The Microbiology of Acute Exacerbations in Chronic Rhinosinusitis - A Systematic Review

Oghenefejiro Okifo¹, Amrita Ray¹* and David A. Gudis²

¹ Department of Otolaryngology – Head & Neck Surgery, Henry Ford Health System, Detroit, MI, United States, ² Department of Otolaryngology Head and Neck Surgery, Columbia University, New York City, NY, United States

Background: Acute exacerbations (AE) in chronic rhinosinusitis (CRS) are a common and important clinical issue. However, relatively little is known regarding the underlying microbiology that drives exacerbations or how it relates to the microbiome of CRS. The purpose of this study is to examine the literature to characterize the microbiome associated with acute exacerbations in a chronic rhinosinusitis setting. Understanding this disease process may facilitate targeted antibiotic therapy, reduced antibiotic resistance, and offer more effective disease control and treatment efficacy.

Objective: To characterize the microbiome associated with acute exacerbations of chronic rhinosinusitis (AECRS).

Methods: We conducted a systematic review of the literature on Medline, Embase, and Web of Science databases from January 1990-June 2021 to identify studies related to AE in CRS. Exclusion criteria include non-English, non-human studies, and case reports. Studies without culture or PCR data were also excluded.

Results: Fourteen studies were identified which provided detailed data regarding sinus microbiome in AECRS patients. In these patients, a total of 1252 individual isolates were identified. While common acute pathogens were identified in high frequencies in the sinonasal cultures (Staphylococcus pneumonia, Haemophilus influenza), the predominant bacteria were Staphylococcus aureus (including methicillin-sensitive Staphylococcus aureus) and Pseudomonas aeruginosa. Patient characteristics that may represent higher risk phenotypes were not consistently collected in the studies. Discussion of antimicrobial sensitivities and/or resistance were included in 7/14 studies.

Conclusions: This systematic review identifies the predominant microbiology species that may contribute to AECRS. Further studies are needed to understand the pathogenic role of bacteria and viruses in AECRS and to identify associated comorbidities and patient phenotypes that may predispose to AE. The optimal treatment regimen for AECRS remains unclear.

Keywords: microbiology, bacteriology, acute exacerbation, chronic rhinosinusitis, chronic sinusitis, sinus infection
INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disorder of sinonasal cavity that remains one of the leading causes for patients to seek healthcare in the United States (Fokkens et al., 2020). Recent research has begun to characterize the microbiome of normal and diseased sinuses, but our understanding of the role of microbes in CRS remains limited. Mucosal dysbiosis appears to be both a central etiologic factor in the pathogenesis of CRS in addition to a consequence of CRS (Yaniv et al., 2020). Numerous other environmental and host mechanisms have been proposed to drive the pathophysiology of CRS including allergy, ciliary dysfunction, mucosal disruption, immunity derangements, and biofilm formation. Ultimately, patients with CRS tend to experience a course of illness characterized by variable degrees of chronic inflammation with periodic acute exacerbations in symptomology, known as acute exacerbations of chronic rhinosinusitis (AECRS).

Enhanced understanding of the microbiology that contributes to AECRS will facilitate the development of targeted treatment regimens to improve symptoms and disease control, while also reducing the need for inappropriate antibiotic administration and the potential for antibiotic resistance. The purpose of this study is to systematically review the published literature to characterize the underlying microbiology of AECRS.

METHODS

We performed a systematic review utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A comprehensive search of Medline, Embase, Web of Science, and Google Scholar databases from January 1990-June 2021 was conducted to identify studies relating to the microbiology of acute exacerbations in CRS. A combination of terms was used to maximize the probability of finding all relevant publications, including but not limited to: “rhinitis”, “sinusitis”, “sinus”, “microbiology”, “acute exacerbation”, “chronic disease”, “bacteriology”, “cultures”, and “PCR”.

