using Dacron swabs and referred to the Department of Microbiology, Parasitology and Hospital Infections. Bacteriological and fungal analysis were performed. Specimens were inoculated on 5% sheep blood agar, MacConkey agar, thioglycolate broth and Sabouraud agar. Media were incubated for 24 hours at 35-37 °C in aerobic conditions and for 48 hours in anaerobic conditions using anaerobic bags (Biomeriux, France) at 35-37 °C. Plates were examined for culture growth, and isolated bacterial and fungal strains were identified. Identification was performed using Graims stains, conventional biochemical tests and the VITEK 2 automated method (BioMerieux, France). Fungal isolates were identified to the genus and species level using Yeast ID 32 (BioMerieux, France) for yeast

isolates and native microscopy for mold isolates. Coagulase-negative staphylococci and diphtheroid bacteria were categorized as normal non-pathogenic upper respiratory tract microbiota, previously known as saprophytic bacteria. Antimicrobial susceptibility was determined using the Kirby-Bauer disk diffusion susceptibility test or E-test according to EUCAST standards[14].

Antibiotic susceptibility patterns were compared to antibiotic prophylaxis therapy recommended by Croatian national guidelines for perioperative prophylactic use of antimicrobial agents in otorhinolaryngology and head and neck surgery and to international and national guidelines for empiric antibiotic therapy for chronic rhinosinusitis[15,16].

Ethical considerations

The study was approved by the University Hospital Centre Sestre milosrdnice Ethical Committee.

Results

During the 4-year study period, 456 samples of paranasal sinuses taken during endoscopic sinus surgery were analysed. Swabs were sampled from maxillary sinuses (372/81.6%), ethmoid sinuses (64/14%), frontal sinuses (16/3.5%) and sphenoidal sinuses (4/0.9%) (Table 1).

Table 1. Paranasal sinus sampling sites

Sinus_Number of swabs	%	
Maxillary	372	81.6
Ethmoid	64	14.0
Frontal	16	3.5
Sphenoid	4	0.9
TOTAL	456	

No bacterial or fungal potential pathogens were detected in 182 samples (39.9%), and inoculated specimens after the incubation period were either sterile or normal upper respiratory tract microbiota was isolated. Forty-five (9.9%) of overall samples were sterile, and normal microbiota was isolated in 137 samples (30.0%).

Twenty-five different bacterial and fungal species were isolated. Bacterial species (23/92%) predominated with 333 isolates. There were 2 fungal isolates, 1 yeast (*Candida glabrata*) and 1 mold (*Aspergillus niger*) (Fig. 1).

Six anaerobic bacterial species (*Peptostreptococcus* spp., *Propionibacterium* spp., *Bacteroides* spp., *Fusobacterium* spp., *Veillonella* spp., and *Prevotella* spp.) were isolated with a prevalence of 44.7% (149/333) among all bacterial isolates. The prevalence of gram-positive anaerobic bacterial species (*Peptostreptococcus* spp., *Propionibacterium* spp.) among all anaerobic isolates was 74.5% (111/149).

The prevalence of isolated aerobic bacterial species among all isolates was 55.3% (184/333), with 17 different species isolated. Six different aerobic gram-positive bacterial species with 80 bacterial strains, and 11 gram-negative species with 104 strains were identified, respectively. The most common isolate was *Peptostreptococcus* spp. (56/16.7%), followed by *Propionibacterium* spp. (55/16.4%) and *Staphylococcus aureus (*43/12,8%) (Fig. 2).

Mixed microbiota with minimally 2 species in was isolated 191 (41.9%) samples.

Antibiotic susceptibility and resistance patterns of anaerobic isolates are presented by arrangement in two subgroups, gram-positive and gram-negative anaerobic bacteria (Fig. 3 and Fig. 4). According to EUCAST criteria, antibiotic susceptibility to penicillin, amoxicillin-clavulanate, clindamycin and metronidazole was determined for anaerobic bacteria due to their spectrum of activity.

