Literature Review

Microbiota profile in sinonasal mucosa of chronic rhinosinusitis as an indicator for therapeutic outcome

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is characterized by persistent inflammation of the sinonasal mucosa, which often requires surgical and additional post-operative therapy. Microbial dysbiosis due to the imbalance of commensal bacteria and pathogens plays a crucial role in the inflammatory process within the sinonasal mucosa and in therapy outcome. Further knowledge about the microbiota profile in CRS is needed to improve the management strategy for CRS patients. **Purpose:** To review recent studies on the microbiota profile in sinonasal mucosa of CRS patients, and its potential as an indicator for therapeutic outcome. **Literature review:** Recent data from several studies has documented increased microbiota richness and diversity in post-operative CRS patients' sinonasal mucosa, as well as good post-operative outcomes. Increased genus *Corynebacterium* abundance was also consistently associated with good post-operative outcomes. **Conclusion:** There was a difference in microbiota profiles in pre and post-operative CRS patients, indicating an association with clinical improvement. *Corynebacterium* was associated with better post-operative outcomes. Thus, the presence of these bacteria potentially could be used as an indicator for therapeutic outcome.

Keywords: chronic rhinosinusitis, microbiota, endoscopic sinus surgery, therapeutic outcome

ABSTRAK

Latar belakang: *Rinosinusitis kronis (RSK) merupakan kondisi inflamasi yang menetap pada mukosa sinonasal dan sering memerlukan operasi dan terapi tambahan pasca-operasi. Kondisi disbiosis mikrobiota akibat ketidakseimbangan bakteri komensal dan patogen diduga memengaruhi proses inflamasi pada mukosa sinonasal dan luaran terapi. Diperlukan pengetahuan tentang profil mikrobiota pada RSK sehingga diharapkan dapat meningkatkan strategi penanganan pasien RSK.* ***Tujuan:*** *Mempelajari studi terkini tentang profil mikrobiota pada mukosa sinonasal pasien RSK, dan potensinya sebagai indikator luaran terapi.* ***Tinjauan pustaka:*** *Data terkini dari beberapa penelitian menemukan peningkatan kekayaan dan keragaman mikrobiota pada mukosa sinonasal pasien RSK pasca-operasi dan memiliki hubungan dengan luaran operasi yang baik. Peningkatan kelimpahan genus* Corynebacterium *ditemukan secara konsisten berkaitan dengan luaran operasi yang baik.* ***Kesimpulan:*** *Terdapat perbedaan profil mikrobiota pada pasien RSK pra dan pasca-operasi yang mengindikasikan kaitannya dengan perbaikan klinis.* Corynebacterium *adalah bakteri yang ditemukan memiliki hubungan dengan luaran operasi yang lebih baik, sehingga keberadaan bakteri ini berpotensi untuk dapat dimanfaatkan sebagai indikator luaran terapi.*

Kata kunci: *rinosinusitis kronis, mikrobiota, operasi sinus endoskopik, luaran terapi*

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a persistent inflammatory condition of the nasal and paranasal sinuses (sinonasal) mucosa with a duration of more than 12 weeks. CRS is a disease with a high prevalence in several countries, such as United States (12%), China (8%), South Korea (11%), Brazil (5.5%), and Iran (28%).[1] Epidemiological studies at Dr Mohammad Hoesin Palembang Central General Hospital reported that out of 140 rhinosinusitis patients in 2015, 73 of them (52.1%) were CRS patients.[2] Additionally, the data from the Department of Rhinology-Allergy, Ear Nose and Throat Health Sciences Head and Neck Surgery (ENT-KL), Dr Hasan Sadikin Bandung Central General Hospital recorded 46% of rhinosinusitis cases in 2011.[3] Besides its high prevalence, CRS also contributes to decreasing work productivity and increasing the burden of medical and surgical costs.[4,5]

CRS patients are generally treated with oral antibiotics, topical/oral corticosteroids, and nasal saline irrigation. If there is no improvement, the patient must undergo endoscopic sinus surgery and followed by post-operative medical therapy.[1] The aim of surgery is to restore mucociliary function and improve nasal aeration and ventilation to improve the sinonasal mucosal environment, accelerate topical drug action and improve medical therapy efficacy. CRS patients generally experience improvement after undergoing endoscopic sinus surgery, but the other 6-25% still did not show improvement in clinical symptoms, thus requiring further treatment and additional surgery.[1,7]

