Complications to acute bacterial rhinosinusitis in children - a prospective study; bacterial cultures, virus detection, allergy sensitization and immunoglobulins*

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Abstract

Background: Prospective studies of complications due to acute rhinosinusitis are lacking, bacterial cultures are hard to obtain and the role of airborne allergies, viruses and immunoglobulin levels are unclear. The aim was to investigate the role of bacteria, viruses, allergy and immunoglobulins in children hospitalized due to rhinosinusitis.

Methodology: A prospective cohort study in Stockholm, Sweden, of children up to 18 years of age, hospitalized due to acute bacterial rhinosinusitis, from April 1st, 2017 to April 1st, 2020.

Results: Of 55 children included, 51% had a positive viral nasopharyngeal PCR and 29% had a positive allergy sensitization test. A higher percentage of middle meatus cultures were positive for bacterial growth compared to nasopharyngeal and displayed a wider array of bacteria. Dominating bacteria were *S. milleri* in surgical (7/12 cases), *S. pyogenes* in middle meatus (13/52 cases), and *S. pyogenes* and *H. influenza* in nasopharyngeal cultures (8/50 cases respectively). Nasal cultures were negative in 50% of surgical cases. An association was found between *S. pyogenes* and peak CRP; H. influenzae and peak CRP; *S. pneumoniae* and peak CRP; and possibly between *M. catarrhalis* and days of IV antibiotics. Further, an association between influenza A/B and *S. pyogenes*; a positive viral PCR and lower grade of complication and peak CRP; and a possible association between influenza virus and lower grade of complication. Allergy sensitization was possibly associated with a higher number of days with IV antibiotics. No immunoglobulin deficiencies were found.

Conclusions: There seem to be differences in the patterns of bacterial growth in nasopharyngeal, middle meatus and surgical cultures in children with complications to acute bacterial rhinosinusitis. Presence of certain viruses and sensitization to airborne allergies seem to play a role in complications to acute bacterial rhinosinusitis in children.

Key words: acute sinusitis, children, viruses, allergy, immunoglobulins

Introduction

Acute bacterial rhinosinusitis (ABRS) with complications is rare but serious conditions in children and adolescents and can potentially cause severe invasive infections where prompt recognition and proper management is paramount. The bacterial aetiology is often difficult to establish in children and changing trends in culture findings from airways and from abscesses following the introduction of pneumococcal vaccine have been reported [1-5]. Furthermore, ongoing viral infection, allergic rhinitis and immunoglobulin deficiency are factors that have been implicated in the pathogenesis of ABRS [6]. Prospective studies are lacking, both regarding bacterial aetiology and potential links between complicated ABRS and concurrent viral infection, allergic rhinitis, and immunoglobulin deficiency [7, 8].

The difficulty to obtain representative bacterial cultures from children with complications to ABRS is multifaceted. Sinus punctures demand anaesthesia in most children. The swollen nasal mucosa can prevent open drainage from sinuses to the nasal cavity. The clinical representability of nasopharyngeal cultures in children has been questioned due to the physiologically rich nasopharyngeal flora and the natural state of colonization of the adenoid, with commensals and potentially pathogenic airway bacteria. Surgical cultures are often obtained after the initiation of intravenous (IV) antibiotics and may therefore be negative. New diagnostic methods have emerged to determine presence of bacteria, including broad-range PCR and DNA sequencing, but to our knowledge, there are no studies that have used this method to analyse the presence of bacteria in complications to ABRS in children.

Immunodeficiency has been considered a risk factor for rhinosinusitis, and there are studies that implicate a connection to chronic rhinosinusitis in adults related to immunodeficiency [9, 10]. To our knowledge there are no prospective studies measuring immunoglobulin levels in children with complicated ABRS.

A prospective cohort study was performed with the primary aim to compare the bacterial findings in cultures from different sites in the same individual. Nasopharyngeal, middle meatus and surgical (bacterial swab culture, bacterial tissue culture, and broad-range 16S rDNA PCR) cultures were obtained in children hospitalized due to complications of acute bacterial rhinosinusitis. The secondary aims were to investigate if children with complications due to ABRS are more likely to have confirmed sensitization to allergies, concomitant viral infection or abnormal immunoglobulin levels.

Materials and methods

Study design and population

This study was a prospective cohort study in Stockholm, Sweden. The study population was children from birth to 18 years of age, hospitalized due to acute bacterial rhinosinusitis. Information about the study was spread to all the paediatric and ear- nose- and throat (ENT) care units in Stockholm, and patients were included by a paediatrician or an ENT surgeon, either at the emergency unit or when admitted to a ward. To be included, the caregivers had to sign an informed written consent, and the participants older than 15 had to sign an additional informed written consent. The study period was April 1st, 2017 to April 1st, 2020. The first case included was admitted September 6th, 2017 and the last included case was admitted March 23rd 2020.