The vast majority of both anaerobic bacteria subgroups were susceptible to amoxicillin-clavulanate, namely 100% of gram positive and 90% of gram-negative anaerobic bacteria. Among gram-positive anaerobic bacteria, all isolates were susceptible to penicillin, which also indicates susceptibility to amoxicillin. However, gram-negative anaerobes were mostly penicillin resistant (69%). The highest resistance rate was to metronidazole, with an overall 93% resistance among gram-positive anaerobes. The other subgroup of anaerobic bacteria, gram-negative anaerobes, showed resistance to metronidazole in 11% of strains. Both subgroups showed similar clindamycin resistance: 32% and 37%, respectively.

Antibiotic susceptibility of aerobic bacterial species is presented separately for most frequent isolates, *Staphylococcus aureus, Pseudomonas* spp. and all *Enterobacterales* species.

Staphylococcus aureus isolates were moderately resistant to sulfametoxazole-trimetoprime (4%) and

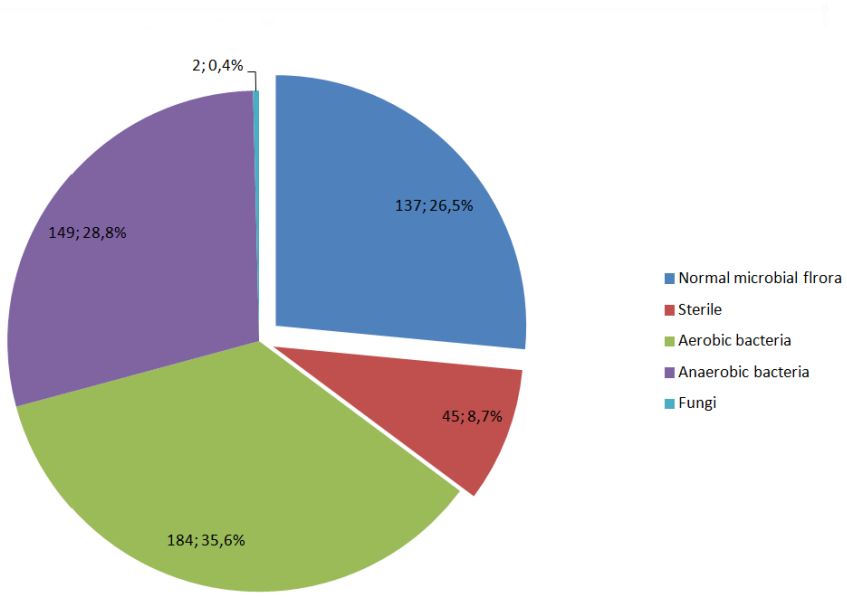

Fig. 1. Distribution of microbiology reports and isolated microbial species.

