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Microbial Prevalence and Antimicrobial Resistance in Children and Adolescents with Chronic Rhinosinusitis in South Indian Population

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Abstract

Objective: Chronic rhinosinusitis (CRS) is a common multifactorial upper respiratory disease with a key role of microbes in worsening of disease and its associated co-morbidities. Further, significant region specific variation in patient demographics and antibiotic resistance of causative bacteria are reported to pose difficulty in diagnosis and treatment. In India, studies on the etiology and antibiotic resistance in chronic rhinosinusitis are very meager, especially in children. The present study aimed to determine the prevalence of common causative microbes and their antibiotic resistance in children and adolescents with chronic rhinosinusitis in South Indian population.

Subjects and methods: The present study was conducted on 89 children and 99 adolescents with chronic rhinosinusitis who visited MAA ENT Institute, Hyderabad, South India. The study samples were collected under the nasal endoscopic guidance from the middle meatus at first visit and sinuses at surgery. Conventional and VITEK-2 methods were used for identification and antibiotic sensitivity of the microbes. Chi-square test and multinomial logistic regression was applied to determine statistical differences between the variable using PASW v. 18.0 software (SPSS Inc., Chicago, IL).

Results: The male-female ratio was 2:1 with an average children age of 8.9 ± 3.65 years and 16.1 ± 1.23 years in adolescents. The risk for adenoids was seen in 49.2 % of children (OR; 2.6: 95% CI: 1.63-4.06) while allergic fungal sinusitis (18.1%, OR: 2.7; 95% CI: 1.12-6.57) and nasal polyps (26.6%, OR: 2.3; 95% CI: 1.07-4.86) was commonly seen in adolescents. About 26.6% of adolescents with fungal positivity also showed bacterial infection. Aspergillus flavus (68%) was the most common fungi identified. Bacterial culture rate was positive in 46.8% of the total subjects of which Streptococcus aureus was the most common bacteria (59.1%) followed by *Streptococcus pnuemoniae* (21.2%), *Klebsiella* sp. (11.4%), *Pseudomonas aeruginosa* (11.4%) and β hemolytic streptococci (1.1%). No Methicillin-resistant *Staphylococcus aureus* strains could be identified. *Streptococcus pneumonia* (63.2%) was commonly identified in younger children and *Pseudomonas aeruginosa* (80%) was mostly seen in adolescents. The frequency of bacterial positivity in adolescents with CRS when compared to CRS children was high and varied between different associated co-morbidities. High antibiotic resistance in *Staphylococcus aureus* was seen towards gentamicin (73%) and co-trimoxazole (64%), *Streptococcus pnuemoniae* to gentamicin (58%), co-trimoxazole (68%) and meropenem (32%), *Pseudomonas aeruginosa* to co-trimoxazole (100%), cefatoximine (60%) and cefatazidime (50%) while *Klebsiella* sp. to gentamicin (80%) and co-trimoxazole (60%). *Streptococcus aureus* showed high sensitivity to cefatoximine (95.8%) and *Streptococcus pnuemoniae* for ofloxacin (100%), ciprofloxacin (89.5%) and cefazolin (89.5%). *Pseudomonas aeruginosa* showed high sensitivity for amikacin (100%) and ciprofloxacin (80%) and *Klebsiella* sp. for amikacin (100%)

Conclusion: Significant regional specific variation in bacterial etiology that differed with age, severity and co-morbidities was observed in children and adolescents with chronic rhinosinusitis. High antimicrobial resistance in the cultures of chronic rhinosinusitis patients at their first visit and also at sinus surgery warrants urgent need for early initiation of personalized interventions for better management of the infectious disease.

Keywords: Chronic rhinosinusitis; Allergic fungal sinusitis; Nasal polyps; Adenoids; Antibiotic sensitivity; Functional endoscopic sinus surgery; Chronic suppurative otitis media

Introduction

Chronic rhinosinusitis (CRS) is a common multifactorial inflammatory disorder of the upper airway system that drastically affects the patient's quality of life across all ages and socioeconomic conditions of millions of people worldwide [1]. About 5-15% of the worldwide population is affected with chronic rhinosinusitis yet

paucity of data exists in relation to etiopathogenesis, especially in children [2]. Various demographic and socioeconomic factors are reported to cause differences in CRS manifestation which affects management and recurrence rate of the disease [3,4]. Clinico-pathophysiological mechanisms such as immaturity of the immune system, smaller ostia of the sinuses, increased respiratory tract infections and adenoidal hypertrophy in children while tissue remodeling and greater irreversible scarring due to inflammation in adults contribute to the disease worsening in chronic rhinosinusitis [5]. Further, presence of nasal pathogens leads to longer mean duration of symptoms and greater severity of the inflammation [6]. The role of bacteria differed with respect to different chronic rhinosinusitis comorbidities which further increase variation in disease management in children as well as in adults [7,8].