Several studies had attempted to analyze various factors that may influence persistent inflammation in CRS, such as host, environmental, and microbial factors.[7] The interest in microbial factors has increased-for identifying various etiological agents-since techniques have been more developed in the microbiology laboratory. Microbiota is defined as a community of microorganisms in a niche.[8] The dysbiosis occurs when there is a disturbance in the microbiota population balance, which causes colonies of commensal organisms to be replaced by opportunistic pathogens.[9] Dysbiosis can result from an inflammatory reaction, and the use of antibiotics leading to damaged epithelial integrity, increased inflammatory reactions, and the risk of chronic disease.[10] Several molecular-based studies have found different microbiota profiles in the sinonasal mucosa of healthy people and CRS patients, indicating a role for microbial dysbiosis in the pathogenesis of CRS.[11–14] The microbiota profile assessment is based on richness, diversity, prevalence, and abundance.

With the increasing attention of clinicians towards microbial factors in the clinical course of CRS, it is necessary to conduct a literature review to analyze the changes in existing data of the microbiota profile on the sinonasal mucosa of CRS pre and post-operative. Besides, microbiota potential as an indicator of therapy outcome should be assessed, hence could be applied along with the current, standard outcome indicators of CRS therapy, such as subjective assessment of clinical symptom using the visual analog scale (VAS) or sinonasal outcome test (SNOT-22), or objective assessment of anatomical changes using the Lund-Kenney endoscopic score. We hope that this literature review could become the basis for further studies to develop and enrich therapy outcome indicators to optimize CRS management.

LITERATURE REVIEW.

The microbiota profile in healthy and CRS sinonasal mucosa

The use of molecular-based microbiota identification methods has shown that the sinonasal mucosa is not a sterile area but is niche to a complex and diverse microbiota. The diverse microbial community can be seen in the microbiota analysis result, consisting of more than 1000 bacteria genera in the sinonasal mucosa of healthy individuals.[12,14] This microbiota acts in symbiosis with the immune system to maintain the microbiota population's balance and mucosal integrity and suppress pathogenic microbiota growth.[15] Therefore, it is likely that this bacterial community's balance can affect the sinonasal mucosa's environmental conditions. Table 1 describes microbiota profiles in sinonasal mucosa of CRS and control groups in terms of microbiota richness, diversity, and abundance.

There are several terms used to describe the microbiota profile: **'prevalence'** is the presence of a bacterium from the total sample in the study; **'abundance'** is the absolute number of specific bacteria in a sample, and 'relative abundance' refers to the proportion of specific bacteria from the total individual number of bacteria in a community; **'richness'** is described by the number of unique microbiota taxa (species/genera) per sample; **'evenness'** calculates the similarity in the relative abundance of various taxa to describe whether a microbiota community is dominated by one or several bacteria; **'diversity'** is a combination of the level of richness and the level of evenness expressed in the form of an index which is generally calculated by the Shannon diversity index and Simpson diversity index.[16]

Jain et al.[17] in 2017 observed the microbiota profile in 23 CRS patients and found that the microbiota in CRS patients, based on prevalence and abundance, was dominated by genus *Staphylococcus* (95.7%;13.2%), *Streptococcus* (95.7%; 17.7%), and *Corynebacterium* (100%; 16.9%).

Table 1. Microbiota profile in sinonasal mucosa of CRS and control

Author; Year	Participants	Indicator		
		Richness	Diversity	Abundance
Gan et al.; 2019[11]	59 CRSwNP 27 Control	Control > CRSwNP	Control = CRSwNP	- The abundance of *Corynebacterium* and *Dologsigranulum* in controls > CRS
Gan et al.; 2020[12]	77 CRSwNP 36 CRSsNP 34 Control	Control > CRSwNP Control = CRSsNP	Similar between three groups	- The abundance of *Corynebacterium* and *Dologsigranulum* in controls > CRSwNP and CRSsNP
Kim et al.; 2020[18]	31 CRSwNP [Eos] and CRSwNP [Non-Eos] 6 controls	-	Similar between three groups	- CRSwNP [Eos]: *Lachnoclostridium* ↑ - CRSwNP [Non-Eos]: *Lachnospiraceae* ↑; and *Mesorhizobium* ↓ - Control: *Anaerococcus* and *Tepidomonas* ↑
Hoggard et al.; 2017[13]	94 CRS 29 Control	Control = CRS	Controls > CRS	- Control: dominated by *Corynebacterium* and *Staphylococcus*. - CRS: *Corynebacterium* ↓, *Staphylococcus* ↑, *Streptococcus* ↑, *Haemophilus* ↑, *Pseudomonas* ↑, and *Moraxella* ↑