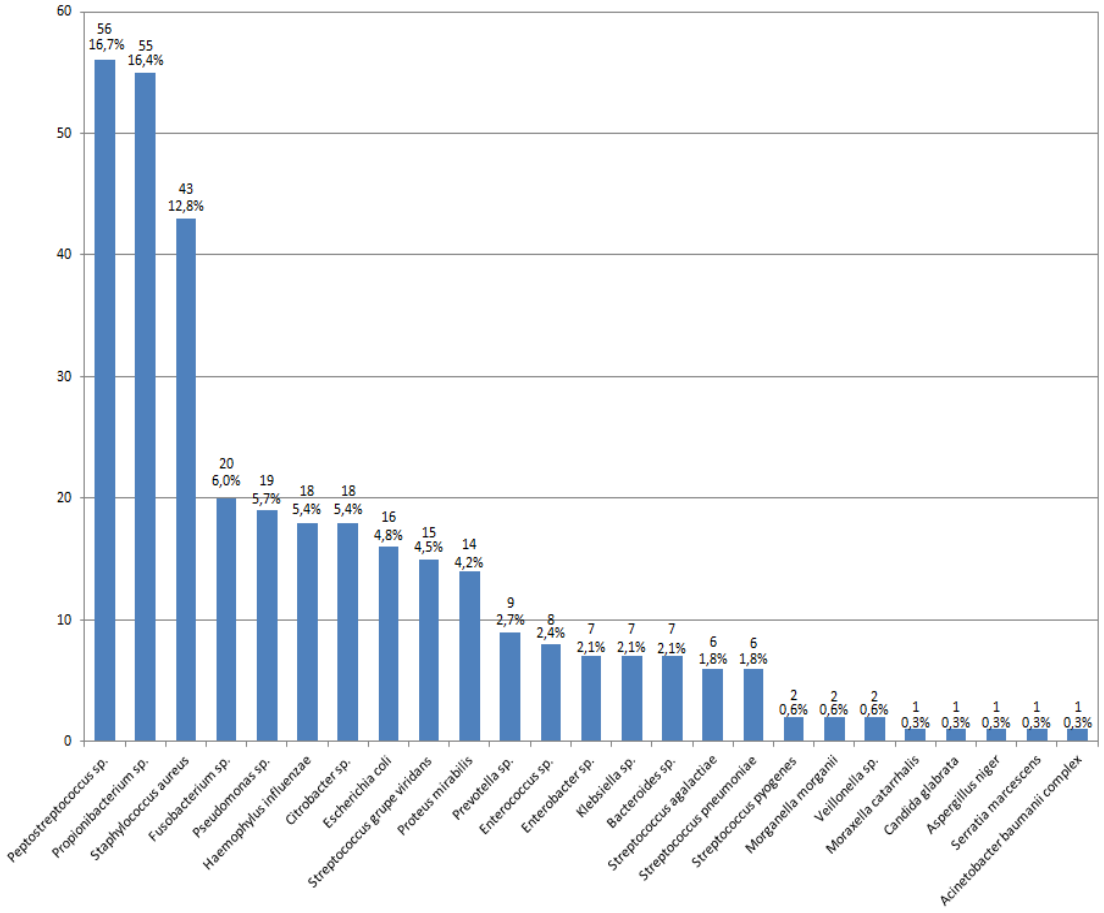

Fig. 2. Isolated bacterial and fungal species (N=335).

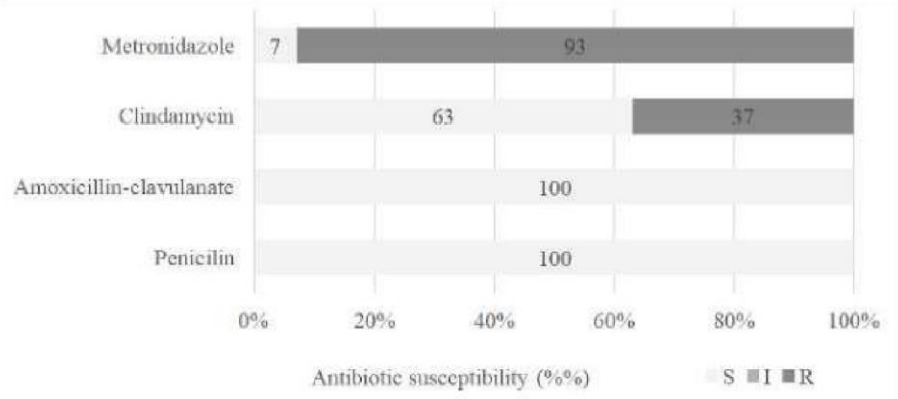

Fig. 3. Antibiotic susceptibility pattern of gram-positive anaerobic bacteria (N=111).

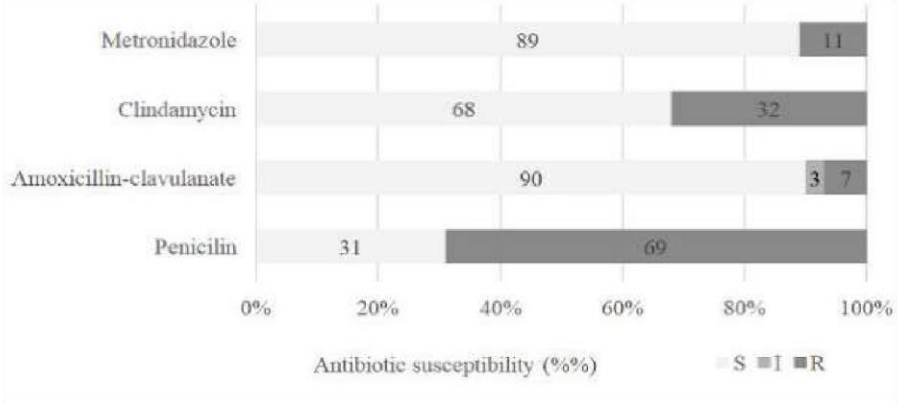

Fig. 4. Antibiotic susceptibility pattern of gram-negative anaerobic bacteria (N=38).