Study Selection

Titles and abstracts of all the relevant studies were reviewed by 2 independent authors (OO and AR). Included studies addressed the microbiology of AECRS with either culture or PCR data; studies without culture or PCR data were excluded. Studies were excluded if they were pediatric, non-English, non-human studies, and case reports.

Data Extraction and Analysis

Data included year of publication, study design, age range, diagnostic criteria, bacterial findings, and immune-histologic findings. After analysis of each article, summary tables were developed. In articles where various data groupings were provided, only the relevant data for the AECRS patient population were extracted and used for analysis.

A summary of the methods is provided in Figure 1.

RESULTS

Included Studies

Our initial database search identified 596 articles. Duplicate articles, non-English articles, those without full-text or without extractable data were excluded. A total of 14 articles met the final inclusion criteria for systematic review and underwent further full text review. These studies explored the underlying microbiology in AECRS.

Microbiology in AECRS

The details of the included studies exploring the microbiology of AECRS are summarized in Table 1. The bacteria that were identified with association to AECRS are listed in Table 2.

There was significant diversity in the bacteria that were associated with AECRS. The aerobic bacteria included: Staphylococci species which included both coagulase-negative Staphy species and methicillin-resistant Staph species, Streptococcus species, Haemophilus influenzae, Pseudomonas aeruginosa, Enterobacteriaceae, and Moraxella catarrhalis. The predominant anaerobic bacteria that were identified included: Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus, and Propionibacterium acnes, although only limited studies specifically tested or commented on anaerobic growth (Matthews et al., 1993; Vaughan and Carvalho, 2002; Brook et al., 2005; Brook, 2006). Facultative bacteria included the Escherichia species and Klebsiella pneumonia. The Staphylococci species were the most frequently identified culture-positive bacteria.

While most of the studies utilized culture data, one study did include speciation via polymerase chain reaction in addition to standard culture alone (Vandelaar et al., 2019). All included studies also commented on aerobic bacterial growth, but anaerobic growth was not routinely reported.

Discussion regarding antibiotic therapy, resistance, and sensitivities was noted in 7 of the 14 studies listed (Table 3), although the extent of analysis varied widely by study.

DISCUSSION

Our review demonstrates significant diversity in the various bacteria that were associated with AECRS. Staphylococci species were the most frequently identified bacteria, followed by Pseudomonas aeruginosa, Streptococcal species, and Haemophilus influenzae. Among the Staphylococcal species, various subspecies were identified including S. aureus, MRSA, and coagulase-negative Staphylococci. Of note, Rujanavej et al. demonstrated a substantial rise in MRSA isolates from intranasal cultures since the year 2000 and beyond, underscoring the need to consider MRSA coverage in cases of AECRS (Rujanavej et al., 2013). It is also interesting to note the high prevalence of Pseudomonas species; given the Pseudomonal ability to produce biofilms and multidrug resistance, these findings underscore the value of targeted, antimicrobial therapy (Bhattacharyya and Kepnes, 1999). Of note, there were multiple studies to indicate that anaerobic
Identification of studies via databases and registers

Records identified from Medline, Embase, Web of Science, Google Scholar: Databases (n = 584) Registers (n = 12)

Records removed before screening: Duplicate records removed (n = 207)

Records screened (n = 389)

Records excluded (non-English, non-human studies, case reports) (n = 20)

Reports sought for retrieval (n = 369)

Reports not retrieved (n = 0)

Reports assessed for eligibility (n = 369)

Reports excluded: Not applicable to current study (n = 355)

Studies included in review (n = 14)