Ramakrish-nan et al.; 2015[14]	56 CRS 26 controls	Control = CRS	Control = CRS	- Both CRS and controls were dominated by *Staphylococcus*, *Corynebac-terium* and *Propionibacterium*

Note: CRS = chronic rhinosinusitis; CRSw NP = chronic rhinosinusitis with nasal polyps; CRSsNP = chronic rhinosinusitis with-out nasal polyps; CRSwNP [Eos] = Eosinophilic CRSwNP ; CRSwNP [Non-Eos] = Non-Eosinophilic CRSwNP; ↑ = higher; ↓ = lower.

Different study by Gan et al.[11] in 2019 observed differences in microbiota profiles between CRS patients with nasal polyps (CRSwNP) and controls and discovered that the microbiota richness was higher in control, but there was no difference in terms of their diversity. Microbiota in control was dominated by *Corynebacterium* (20.35%), *Staphylococcus* (18.03%), *Dolosigranulum* (8.52%), *Lactobacillus* (5.93%), *Streptococcus* (5.66%), *Propionibacterium* (4.40%), *Escherichia-Shigella* (3.61 %), *Moraxella* (3.18%), and *Ralstonia* (1.68%). When compared to CRSwNP, the abundance of *Corynebacterium* and *Dologsigranulum* was higher in controls. In addition, Gan et al.[12] in 2020 reported another study to compare the microbiota profile between CRSwNP, CRS without nasal polyp (CRSsNP) patients, and controls. The microbial richness was higher in controls than CRSwNP, but no significant difference were found between controls and CRSsNP. Besides, there were no significant differences in microbial diversity between the three groups. Moreover, *Corynebacterium* and *Dologsigranulum* were also surprisingly higher in control than CRSwNP and CRSsNP.

Meanwhile, Kim et al.[18] in 2020 observed the microbiota profile in sinonasal mucosa of CRSwNP [Eos], CRSwNP [Non-Eos], and the control group and reported no significant difference in microbial diversity between the three groups. The abundance of *Anaerococcus* and *Tepidomonas* was higher in controls, and *Lachnoclostridium* was found higher in CRSwNP [Eos], whereas *Lachnospiraceae* was higher, and *Mesorhizobium* were lower in CRSwNP [Non-Eos].

The microbiota profile study in CRS patients and controls conducted by Hoggard et al.[13] in 2017found high variability in the bacterial community with a range of 2-128 types of bacteria in each subject. A more varied microbiota was found in the control group and dominated by *Corynebacterium* and *Staphylococcus*. On the other hand, lower microbial diversity was found in CRS patients, accompanied by a decrease in the abundance of *Corynebacterium* and an increase of *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Pseudomonas*, and *Moraxella*.

Another study by Ramakrishnan et al.[14] in 2015 found no difference in microbial richness and diversity between CRS patients and controls. The abundance of microbiota in both CRS patients and controls was dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium.*

The microbiota profile in post-operative CRS patient

Several studies had assessed endoscopic sinus surgery outcomes using various indicators, including recurrence of nasal polyps, endoscopic scores, and symptom scores (Table 2).[12,14,17,18] The recurrence of nasal polyp was assessed based on symptoms, nasal endoscopy, and sinus CT examination during the 1-year post-operative follow-up.[12] Optimal criteria for endoscopic scores were characterized by a reduction in the endoscopic score (> 50%), no requirement for revision surgery, and no use of additional antibiotics or steroids six months prior to the postoperative follow-up visit.[14,18] The symptom score was assessed using a format of the severity rate

scaling from 0 to 5 for five nasal symptoms: nasal obstruction, anterior and posterior rhinorrhea, pain or sinus pressure, and anosmia.[17]