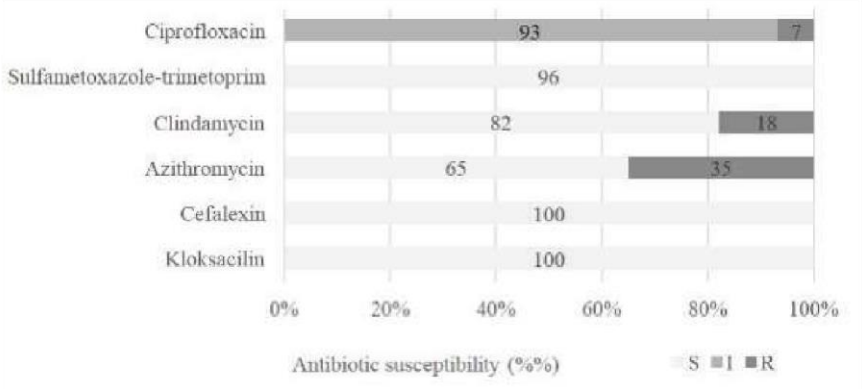

Fig. 5. Antibiotic susceptibility pattern of Staphylococcus aureus (N=43).

clindamycin (18%), with the highest resistance rate to azithromycin (35%) (Fig. 5).

Among *Enterobacterales* isolates (*Citrobacter spp.*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, and *Morganella morganni*), amoxicillin had the lowest susceptibility, with 78% resistant isolates. Parenteral cefuroxime showed a resistance pattern in 19% of isolates. The combination of amoxicillin with beta-lactamase inhibitor (clavulanate) was active against the majority of isolates, with a 22% resistance

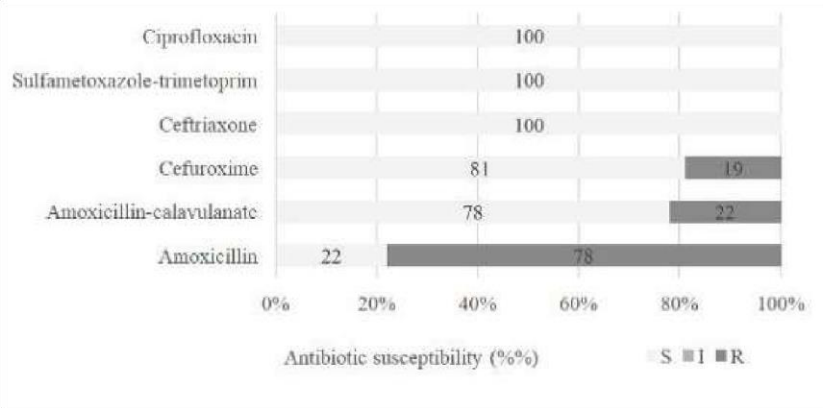

Fig. 6. Antibiotic susceptibility pattern of Enterobacterales (N=64).

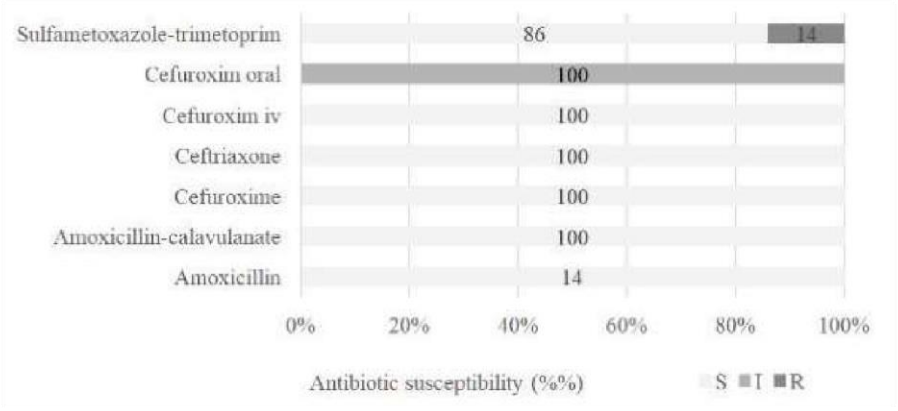

Fig. 7. Antibiotic susceptibility pattern of Haemophilus influenzae (N=18).