Sinusitis and its associated complications are more frequently treated with antibiotics to prevent the onset of complications and the need for surgical interventions [9]. Antibiotic treatment can promote subsequent growth of various bacteria, often to new multidrug resistant strains, on the mucosal epithelium with frequencies and changes that may vary with the use of different antibiotics, between age groups and clinical entities [10,11]. Misdiagnosis of the symptoms in many cases with upper respiratory tract infections, indiscriminate prescribing of antibiotics by general practitioners including broad-spectrum antibiotics, and ease of obtaining antibiotics has promoted the microbial resistance for many antibiotics [12,13]. The susceptibility trends among common pathogens appear to have stabilized over the past years as measures have been taken up in many countries but high prevalence of multidrug resistance remains as a major concern [13,14]. Also, the Center for Disease Control and Prevention (CDC) recently estimated that antimicrobials usually prescribed often to treat acute respiratory tract infections in children and adults are still at inappropriately high rates. Continuing research is therefore needed to refine physician awareness and to evaluate regional differences in antibiotic resistance that may result in variations with significant effects upon disease progression and management.

In India, very meager studies are been reported on etiology of chronic rhinosinusitis, especially in children. The choice of antibiotics is discretionary and usually not made based on microbial culture and sensitivity results which promotes the high risk for bacterial resistance. Misconceptions exist about the use and indications of antibiotics and lack of knowledge regarding antibiotic resistance is prevalent in India [15]. The purpose of this study was to determine the etiology, and the prevalence of major bacterial and fungal pathogens and antibiotic resistance of the identified bacteria in children and adolescents of South Indian population.

Study, Subjects and Methods

188 CRS subjects including 89 children and 99 adolescents who underwent treatment at MAA ENT Hospitals, Hyderabad were considered for the study. Clinical diagnosis was based upon presence of two or more symptoms of nasal obstruction, nasal congestion, anterior nasal discharge, posterior nasal drip, facial pain, cough; atleast one of the endoscopic signs of nasal polyps, mucosal obstruction and/or mucopurulent discharge mainly from middle meatus, oedema and mucosal changes within the ostiomeatal complex and/or sinuses as seen through computed tomography. The criteria for the diagnosis of nasal allergy were mainly by the symptoms such as nasal discharge, nasal itching and sneezing for more than 5 times a day. Diagnosis of adenoids was made when greater than 50% of nasopharyngeal space occupied by soft tissue in the X-ray neck lateral view. The confirmation of diagnosis was by X-ray in subjects less than 13 yrs and computed tomography scan in subjects more than 13 yrs. Subjects who have not been on antibiotic therapy during the first visit and who have stopped their antibiotic use for atleast 3 weeks before surgery were included in the study. CRS subjects with immune compromised conditions, cystic fibrosis and nasocominal infections were excluded. The study samples were collected in the first visit if purulent discharge was present in the middle meatus and in patients when discharge was not seen in the middle meatus due to blockage of sinus opening the samples were collected at the surgery under the nasal endoscopic guidance. Surgical interventions were done when the condition could not be managed by the therapeutic interventions. Identification and antibiotic sensitivity of the microbes were performed by the conventional and VITEK-2 method. Data related to detailed medical history, clinical findings and the findings of endoscopic examination, computed tomography scanning and microbiological assessments were recorded and the data obtained was analyzed using PASW ver. 18.0 (SPSS Inc. Chicago, US). Continuous data was presented as means and standard deviations. Chi-square test and multinomial logistic regression was used to determine statistical differences between the age, sex, co-morbidities, type of microbial pathogen and their antibiotic sensitivity and resistance. The study was performed after approval of the institutional research ethics committee for biomedical research.