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**TABLE 1 | Descriptive studies of acute microbiology in adult patients with CRS.**

| Study Author/year | Study Description |
|-------------------|-------------------|
| Matthews BL. et al., 1993 (Matthews et al., 1993) | Clinical trial evaluating cefixime for acute sinusitis or AECRS. N=42 |
| Vaughan WC. Et al. 2002 (Vaughan and Carvalho, 2002) | Cultures obtained in AECRS patients who have undergone prior ESS; examining role of nebulized antibiotics for AECRS. N=42 |
| Namyslowski G. et al., 2002 (Namyslowski et al., 2002) | Clinical trial evaluation of Augmentin and Cefuroxime for AECRS. N=122 |
| Bhattacharyya N. et al., 2004 (Bhattacharyya et al., 2004) | Prospective controlled cohort study. Cultures from pre-op AECRS were compared to post-op ESS. N=17 |
| Brook I. et al., 2005 (Brook et al., 2005) | Aerobic and anaerobic cultures of maxillary sinus secretions. N=7 |
| Brook I. 2006 (Brook, 2006) | Aerobic and anaerobic cultures of CRS and AECRS patients. Similar organism isolated from both patient groups. N=30 |
| Cincik H. et al., 2006 (Cincik and Ferguson, 2006) | Cultures of patients with CRS and AECRS; serial cultures performed. N=27 |
| Coffey CS. et al., 2006 (Coffey et al., 2006) | Cultures of patients with AECRS. Did look at drug resistance. N=77 |
| Ikeda K. et al., 2011 (Ikeda et al., 2011) | Cultures of patients with AECRS and asthma, s/p ESS. N=42 |
| Jiang ZY. et al., 2015 (Jiang et al., 2015) | Retrospective review to examine role of endoscopically driven antibiotic therapy on patient symptoms and endoscopy findings. N=105 |
| Yan CH. et al., 2018 (Yan et al., 2018) | Examined role of culture directed (N=61) vs non-directed (N=61) antibiotics in AECRS. |
| Vandelaar LJ. et al., 2019 (Vandelaar et al., 2019) | Cultures of CRSwNP, CRSwNP and AFS patients during AECCRS. N=134 |
| Szaleniec J. et al., 2019 (Szaleniec et al., 2019) | Cultures of patients with AECRS, s/p ESS. Did look at drug resistance, and bacteriophage susceptibility. N=50 |
| Yaniv D. et al., 2020 (Yaniv et al., 2020) | Retrospective review of AECRS patients and how bacterial isolates change over time. Did look at drug resistance. N=112 |
90.9% of patients during acute exacerbations (Ikeda et al., 2011), Haemophilus influenzae, S. aureus, and/or nasal corticosteroids. Targeted treatment for AECRS requires a better understanding of its pathophysiology. Despite being poorly understood, several factors have been noted to drive this dysbiosis including mucosal inflammation, impaired mucociliary clearance, biofilm formation, chronic mucosal disruption, atrophic rhinitis, transient viral infections and immunologic changes, and arising antibiotic resistance (Lee et al., 2018). Colonization by opportunistic pathogens such as *S. aureus* and *Pseudomonas aeruginosa* have been shown to trigger inflammation that is worsened by defects in the innate immune response.

There is significant evidence that alterations of the sinonasal microbiome are a direct driver of CRS inflammation and acute exacerbations (Rank et al., 2013; Divekar et al., 2015). While not a specific focus of this study, it should be noted that while antibiotic sensitivities were not routinely obtained in all of the included studies, significant multidrug resistance was reported. Thus, there is a growing body of literature to support culture-directed antibiotics to address microbiome shifts that are likely contributing significantly to the underlying disease process.

These intermittent and persistent disorders of the upper airway (including but not limited to asthma, allergic rhinitis, bronchitis, etc.) may represent gradients along a spectrum rather than each being a distinct pathology. In this unified airway theme, inflammatory disruptions in one subsite may affect the homeostasis in others. While this has been studied primarily in allergic disease, less is known about the impact of other adjunct upper airway disorders. For example, new evidence suggests that nasal hyperreactivity to nonspecific allergens may trigger symptoms mimicking AECRS, confounding the clinical picture (Doulaptsi et al., 2020). Additionally, in recent years, the concept of severe chronic upper airway disease (SCUD) has been proposed to define patients with CRS (with or without polyps) and allergic, nonallergic or occupational rhinitis, whose symptoms are refractory to traditional guideline based treatments. It is worth considering whether these patients represent a group of SCUAD patients, and if so, how to best address the multifactorial underlying etiologies driving the clinical worsening of symptoms (Prokopakis et al., 2014). Thus, cultures obtained during such episodes may not necessarily reflect a true microbiome picture of pure AECRS.