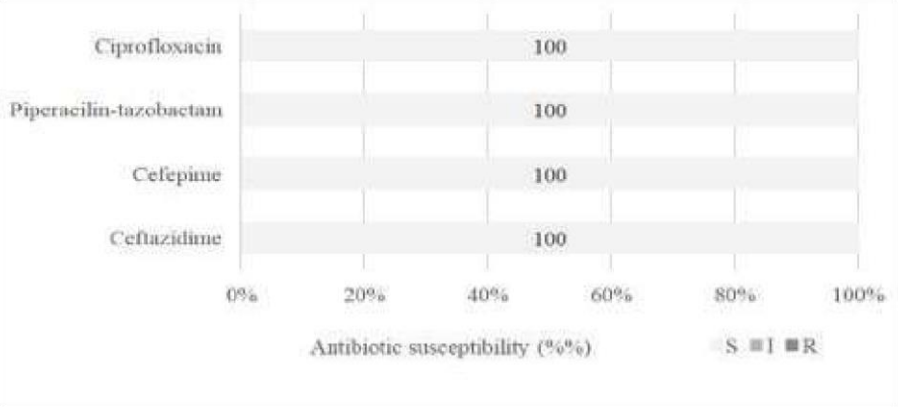

Fig. 8 Antibiotic susceptibility pattern of Pseudomonas spp. (N=19).

rate. Ceftriaxone, sulfamethoxazole, and ciprofloxacin were active against all isolated enterobacterial strains (Fig. 6).

Antimicrobial susceptibility of *Haemophilus influenzae* isolates to amoxicillin, amoxicillin-clavulanate, parenteral cefuroxime, and ceftriaxone was 100%, with decreased susceptibility to sulfametoxazole-trimeptoprim (86%) (Fig. 7).

All *Pseudomonas spp.* isolates were susceptible to anti-pseudomonal antimicrobials (ceftazidime, cefepime, piperacillin- tazobaktam, and ciprofloxacin (Fig. 8).

Due to the intrinsic resistance to macrolide, lincosamide, and streptogramin B antibiotics in *Haemophilus influenzae* and *Enterobacterales*, susceptibility to azithromycin and clindamycin was not reviewed.

Antifungal susceptibility to *Candida glabrata* and *Aspergillus niger* was not determined since isolated species were not systemic fungal infection causative agents but were considered mucosal colonization.

Discussion

Our results showed that more than one third of all samples had no potential pathogen isolated and were either sterile or normal upper respiratory tract microbiota was identified. This is concordant with previous data showing that in samples taken by sinus puncture or endoscopically assisted middle meatus swab bacterial pathogens were recovered in only 53% of cases, and with the fact that no high-level evidence supports the use of antibiotics in CRS, unlike acute bacterial sinusitis or exacerbations of CRS[1].

This is a reminder that not every sinusitis should be treated with an antimicrobial drug, especially when increasing resistance to antibiotics is taken into consideration. Several studies have shown that early and unnecessary antibiotic treatment does not prevent complications of bacterial sinusitis. Additionally, it has been established that antibiotic treatment influences normal microbiota composition diversity and creates the dominance of antibiotic-resistant species. These changes in microbiota structure may predispose a patient to secondary infection, often with resistant causative agents[2,16-21].

The exact pathogenesis and the role microbes play in CRS remains unclear. Since microbial communities and their biofilm formation, rather than single planktonic bacterial cells, are implicated in CRS pathogenesis, it is of uttermost importance to determine the exact species in patients with CRS. Our results, though using culture-based isolation techniques, support these findings. Polymicrobial microbiota and simultaneous existence of multiple pathogens were confirmed in a significant proportion of samples (41.9%).