Results

The mean age of children was 8.9 ± 3.65 years and 16.1 ± 1.23 years in adolescents. Male preponderance of 2:1 was noticed in both children and adolescents. 51.6% of the CRS children with adenoids were affected with allergic rhinitis, 32.2 % cases with CSOM and 16.6% cases with asthma. Allergic fungal sinusitis (AFS) was commonly found in adolescents (18.1%) of which 57.1% of cases had nasal polyposis while 19.9% had asthma. Allergic Rhinitis was the most common co-morbidity in both the age groups. Allergic rhinitis with nasal polyps was present in 21.2% of CRS subjects and 4.2% of CRS subjects had allergic rhinitis with nasal polyps and asthma. Of the total subjects, 36.7% of cases underwent primary and 10.1% of cases had revised functional endoscopic sinus surgery (FESS). The distribution of risk factors and co-morbidities of CRS in children and adolescents is given in Table 1.

Characteristic	Total	Children	Adolescents	p-value	Odds Ratio (95% CI)
Sex	188	89 (47.3)	99 (52.7)		
Male	130 (69.1)	61 (68.5)	69 (69.7)	0.876	1.056 (0.568-1.962)
Female	58 (30.9)	28 (31.5)	30 (30.3)		
Risk Factors/Co-morbidities					
Adenoids	63 (33.5)	44 (49.4)	19 (19.2)	<0.001	2.6 (1.63-4.06)

Allergic rhinitis	102 (54.2)	43 (48.3)	59 (59.6)	0.143	0.81 (0.62-1.06)
Fungal Sinusitis	26 (13.8)	8 (9)	18 (18.1)	0.035	2.7 (1.12-6.57)
Nasal Polyps	38 (20.2)	12 (13.5)	26 (26.3)	0.045	2.3 (1.07-4.86)
Tonsillitis	78 (41.5)	38 (42.7)	40 (40.4)	0.769	1.06 (0.75-1.48)
Otitis Media	79 (42.0)	32 (36)	47 (47)	0.139	0.75 (0.54-1.07)
Asthma	23 (12.2)	14 (15.7)	9 (9.1)	0.186	1.73 (0.79-3.80)
History of sinus surgery					
No Surgery required	100 (53.2)	48 (53.9)	52 (52.5)	0.615	ref a
Sinus Surgery	69 (36.7)	34 (38.2)	35 (35.4)	0.87	0.950 (0.514 - 1.755)
Sinus Surgery Revision	19 (10.1)	7 (7.9)	12 (12.1)	0.374	1.582 (0.576 - 4.351)

Table 1: Demographic and clinical characteristics of children and adolescents with chronic rhinosinusitis (N=188), a p-value significance is based on multinomial logistic regression (2-sided), p-value significance is based on Fisher's Exact Test (2-sided), Odds ratio computed based on chi-square test.

A total of 88 bacterial isolates were recovered of which 94.3% were positive for single culture and 5.7% had multiple cultures. 80.6% of the cultures were Gram-positive cocci, 22.7% gram-negative rods and 5.6% were mixed cultures of gram positive cocci and gram negative rods. Co-infection of bacteria and fungus was noted in 4.4% of adolescents. S.aureus was the most frequently cultured organism (59.9%), followed by *S. pneumonia* (21.5%), *P. aeruginosa* (11.4%), *Klebsiella* sp. (11.4%) while no methicillin resistant *Staphylococcus aureus* strains could be identified. *Klebsellia* sp. was identified more frequently (60%) in polymicrobial infections. *Aspergillus flavus* was the most common fungi identified. *Staphylococcus aureus* was the most common pathogen in both the age groups, *Streptococcus pneumonia* was commonly identified in younger children and *Pseudomonas aeruginosa* was mostly seen in adolescents at their first visit. The distribution of microbes with respect to age in CRS subjects is given in Figure 1. The prevalence of bacteria with respect age and severity is given in Figure 2.