Generally, CRS patients improved after undergoing endoscopic sinus surgery, but some patients still showed a suboptimal surgical outcome, as shown in Table 2. About 12 out of 77 CRSwNP patients still experienced recurrent polyps, while 14 out of 27 CRS patients demonstrated suboptimal outcomes.[12,14] Furthermore, variation was found in CRS patients' symptom score after surgery: symptom score decreased in 21 CRS patients, an increased score was reported in one patient while another patient showed no changes when compared to preoperative symptom score.[17] Kim et al.[18] assessed surgical outcome using a similar indicator with Ramakrishnan et al.[14], but there were no available data describing the number of patients based on surgery outcome.

Table 2. Post-operative CRS outcome report

Author; Year	Design	Participants	Intervention	Follow-up	Therapeutic outcome	
					Indicator	Result
Gan et al.; 2020[12]	Cohort	77 CRSwNP	Endoscopic sinus surgery	1 year	- Post-operative recurrent or nonrecurrent polyps	- Recurrent group (n = 12) - Nonrecurrent group (n = 65)
Kim et al.; 2020[18]	Cohort	31 CRSwNP	Endoscopic sinus surgery	6 months	- Post-operative optimal or suboptimal outcome	- Optimal outcome (n = N/A) - Suboptimal outcome (n = N/A)
Jain et al.; 2017[17]	Cohort	23 CRS	Endoscopic sinus surgery	4 months	- Pre and post-operative symptom score	- Decreased symptom score (n= 21) - No changes (n= 1) - Symptom score increased (n= 1)
Rama-krishnan et al.; 2015[14]	Cross-sectio-nal	27 CRS	Endoscopic sinus surgery	6 months	- Post-operative optimal or suboptimal outcome	- Optimal outcome (n = 13) - Suboptimal outcome (n = 14)

Note: CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; Optimal outcome = reduction in endoscopic score > 50%, no revision surgery, and no post-operative systemic antibiotics/steroids before 6-month post-operative follow-up; Symptom score = Scale of severity from 0 - 5 for symptoms of nasal obstruction, rhinorrhea, sinus pain, and anosmia; * Jain et al. did not group subjects based on symptom scores.

Table 3. Microbiota profile in post-operative CRS patient

Author; Year	Participant (n)	Indicator	Bacteria	Microbiota Profile
Gan et al.; 2020[12]	- Recurrent polyp (12) - Nonrecurrent polyp (65)	Abundance	*Corynebacterium* *Staphylococcus*	- Staphylococcus abundance: No difference between pre and post-operative. - The abundance of *Corynebacterium* in nonrecurrent polyp: Post-operative > Preoperative. - The abundance of microbiota in recurrent polyp: Pre and post-operatively did not differ
Kim et al.; 2020[18]	- Optimal outcome - Suboptimal outcome	Abundance	*Corynebacterium* *Anaerococcus* *Tepidomonas*	- The abundance of *Corynebacterium*, *Anaerococcus* and *Tepidomonas* at optimal outcome > suboptimal
Jain et al.; 2017[17]	- Post-operative CRS patient with measured symptom score (23) *	Richness Diversity Abundance	*Corynebacterium* *Staphylococcus* *Streptococcus* *Propioni-bacte-rium*	- The richness of the microbiota in post-operative CRS is increased. - The microbiota diversity in post-operative CRS did not differ. - Abundance in post-operative CRS: *Staphylococcus* >, Streptococcus <; No changes of *Corynebacterium*, and *Propionibacterium.* - *Staphylococcus* and *Streptococcus* abundance is not associated with symptom scores. - Decrease *corynebacterium* abundance was associated with increase symptom scores.
Ramakrish-nan et al.; 2015[14]	- Optimal outcome (13) - Suboptimal outcome (14)	Richness Abundance	*Corynebacterium* *Staphylococcus*	- Microbiota richness at optimal outcome > suboptimal - The abundance of *Corynebacterium* and *Corynebacterium tuberculostearicum* at optimal outcome > suboptimal. - The abundance of *Staphylococcus* aureus > 3x at the suboptimal outcome, but not statistically significant

Note: CRS = chronic rhinosinusitis; Optimal outcome = decreased endoscopic score > 50%, no revision surgery, and no post-operative systemic antibiotics / steroids; > = higher; < = lower; # = Kim et al. did not observe post-operative microbiota profiles, post-operative outcome was correlated with pre-operative microbiota profiles; * = Jain et al. did not group subjects based on symptom scores.