This concept of microbiome shifts during acute exacerbations also mirrors findings from other unified airway subsites. For example, sputum analysis done during acute exacerbations of both chronic obstructive pulmonary disease and chronic bronchitis demonstrate dysbiosis findings similar to those observed in the paranasal sinuses (Dickson et al., 2014; Jubinville et al., 2018). Elevated IL-6 levels have also been linked to patients suffering a CRS exacerbation, suggesting either a viral infection or an altered IL-6 pathway (Yaniv et al., 2020). More robust studies on pathophysiology and treatment

**TABLE 2 | Microbiology in AECRS infections.**

| Number of isolates | Organism growth |
|--------------------|-----------------|
| 258                | S. Aureus       |
| 168                | Pseudomonas aeruginosa |
| 133                | Haemophilus influenzae |
| 126                | Methicillin-sensitive S. Aureus |
| 98                 | Streptococcus pneumonia |
| 60                 | Coag negative staphylococci |
| 47                 | Methicillin-resistant S. Aureus |
| 31                 | Citrobacter diversus |
| 30                 | Escherichia coli |
| 28                 | Staphylococcus epidermidis |
| 25                 | Klebsiella pneumoniae |
| 22                 | Stenotrophomonas maltophilia |
| 20                 | Corynecoccus sp |
| 19                 | Moraxella catarrhalis |
| 17                 | A-hemolytic strep |
| 17                 | Enterobacter sp |
| 17                 | Proteus mirabilis |
| 16                 | Diphtheroids |
| 14                 | Peptostreptococcus species |
| 9                  | Klebsiella oxytoca |
| 8                  | Streptococcus pyogenes |
| 8                  | Acinetobacter sp |
| 8                  | Serratia marcescens |
| 7                  | Streptococcus Group G |
| 6                  | Oral flora (unspecified) |
| 6                  | Acinetobacter |
| 5                  | Moraxella sp |
| 5                  | Citrobacter sp |
| 4                  | Pseudomonas Stutzeri |
| 4                  | B-hemolytic strep |
| 4                  | Microaerophilic streptococci |
| 4                  | Strept alactiae |
| 4                  | Haem. Parainfluenza |
| 4                  | Citrobacter koseri |
| 3                  | Serratia sp |
| 3                  | Bacteroides species % of its |
| 2                  | Citrobacter freundii |
| 2                  | Xanthomonas sp |
| 1                  | Enterobacter aerogenes |
| 1                  | Enterobacter gergoeae |
| 1                  | Alcaligenes fecalis |
| 1                  | Archromobacter sp |
| 1                  | Bacillus sp |
| 1                  | Gemella morbillorum |
| 1                  | Moganella morgani |
| 1                  | Providencia rettgeri |

bacteria are present as well, suggesting that the microbial population in AECRS is a mix of aerobic and anaerobic bacteria. AECRS likely begins with a common viral upper respiratory infection that progresses into a secondary bacterial infection, potentially in an already dysbiotic setting (Brook et al., 2005; Brook, 2006; Cho et al., 2013; Rowan et al., 2015), followed by return to baseline CRS. An exacerbation may also be characterized by worsening sinonasal symptoms, presence of purulence on nasal endoscopy, and/or endoscopically-derived bacterial cultures (Wu et al., 2019; Wu et al., 2020). However, the specific microbiology of these exacerbations remains poorly understood.

Although positive bacterial cultures are identified in up to 90.9% of patients during acute exacerbations (Ikeda et al., 2011), many of the previously utilized treatment paradigms are largely based on the microbiomes of acute or chronic rhinosinusitis states, rather than the particular dysbiome in AECRS.