Bacterial culture rate was positive in 46% of the total subjects and varied with comorbidities, 44.7% of cases presented with allergy, 47.1% with nasal polyps, 54.5% asthma, 30.4% otitis media, 36.7% adenoids, 42.9% tonsillitis subjects. 57% of allergic fungal sinusitis subjects had nasal polyps. The bacterial prevalence in CRS subjects with regard to comorbidities and age is given in Figure 3. In CRS children with adenoids the microbial culture rate was 35.5% of which *S. aureus* was present in 72.7% of cases and *S. pneumonia* was seen in 18.1% of cases. In subjects with CSOM, bacterial positivity was found in 29.7% of the cultures of which *S. aureus* was 45.4% and *Streptococcus pneumonia* was identified in 36.3% cases. *Staphylococcus aureus* was seen in 59% of bacterial positive cases in CRS subjects with allergic rhinitis. About 77% of isolates from adolescents with nasal polyps showed bacterial positivity. The prevalence of gram positive bacteria also differed with co morbidities, *S. aureus* was seen in 72.7% and *S. pneumonia* was seen 18.1% in CRS subjects with adenoids while in case of CRS subjects with CSOM, *S. aureus* was identified in 45.4% and *Streptococcus pneumonia* in 36.3% cases.

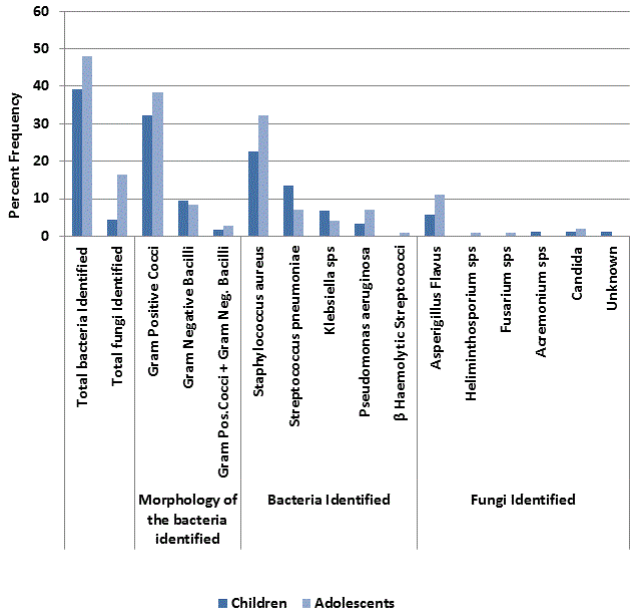

Figure 1: Distribution of microbes identified in CRS subjects with respect to age.

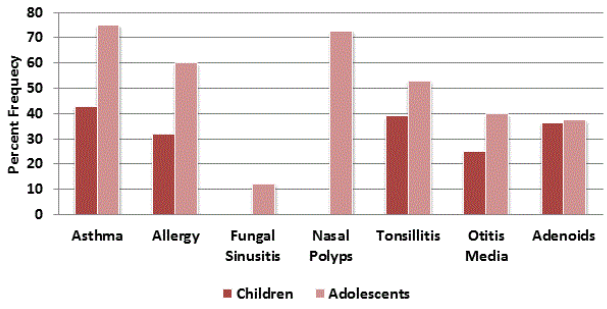

Figure 2: Prevalence of bacteria identified in CRS subjects with respect to co-morbidities.

Antibiotic resistance was observed in all the gram positive and gram negative bacterial isolates which differed with comorbidities and severity of the disease (Figure 4). High antibiotic sensitivity of *Staphylococcus aureus* was seen against cefatoximine (95.8%), *Streptococcus pnuemoniae* for ofloxacin (100%), cefazolin (89.5%), and cefatoximine (89.5%), *Pseudomonas aeruginosa* for amikacin (100%) and ciprofloxacin (80%) and *Klebsiella pnuemoniae* for amikacin (80%). All the *Staphylococcus aureus* isolates obtained at

revision surgery were resistant to cotrimoxazole, 75% to amoxicillin clavunate and 50% to gentamicin. However, no difference in the antibiotic sensitivity was observed between the children and adolescents.

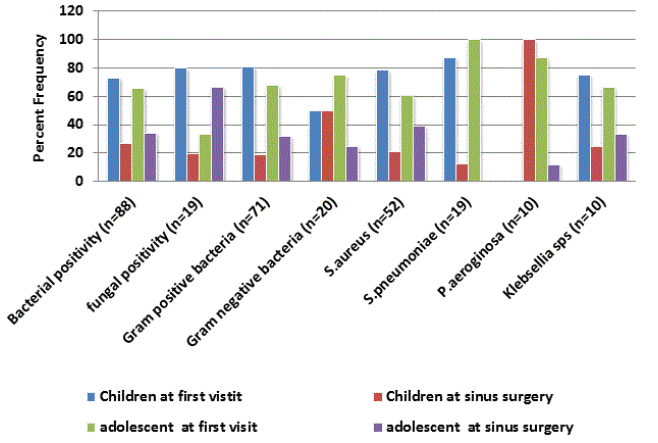

Figure 3: Distribution of bacterial species identified in CRS subjects with respect age and time of visit.