Data from several studies on the microbiota profile in post-operative CRS patients are presented in Table 3. The study conducted by Jain et al.[17] in 2017 showed an increase in microbiota richness in post-operative CRS. On the other hand, Ramakrishnan et al.[14] found an increase in microbiota richness and diversity of the sinonasal mucosa of post-operative CRS, and it was significantly associated with optimal surgical outcome. Meanwhile, Gan et al.[12] found no difference in pre and post-operative microbiota profiles in recurrent CRSwNP patients.

However, a change in the relative abudance of some bacteria in post-operative CRS has been reported in some studies, while others have found its association with surgical outcomes. Gan et al.[12] discovered an increased relative abundance of *Corynebacterium* in nonrecurrent CRSwNP than preoperative. Meanwhile, Jain et al.[17] found an increased abundance of *Staphylococcus* in 18 out of 23 (78%) post-operative CRS patients, while *Streptococcus* abundance decreased, and no change in *Corynebacterium* and *Propionibacterium* was observed.

Based on post-operative symptom score, decrease *Corynebacterium* abundance was associated with an increase in symptom scores. Meanwhile, changes in the abundance of *Staphylococcus* and *Streptococcus* were not significantly associated with symptom scores.[17] Ramakrishnan et al.[14] found an increase in the abundance of the genus Corynebacterium and Corynebacterium tuberculostearicum species in post-operative CRS optimal outcome compared with suboptimal outcomes. Aside from that, Staphylococcus aureus was found three times higher in post-operative CRS patients with poor outcomes, but the statistical analysis did not show a significant difference.

Kim et al.[18] in 2020 compared the microbiota profile in preoperative CRS patients with the outcome of endoscopic sinus surgery therapy. In patients with optimal operative outcomes, the preoperative abundance of *Corynebacterium*, *Anaerococcus*, and *Tepidomonas* was higher than in patients with suboptimal outcomes. Thus, the presence of these bacteria may become a potential indicator to predict therapeutic outcomes in CRS patients.

Corynebacterium in CRS

The results of the studies showed a significant relationship between *Corynebacterium* and post-operative CRS patients with better outcomes (Table 4).[12,14,18] In the study conducted by Jain et al.[17], although there was no significant difference in *Corynebacterium* abundance between post-operative and preoperative CRS, *Corynebacterium* decrease in abundance showed a significant association with increased symptom scores. Likewise, Kim et al.[18] (2020) stated that the genus *Corynebacterium* was a potential predictor for the surgical outcome because lower preoperative abundance was associated with suboptimal operative outcomes.

Table 4. *Corynebacterium* in pre and post-operative CRS

Participants	Indicator	Corynebacterium profile		Reference
		Pre-op	Post-op	
Recurrent polyp (12)	Abundance	------- Not different ------		Gan et al.; 2020[12]
Nonrecurrent polyp (65)	Abundance	<	>	
Optimal outcome	Abundance	> #	-	Kim et al.; 2020[18]
Suboptimal outcome	Abundance	< #	-	

CRS patient with measured pre and post-operative symptom score * (23)	Abundance	------- Not different ------	Jain et al.; 2017[17]
Optimal outcome (13)	Abundance	< >	Ramakrishnan et al.; 2015[14]
Suboptimal outcome (14)	Abundance	------- Not different ------	

Description:> = higher; <= lower; # = Kim et al. did not identify the post-operative microbiota profile, the post-operative outcome was correlated with the peri-operative microbiota profile; * = Jain et al. did not group subjects based on symptom scores.