Aerobic bacterial species predominantly cause acute sinusitis, and, as chronicity develops, anaerobes gradually take over their niche[23]. Most commonly isolated pathogens in CRS include anaerobic bacterial species: *Prevotella spp., Fusobacterium spp., Peptostreptococcus spp*. and aerobic bacterial species: *S. aureus*, *M. catarrhalis*, *Haemophilus spp*. and gram negative bacilli. These species were predominantly isolated in our study, with almost equal anaerobic to aerobic ratio (28.8% : 35.6%). Clinically, CRS associated with anaerobes is especially worrisome since most of CRS complications occur when these pathogens are present[24-26]. This further emphasizes the significance of choosing the right antibiotic therapy when indicated.

Antibiotic susceptibility patterns of most common isolated species were in concordance with antibiotic resistance and susceptibility patterns reported in the latest annual Croatian national antibiotic resistance surveillance published by Croatian Committee for Antibiotic Resistance Surveillance[27]. Amoxicillin resistance rate among our *Enterobacterales* species isolates was 78%, whilst national surveillance reports resistance rates ranging between 46% in *Proteus mirabilis* and 100% in *Klebsiella spp*., *Enterobacter spp*., *Morganella morganii, Citrobacter spp*., and *Serratia marcescens.*

In contrast to national average resistance rates, we observed increased azithromycin resistance in *Staphylococcus aureus*. The resistance of our isolates was 35%, whilst national reported resistance is 11%. Due to this high resistance rate in one of the most common isolates, and due to the intrinsic resistance in gram negative bacilli including *Haemophilus influenzae*, azithromycin cannot be recommended as an empirical antibiotic regimen.

We also determined that anaerobic bacterial species found in paranasal sinuses carry resistance to penicillin and consequently to ampicillin and amoxicillin in 78% in gram negative anaerobic species, which is an additional rationale for excluding amoxicillin as first-line empiric treatment in patients with CRS. We observed metronidazole resistance in 2/3 of the cases of isolated anaerobic bacterial species, 93% gram positive and 11% gram negative anaerobes, rendering this drug inadequate as an empirical choice. That finding is supported by are resistance rates of metronidazole presented in national surveillance reports. The resistance rate of gram positive anaerobic bacteria is 57%, and 11% among gram negative anaerobic bacteria.

In addition to empirical antibiotic treatment, surgical antibiotic prophylaxis guidelines for otorhinolaryngology and head and neck surgery advise that metronidazole should be administrated prior to

surgery, since anaerobic pathogens likely occur with major (contaminated, transmucosal) head, neck, and skull base surgeries[15]. The results of our study support the conclusion that an update of surgical prophylaxis guidelines for otorhinolaryngology and head and neck surgery section is needed.

According to our results, amoxicillin combined with clavulanic acid (amoxicillin-clavulanate) is still a valid choice as a broad-spectrum antibiotic in case of CRS, unlike amoxicillin alone. As an alternative to penicillin-derivatives, clindamycin or fluoroquinolones may instead be used, especially if *Staphylococcus aureus* and *Pseudomonas spp*. are suspected. These findings are in line with recent guidelines for antibiotic empirical regimen selection, suggesting amoxicillin-clavulanate as the first-line therapy when antibiotic therapy is warranted for penicillin-non-allergic patients. For adult penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent due to broad-spectrum antibacterial activity. Combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in children with a history of non-type I hypersensitivity to penicillin[28]. Our results are also in line with the latter recommendation. since ceftriaxone, which is a proxy for third generation cephalosporin susceptibility, showed 100% antimicrobial activity to all isolates tested, and anti-anaerobes activity of clindamycin was still maintained as well.

Our study had limitations concerning microbial detection and identification techniques, since conventional culture-based identification were used. However, it is estimated that 25-99% microbial communities, such as ones in CRS, are non-culturable[29,30]. Therefore, further research is needed using non-culturable, gene-targeted methods such as quantitative polymerase chain reaction (qPCR), fluorescence in situ hybridization (FISH), mass spectrometry, DNA microarray, new generation sequencing methods, as well as future-*omics* methods (metagenomics, metatranscriptomics, and metaproteomics).