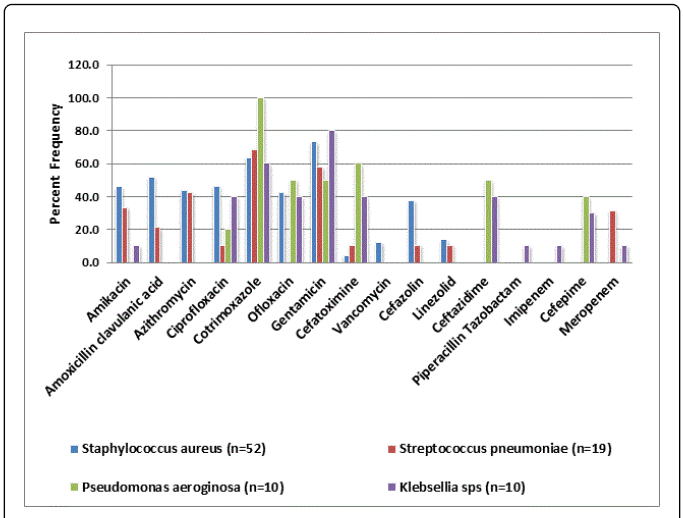

Figure 4: Antibiotic resistance of bacteria identified in CRS subjects.

Discussion

Chronic Rhinosinusitis (CRS) is the common upper respiratory disorder but continues to remain as a neglected disorder, especially in developing countries [16]. Bacterial infection plays a key role in worsening of CRS that can lead to asthma exacerbation, otitis media, recurrent polyps and refractory symptoms during post-sinus surgery [17]. The predominance of aerobic and anaerobic organisms cultured in children was reported to be different from adults and also with reference to site of isolation [18]. In the present study, identical potential pathogens were noticed in middle meatus *and sinus aspirates* which is in agreement with the earlier reports [19-21].

In a recent metanalysis study by Thanasumpun et al. [22] conducted on endoscopically derived bacterial cultures of adults with chronic rhinosinusitis reported Coagulase Negative Staphylococcus followed by *Staphylococcus aureus*, *Haemophilus influenza* and *Pseudomonas aeruginosa* to be the most common aerobes and Peptostreptococcus species and bacteroides species as the common anaerobes [22]. In pediatric chronic rhinosinusitis, polymicrobial infections and positive cultures of three major bacteria: *Haemophilus influenzae* (37.3%), *Streptococcus pneumoniae* (28.4%) and *Moraxella catarrhalis* (11.8%) were in Taiwan population whereas in chronic rhinosinusitis children of German population *Streptococcus pneumoniae* (33%) was the predominant followed by *Haemophilus influenzae* (27%), *Staphylococcus aureus* (13%), *Moraxella catarrhalis* (11%) and Streptococci (7%) [23,24]. In children of Chinese population both alpha-hemolytic Streptococcus (20.8%) and *Haemophilus influenzae* (19.5%) predominated followed by *Streptococcus pneumoniae* (14.0%), Coagulase-Negative Staphylococcus (13.0%), *Staphylococcus aureus* (9.3%) and anaerobes (8.0%) [25]. Unlike the above reported studies, the present study identifies *Staphylococcus aureus* (35%) to be the most common pathogen in both the age groups while other bacteria identified were *S. pneumonia* (22.3%) and *P. aeruginosa* (9%) showing variation with respect to severity and age of the chronic rhinosinusitis subjects. 64.7% subjects undergoing sinus surgery were positive for *S. aureus*. Polymicrobial infection was seen in only in 2.7% of study subjects. Also, no anaerobes were identified in children and adolescents with CRS which is not in agreement with the study conducted by Slack et al. [26].