Currently, there are no consistent treatment guideline for AECRS, but management usually involves short-term antibiotics and/or nasal corticosteroids. Targeted treatment for AECRS requires a better understanding of its pathophysiology. Despite being poorly understood, several factors have been noted to drive this dysbiosis including mucosal inflammation, impaired mucociliary clearance, biofilm formation, chronic mucosal disruption, atrophic rhinitis, transient viral infections and immunologic changes, and arising antibiotic resistance (Lee et al., 2018). Colonization by opportunistic pathogens such as *S. aureus* and *Pseudomonas aeruginosa* have been shown to trigger inflammation that is worsened by defects in the innate immune response.

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### TABLE 3 | Key points mentioned regarding antibiotic resistance in key studies.

| Commentary regarding Antibiotic resistance |
|--------------------------------------------|
| **Matthews et al., 1993** | - Looked purely at resistance or susceptibility to cefoxime and amoxicillin only |
|                           | - 80% of isolates were susceptible to cefoxime, 65% susceptible to amoxicillin |
| **Brook et al., 2005** | - Out of 7 patients, 5 were noted to developed antibiotic resistance through B-lactamase production |
|                           | - Noted instance of S. pneumoniae resistance to penicillin |
| **Brook, 2006** | - 40% of isolates in AECRS patients developed antibiotic resistance through B-lactamase production versus 26% of CRS patients |
|                           | - S. pneumoniae in AECRS patients were also found to have higher rates of penicillin resistance compared to 0% in CRS patients |
| **Coffey et al., 2006** | - Notes that lab did not routinely check for resistance for many of the microbes cultured |
|                           | - In S. aureus and Pseudomonas species drug resistance was present in 10/48 (21%) and 16/20 (80%), respectively |
| **Ikedo et al., 2011** | - Susceptibility tests for S. pneumonia, MRSA, P. aeruginosa, and H. influenzae done on 35 isolates (Table 1) against Ampicillin, Methicillin, Cefotaxime, Cefoperazone/sublactam, Gentamicin, Minomycin, and Levofloxacin |
|                           | - Levofloxacin showed excellent efficacy against S. pneumoniae. |
|                           | - MRSA was remarkably resistant to all antibiotics except for minomycin. |
|                           | - Two isolates of P. aeruginosa was resistant to ampicillin and the third-generation cephalosporins while levofloxacin showed poor activity against only one isolate. |
|                           | - The third-generation cephalosporin and levofloxacin were sensitive to H. influenzae. |
| **Szalanci et al., 2019** | - Mechanisms of antibiotic resistance were identified in 28% of the isolates Consequently, antibiotic-resistant bacteria were carried by 46% of patients. |
|                           | - High rates of resistance noted to amoxicillin/clavulanate (18% of isolates, 28% patients), macrolides (25% of strains, 42% of patients) and clindamycin (30% of strains, 40% of patients). |
|                           | - Resistance to fluoroquinolones and aminoglycosides was very uncommon (6% of isolates, 10% patients). |
|                           | - All isolates including MRSA were sensitive to linezolid. |
| **Yaniv et al., 2020** | - Resistant strains identified were either penicillin-resistant Pneumococcus or ciprofloxacin-resistant Pseudomonas. |
|                           | - The lowest rates of resistance were noted for fluoroquinolones. |

options, including randomized controlled trials, are needed to better understand AECRS.

In addition, the articles reviewed included patients at various stages of intervention or recent antimicrobial treatment. It is also worth noting that patients with AECRS are known to have higher prevalence of comorbid conditions including allergic rhinitis, asthma, autoimmune, or other atopic diseases (Kwah et al., 2020). Most of the included studies lacked comprehensive demographic data regarding these and other relevant comorbidities such as respiratory pathologies, diabetes, or extensive obstructive polyposis. Additionally, no study mentioned the role of an inflammatory pathology or the role of other microbes. However, the literature is limited in understanding the delicate balance of the baseline microbiome or the role of other microbes. Although rhinovirus presence has been identified as being the most prevalent virus in CRS exacerbation in some studies, its significance in exacerbation is unclear (Cho et al., 2013; Yaniv et al., 2020).