Conclusion

Our study resulted in the isolation of the expected pathogens. The species isolated and their numbers were in line with the literature data. However, regarding their antibiotic sensitivity, our findings suggest a shift, specifically within the anaerobe group of bacteria. Since CRS, and especially CRS with complications, is initially treated with empirical antibiotic therapy, we conclude that metronidazole can no longer fulfil this role. It can be prescribed later with other antibiotics when therapy is being adjusted according to the relevant antibiogram. Other microbial causative agents, with anaerobes included, can still be treated with amoxicillin-clavulanate. Alternatives include clindamycin and fluoroquinolones.

Acknowledgments

There are no conflicts of interest to disclose.

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Sažetak

MIKROBIOLOŠKI UZROČNICI KRONIČNOG RINOSINUITISA I NJIHOVA ANTIMIKROBNA OSJETLJIVOST - UTJECAJ NA ANTIBIOTSKU PROFILAKSU I LIJEČENJE

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Kronični rinosinuitis (KRS) je iscrpljujuće stanje koje čini upala nosne sluznice i sluznice paranazalnih sinusa, a zahtjeva konzervativnu i, ponekad, kirurško terapiju. Funkcionalna endoskopska operacija sinusa je kirurška procedura koja se primjenjuje za KRS. Tijekom takve procedure može se vršiti i druga dodatna dijagnostika. Prije samog zahvata provodi se preoperativna antibiotska profilaksa. U tom slučaju, empirijski aplicirana antibiotska terapija treba pokrivati najčešće mikrobne uzročnike za navedeno stanje.

Cilj ove studije bio je identificirati mikrobne uzročnike izolirane iz sino-nazalnih šupljina kod pacijenata koji su bili podvrgnuti endoskopskoj operaciji sinusa te im odrediti bakterijsku osjetljivost kako bi se dobiveni podaci mogli potom usporediti s trenutno važećim smjernicama za antibiotsko liječenje i perioperativnu antibiotsku profilaksu.

Provedeno je retrospektivno kohortno istraživanje na 456 uzoraka prikupljenih od 2016. do 2019. godine u sklopu Klinike za otorinolaringologiju i kirurgije glave i vrata i Zavoda za mikrobiologiju, parazitologiju i hospitalne infekcije na Kliničkoj bolnici Sestara milosrdnica u Zagrebu.

Najčešće izolirani patogeni bili su Peptostreptococcus spp., Propionibacterium spp., Staphylococcus aureus, Pseudomonas spp., Fusobacterium spp. i Haemophilus influenzae. Prema dobivenim antibiogramima može se zaključiti da je empirijska terapija amoksicilin-klavulanskom kiselinom za ove uzročnike zadovoljavajuća. Međutim, primjena metronidazola empirijski ili za preoperativnu kirurško profilaksu se ne preporučuje zbog visokog udjela rezistencije na navedeni antibiotik unutar skupine anaerobnih bakterija.

Ključne riječi: *Kronični rinosinuitis, sinusna endoskopska kirurgija, antibiotska rezistencija, antibiotska profilaksa*

ŽIVOTOPIS

Rođen sam 27. lipnja 1992. godine u Bydgoszczu, Poljska.
2011. godine završio sam gimanzijski smjer Prirodoslovne škole Vladimira Preloga u Zagrebu.
Medicinski fakultet u Zagrebu upisao sam 2011. godine te na istome uspješno diplomirao 2017. godine. Tijekom studija na Fakultetu bio sam angažiran kao demonstrator na Katedri za anatomiju, a u kolovozu 2015. godine radio sam u sklopu studentske stručne prakse na Klinici KABEG Klagenfurt, Austrija. Pripravnički staž doktora medicine pohađao sam na KBC-u Sestre milsordnice, Zagreb, od studenog 2017. do travnja 2018. godine te sam položio Stručni ispit pred ispitnom komisijom Ministarstva zdravstva Republike Hrvatske 23. travnja iste godine. Član sam Hrvatske liječničke komore od svibnja 2018. godine. Od listopada 2018. godine započeo sam specijalizaciju iz otorinolaringologije za Županijsku bolnicu Čakovec, a klinički dio proveo sam na Klinici za otorinolaringologiju, KBC-a Zagreb. Tijekom specijalističkog usavršavanja educirao sam se kako u Republici Hrvatskoj tako i u inozemstvu na brojnim tečajevima i simpozijima iz otorinolaringologije i kirurgije glave i vrata.