The potential of microbiota as an indicator for CRS therapeutic outcome

Several studies showed variations in comparing the microbiota profile between control, CRS, and post-operative groups. However, the profile and microbiota composition tended to change, indicating the involvement of the microbiota community on the sinonasal mucosa in the pathogenesis of CRS. The research results by Jain et al.[17] found increased microbiota richness in post-operative CRS patients, but no significant association was identified with a decrease in post-operative CRS symptom scores. On the other hand, Ramakrishnan et al.[14] found an association between increased wealth and even distribution of microbiota in the sinonasal mucosa of post-operative CRS with optimal operative outcome. Besides, Gan et al.[12] found that the pre and post-operative microbiota profiles in recurrent polyp of post-operative CRSwNP patients did not change significantly. These support the notion that the increase in microbiota richness and diversity is related to the healing process and the mucosal condition's improvement. Thus, the findings of studies in this literature review indicated the potential use of microbial changes as indicators of therapeutic outcome.

Dysbiosis refers to the imbalance of the microbiota community known to increase the risk of developing chronic disease that can occur in three ways: (1) increased pathogenic bacteria from external sources (acquired) or commensal bacteria that grow opportunistically, such as in cholera infection and streptococcal pharyngitis; (2) reduced number of bacteria that have a protective function, causing disease, such as inflammatory bowel disease; or (3) a combination of loss of protective bacteria and the emergence of pathogen, such as *Clostridium difficile* infection in inflammatory bowel disease.[9] Notably, a consistent association between increased *Corynebacterium* abundance and better surgical outcomes in CRS patients were evident in this review,[12,14,18]indicating its possible role as a protective bacteria and the process of dysbiosis in the sinonasal mucosa of patients with CRS might occur due to a decrease in the number of protective bacteria of the sinonasal mucosa. Therefore, the presence of *Corynebacterium* has the potential as an important indicator, especially in assessing the therapeutic outcome of CRS patients.

Corynebacterium is known to be one of the dominant bacteria in the sinonasal mucosa, and this is in line with the results of the studies which reported its high abundance in the control group compared to CRS.[11–14] The potential of the genus *Corynebacterium* as a protective factor in the sinonasal region is evident through the relationship between the presence of these bacteria and decreased virulence and phenotypic changes of *S. aureus,* from a virulent bacterium to a commensal bacterium.[19,20] Apart from that, *C. amycolatum, C. pseudodiphtheriticum,* and *C. accolens inhibited S. aureus* in the Agr-system, causing a reduction in virulent gene transcription, decreased hemolysin enzyme activity, and increased adhesion to epithelial cells; indicating changes of the bacteria to commensal state.[19] Another mechanism used

by C. pseudodiphtheriticum is to selectively suppress the growth of *S. aureus* that activates its Agr-system. Thus, to colonize in the nose, S. aureus is forced to inactivate the Agr-system and stop the expression of its virulent factors, indicating changes in the bacteria phenotype from pathogenic to commensal state.[20] Besides, the protective nature of *Corynebacterium* was supported by the increased resistance to viral and bacterial infections in the respiratory tract of infant mice after administration of topical saline spray containing *C.pseudodiphteriticum* suspension in the nasal area.[21]