Although this discussion regarding AECRS focuses primarily on underlying bacterial pathogens, it is important to keep in mind that viruses and fungi may also be drivers of AECRS. However, the literature is limited in understanding the delicate balance of the baseline microbiome or the role of other microbes.

There is also limited and conflicting literature to describe the role endoscopic sinus surgery (ESS) may play in altering the sinus microbiome, possibly via mechanisms that alter sinonasal aeration, mucociliary clearance, inflammatory profiles, nitric oxide levels, and others. Larson and Han describe their findings in 26 patients, demonstrating that ESS does not significantly alter the pre and post-surgery microbiome (Larson and Han, 2011). Hai et al. specifically examined the effect of ESS on biofilm production, finding that although ESS does not completely eradicate biofilms, it does significantly reduce their density (Hai et al., 2010). Several other studies demonstrate worse patient outcomes after ESS where biofilms are involved (Bendouah et al., 2006; Psaltis et al., 2008; Zhang et al., 2009).

The above discussion illustrates the complexity in appropriately identifying and treating AECRS. In addition to
diligent and thoughtful characterization of clinical symptoms, advancements in molecular technology are already enabling research in the uncharted and fascinating world of this disease, and allow for customized, precision treatment, termed “precision medicine” (Vlastos et al., 2019).

CONCLUSION

This systematic review identifies the predominant microbiology species that may contribute to AECRS. The literature supports a pathogenic role of bacteria and viruses in AECRS distinct from those cultured at baseline for patients with CRS. The optimal treatment regimen for AECRS remains unclear.

AUTHOR CONTRIBUTIONS

OO: data collection, manuscript development. AR: data collection, manuscript development, editing and study design. DG: manuscript development, editing, and study design. All authors contributed to the article and approved the submitted version.

REFERENCES

Bendouah, Z., Barbeau, J., Hamad, W. A., and Desrosiers, M. (2006). Biofilm Formation by Staphylococcus Aureus and Pseudomonas Aeruginosa Is Associated With an Unfavorable Evolution After Surgery for Chronic Sinusitis and Nasal Polyposis. Otolaryngol Head Neck Surg. 134 (6), 991–996. doi: 10.1016/j.otohns.2006.03.001

Bhattacharyya, N., Gopal, H. V., and Lee, K. H. (2004). Bacterial Infection After Endoscopic Sinus Surgery: A Controlled Prospective Study. Laryngoscope 114 (4), 765–767. doi: 10.1097/00005537-200404000-00032

Brook, I. (2006). Bacteriology of Chronic Sinusitis and Acute Exacerbation of Chronic Rhinosinusitis. Otolaryngol Head Neck Surg. 125 (10), 1117–1120. doi: 10.1016/j.otohns.2005.10.017

Craig, J. R., Poetker, D. M., Aksoy, U., Allevi, F., Biglioli, F., Cha, B. Y., et al. (2021). Consensus Statement. Int. Forum Allergy Rhinol. 8 (4), 765–785. doi: 10.1002/alr.23484

Hai, P. V., Lidstone, C., and Wallwork, B. (2010). The Effect of Endoscopic Sinus Surgery on Bacterial Biofilms in Chronic Rhinosinusitis. Otolaryngol Head Neck Surg. 142 (3 Suppl 1), S27–S32. doi: 10.1016/j.otohns.2009.09.022

Jiang, Z. Y., Kou, Y. F., and Batra, P. S. (2015). Endoscopic Culture-Directed Antibiotic Therapy: Impact on Patient Symptoms in Chronic Rhinosinusitis. Am. J. Otolaryngol. 36 (5), 642–646. doi: 10.1016/j.amjoto.2015.04.009

Lee, D. C., Choi, H., Oh, J. M., Hong, Y., Jeong, S. H., Kim, C. S., et al. (2018). The Effect of Urban Particulate Matter on Cultured Human Nasal Fibroblasts. J. Chemother. 30 (5), 479–489. doi: 10.1111/jcht.12469