Methicillin-resistance *Staphylococcus aureus* (MRSA) is known to be a common causative pathogen for chronic rhinosinusitis with greater recurrence rate and high prevalence and rising incidence in almost all countries [27]. According to a meta analysis study conducted by Macoul et al. the prevalence of MRSA was 1.8%-20.7% for CRS subjects [28]. The present study could not identify any MRSA strains and other predominant bacteria as reported in other studies in chronic rhinosinusitis children and adolescents. Also, a study from Karnataka, South India, reported only 3% of MRSA strains in CRS which indicates lesser burden of MRSA in community acquired infectious diseases in South Indian population [29].

Nasopharyngeal carriage of the *S. pneumoniae* was associated with younger age and considered to protect against colonisation by major pathogens such as *Staphylococcus aureus* and *Haemophilus influenzae* and thereby reducing their likelihood of causing invasive disease [30]. Reduction of pneumococcal carriage in children and increase in the incidence of *S. aureus* related infections was also attributed due to immunization with pneumococcal conjugate vaccine [31]. The present study finds *Streptococcus aureus* in 42.6% of bacterial isolates identified from younger children and 55.7% of subjects, who underwent sinus surgery, thereby supports the study conducted by Shaikh et al. [32].

Multiple co-morbidities like adenoids, otitis media, allergic rhinitis, asthma and nasal polyps are associated with chronic rhinosinusitis [1]. Significant correlation was seen between bacterial isolation rate of adenoid cultures to sinusitis grade and chronic suppurative otitis media [33,34]. Pathogens isolated from adenoids were also resistant to antibiotics that allowed infection to persist with an increased incidence of acute and unresolved otitis media [35]. Recent evidence suggests that the degree of atopy, is not associated with progression to chronic rhinosinusitis in pediatric age group but asthma is significantly associated which suggests a link between upper and lower airways and

independent of allergic etiology [36]. In the present study, the prevalence of adenoids was more common in CRS children while nasal polyps were more commonly seen in CRS adolescents. Allergic rhinitis was the predominant comorbidity seen in children as well as in adolescents. Further, an association higher rate of *Staphylococcus aureus* was seen with allergic rhinitis as reported by Refaat et al. [37]. A significant correlation between allergy, asthma, rhinosinusitis and high positive rate of bacteria was also observed which is in accordance with earlier reports [38-40]. Increase in bacterial positivity in allergic rhinitis subjects with nasal polyps and asthma was found which is similar to the observation made by Ramakrishna et al. [41]. A very high frequency of bacterial positivity was noticed in CRS adolescents with nasal polyps. However, the study could not identify any microbes in the isolates from CRS children with nasal polyps.

With regard to allergic fungal sinusitis (AFS), Ferguson et al, noted a geographical variability in the incidence of AFS and fungal species associated with the disease process. In the Southern United States, dermatiaceous fungi are the most common when compared with the Northern United States, while Aspergillus species was the cause in most cases reported in the Middle East [42]. However, none of the allergic fungal sinusitis case was noticed in the northwest of Turkey [43]. In the present study, prevalence of 13.8% of allergic fungal sinusitis was noted in the study subjects and was more commonly seen in adolescents (68%). *Asperigillus flavus* being the most common fungi noted in both the age groups. Incidence of fungal sinusitis with nasal polyposis was reported to be 7% by Braun et al. [44]. Telmesani [45] reported allergic fungal sinusitis with nasal polyposis as 12.1% and with asthma as 30% to 40% [45]. In the present study, a very high prevalence of 57.1% of allergic fungal sinusitis with nasal polyposis was observed. Asthma was observed in 19.9% of allergic fungal sinusitis subjects.

Different survival strategies and mechanisms are adopted by the pathogens causing difficulty in management of severe infections [11]. Increase in evolution of antibiotic resistance usually to multiple drugs in almost all bacterial pathogens has enhanced the chances of survival and extension into the community [11,46]. Since the present study has observed ethnic variation in the prevalence of microbes and antibiotic resistance in isolates of both the age groups it signifies the importance of microbial evaluation before initiations of any therapeutic interventions.

Conclusion

To our knowledge this is the first study to report etiology and antibacterial resistance in chronic rhinosinusitis children and adolescents in Indian population. The bacterial and fungal prevalence varied with respect to age, severity and co-morbiditites. High rate of antibiotic resistance in all the microbial isolates, *Staphylococcus aureus*, *Streptococcus pnuemoniae*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* warrants utmost need for early initiation of personalized interventions and management measures in chronic rhinosinusitis children and adolescents.

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