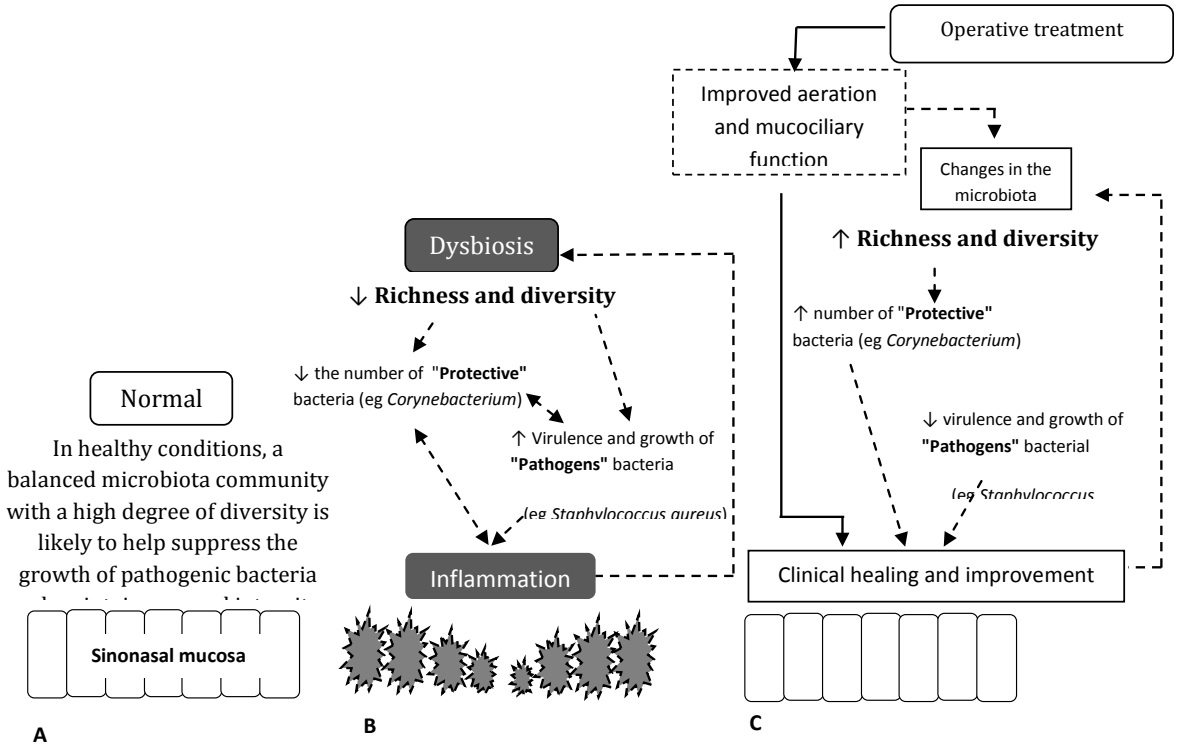

Figure 1. Schematic illustration of the relationship between the microbiota profile of the sinonasal mucosa with the course of CRS, A) normal (healthy) conditions, B) inflammatory conditions (CRS), C) post-operative treatment healing period

Despite its protective function in the sinonasal region, some studies have reported *Corynebacterium* as a pathogen, associating it with an increase in T-helper 2 lymphocytes, IL-5 and eosinophils, which are inflammatory mediators deemed responsible for the pathogenesis of polyp formation in CRSwNP.[22] Another study also found that 14 of 16 (87.5%) strains of *C. tubercolestearicum* from various clinical specimens have multi-drug resistance, which may be associated with recalcitrant CRS.[23] Therefore, there is a need to investigate the relationship between various *Corynebacterium* species with the CRS pathogenesis and therapeutic outcome.

Studies in the last decade have identified *Staphylococcus*, especially *S. aureus*, as having a potential role in CRS's pathogenesis. Based on the culture results in previous studies, *S.aureus* is a bacteria that was found higher in CRS patients, and these Gram-positive bacteria are also the most dominant bacteria found in CRS patients with recurrent symptoms after surgery.[24] This is one of many findings demonstrating virulence factors possessed by *S. aureus* bacteria such as enterotoxin, a superantigen that can stimulate hyper-activation of the immune response through the T helper-2 pathway eosinophilic inflammation resulting in edema and polyp

formation in CRSwNP.[25] Another virulence factor is the ability of *S. aureus* to form biofilms and intracellular colonies as different phenotypes. These actions enable *S. aureus* to withstand antimicrobial and immune response to become a bacterial reservoir for further infection even after treatment, hence causing CRS with recurrent symptoms.[26,27]

However, the prevalence and relative abundance of *S.aureus* in CRS and its association with the operative outcome had not shown consistent results based on the recent molecular findings.[12–14,17] Jain et al.[17] and Tuchscherr et al.[28] stated that the different results were probably influenced by *S. aureus* phenotype; CRS with a poor outcome was colonized by virulent *S. aureus*, while the control group or CRS with good outcome were colonized by commensal *S. aureus.* Agr-system, sar A, and Sigma SigB factors are known as crucial regulators of *S.aureus* virulence, enterotoxin production, and phenotypic changes by forming biofilms or intracellular colonies.[28,29] Therefore, further studies are needed to determine the association between *S. aureus* and CRS by analyzing its relative abundance, virulence factors, and phenotype changes.

In conclusion, various studies have shown differences in microbiota profiles, especially in terms of bacterial richness and abundance between pre and post-operative CRS patients, which indicates an association with their clinical improvements. Additionally, *Corynebacterium* has been found to contribute to better therapeutic outcome; thus, the presence of these bacteria could be used as an indicator for CRS therapy.

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