Okifo et al. Systematic Review of Microbiology in AECRS
Data From a Pilot Study. Am. J. Rhinol. Allergy 27 (2), 98–101. doi: 10.2500/ajra.2013.27.3850

Rowan, N. R., Lee, S., Sahu, N., Kanaan, A., Cox, S., Phillips, C. D., et al. (2015). The Role of Viruses in the Clinical Presentation of Chronic Rhinosinusitis. Am. J. Rhinol. Allergy 29 (6), e197-e200. doi: 10.2500/ajra.2015.29.4242

Rujanavej, V., Soudry, E., Banaei, N., Baron, E. J., Hwang, P. H., and Nayak, J. V. (2013). Trends in Incidence and Susceptibility Among Methicillin-Resistant Staphylococcus Aureus Isolated From Intranasal Cultures Associated With Rhinosinusitis. Am. J. Rhinol. Allergy 27 (2), 134–137. doi: 10.2500/ajra.2013.27.3858

Szaleniec, J., Gibala, A., Parasion, S., Składzien, J., Stręk, P., et al. (2019). Exacerbations of Chronic Rhinosinusitis—Microbiology and Perspectives of Phage Therapy. Antibiotics (Basel). 8 (4), 175. doi: 10.3390/antibiotics8040175

Vandelaar, L. J., Hanson, B., Marino, M., Yao, W. C., Luong, A. U., Arias, C. A., et al. (2019). Analysis of Sinonasal Microbiota in Exacerbations of Chronic Rhinosinusitis Subgroups. OTO Open 3 (3), 2473974X19875100. doi: 10.1177/2473974X19875100

Vaughan, W. C., and Carvalho, G. (2002). Use of Nebulized Antibiotics for Acute Infections in Chronic Sinusitis. Otolaryngol Head Neck Surg. 127 (6), 558–568. doi: 10.1067/mhn.2002.129738

Vlastos, I., Gkouskou, K., Douaptis, M., Karatzanis, A., and Prokopakis, E. P. (2019). Precision Medicine in Rhinosinusitis. Curr. Allergy Asthma Rep. 19 (2), 12. doi: 10.1007/s11882-019-0850-x

Wu, D., Bleier, B. S., and Wei, Y. (2019). Current Understanding of the Acute Exacerbation of Chronic Rhinosinusitis. Front. Cell Infect. Microbiol. 9. doi: 10.3389/fcimb.2019.00415

Wu, D., Bleier, B. S., and Wei, Y. (2020). Definition and Characteristics of Acute Exacerbation in Adult Patients With Chronic Rhinosinusitis: A Systematic Review. J. Otolaryngol Head Neck Surg. 49 (1), 62. doi: 10.1186/s40463-020-00459-w

Yaniv, D., Stern, D., Vainer, I., Ben Zvi, H., Yahav, D., and Soudry, E. (2020). The Bacteriology of Recurrent Acute Exacerbations of Chronic Rhinosinusitis: A Longitudinal Analysis. Eur. Arch. Otorhinolaryngol. 277 (11), 3051–3057. doi: 10.1007/s00405-020-06157-7

Yan, C. H., Tangbunrungtham, N., Maul, X. A., Ma, Y., Nayak, J. V., Hwang, P. H., et al. (2018). Comparison of Outcomes Following Culture-Directed vs Non-Culture-Directed Antibiotics in Treatment of Acute Exacerbations of Chronic Rhinosinusitis. Int. Forum Allergy Rhinol. 8 (9), 1028–1033. doi: 10.1002/air.22147

Zhang, Z., Han, D., Zhang, S., Han, Y., Dai, W., Fan, E., et al. (2009). Biofilms and Mucosal Healing in Postsurgical Patients With Chronic Rhinosinusitis. Am. J. Rhinol. Allergy 23 (5), 506–511. doi: 10.2500/ajra.2009.23.3376

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