Data collection

Inclusion criteria were ABRS diagnosis and hospitalization. The criteria for ABRS according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [11] were used to verify the rhinosinusitis diagnosis. Acute rhinosinusitis in children was defined as symptoms of nasal obstruction and/or discoloured nasal discharge and/or a cough with a duration of less than 12 weeks, together with clinical signs confirmed by endoscopic examination of the nose and/or computed tomography (CT). A bacterial infection was considered in the presence of at least three symptoms/signs of discoloured mucus, severe local pain, fever >38°C, elevated C-reactive protein (CRP)/ erythrocyte sedimentation rate (ESR) and 'double' sickening [11]. Only patients resident in the Stockholm region were included. Four initially included patients were excluded from the analysis; one was a resident of another region and three had a different conclusive diagnosis than acute rhinosinusitis (skin infection, throat infection, and vasculitis).

Data was gathered according to a standardized study protocol including: date of admission; age; gender; previously known allergies; vaccination status; medical history; medications; if antibiotics had been given before admission and if so, which antibiotic and how many doses; number of days with upper respiratory infection symptoms; number of days with worsening symptoms; and presence of redness and/or swelling around the eye. Furthermore, the protocol included laboratory tests including CRP; ESR; white blood count (WBC); electrolytes; immunoglobulin levels (IgG, IgM and IgA); allergy screening test (Phadiatop, fluoroenzymeimmunoassay FEIA, by Thermo Fisher Scientific: total IgE and IgE of: cat, dog, horse, birch, timothy, mugwort, *Cladosporium herbarum*, Dust mite *Dermatophagoides pteronyssinus*, and Dust mite *Dermatophagoides farina*); viral nasopharyngeal PCR swab and blood cultures. A blind bacterial swab was obtained from the nasopharynx (NPH), and an aimed bacterial swab was taken from the nasal middle meatus (MM) by an ENT surgeon. From the children undergoing surgery, a bacterial swab culture, a bacterial tissue culture and samples for broad-range 16S rDNA PCR were collected from the surgical site. After discharge, further data were gathered such as length of hospital stay, number of days with IV antibiotics, peak CRP, peak WBC, mode of radiology and radiology results, and type of surgery. The criteria for surgery in the study were the same as used in current clinical practice, where the decision to take the patient to surgery depended on the combined results of imaging, clinical findings and clinical course.

CT and Magnetic Resonance Imaging (MRI) images were reviewed by a specialist in radiology and categorized into orbital, intracranial or osseous complication (Table 1). The orbital complications were classified according to Chandler [12], where each orbital complication was graded according to the most severe complication present (Table 1). The study was approved by the Ethics Review Board in Stockholm, Sweden (application number 2017/296-31).

Statistical analysis

In the statistical analysis the types of bacteria in the different

Table 1. Complications of acute rhinosinusitis divided into orbital, intracranial and osseous complications.

Osseous	Osteomyelitis, subperiosteal abscess (Potts puffy tumor), subgaleal abscess
Intracranial	Meningitis, encephalitis, cerebritis, subdural or epidural empyema, epidural abscess, brain abscess, cavernous sinus thrombosis
Orbital	Preseptal cellulits/abscess, orbital cellulitis, subperiosteal abscess, myositis of extraocular muscles, optic neuritis Chandler's classification of orbital complications [12] 1. Preseptal cellulitis (inflammatory edema limited to eyelid) 2. Orbital cellulitis (inflammatory edema involving eye globe) 3. Subperiosteal abscess (pus between bone and periosteum) 4. Orbital abscess (pus in orbital contents)

cultures were described and categorized. The bacteria categorized as "others" were *Bacteroides fragilis* (MM culture), and five bacteria found in surgical cultures: *Campylobacter* species, Anaerobe mixed flora, *Fusobacterium nucleatum*, *Prevotella* species and *Klebsiella oxytoca*. Contaminated cultures were regarded as negative cultures. In the bacteria distribution analysis, each type of bacteria was compared to the cases without that bacteria, as a binary variable. Fisher's exact test was used to estimate whether the distribution of bacteria differed in the different cultures. The exposures were: type of bacteria, viral PCR positive/negative for any virus, viral PCR positive/negative for influenza virus, and positive/negative Phadiatop. The outcomes were: grade of complication (ordinal variable), days of IV antibiotics (ordinal value) and peak CRP value (continuous variable). Grade of complication was a scale 1-5, from least severe to most severe, as follows: 1 – preseptal cellulitis, 2- orbital cellulitis, 3- subperiosteal abscess, 4- orbital abscess, and 5- intracranial complication. The cases that did not have a CT or MRI performed and had clinical signs of preseptal cellulitis were considered as grade 1. Ordered logistic regressions was used to estimate the associations between exposures and grade of complication and days of IV antibiotics. Linear regression was used to estimate the associations between exposures and the peak CRP value. The standard errors were obtained by robust estimator. The analyses were conducted in Stata (MP 15.1, StataCorp LLC, College Station, TX, USA).

Results

General data

A total of 55 children were included. For descriptive data, see Table 2. CRP and WBC were collected in all admissions and ESR in 38% of the cases. 12 children had previous identified diseases, of which five had asthma or wheezing. Other diagnoses were neuropsychiatric diagnoses (n=5), obstructive sleep apnoea, developmental disorder, epilepsy and recurrent urinary tract infection. Four children had a verified airborne allergy at inclusion, and two of these had verified asthma. The mean number of days with common cold symptoms before admission was 6.8 days, the mean number of days with worsening symptoms before admission was 1.7, and mean number of days admitted and days with IV antibiotics was 3.2. Median age of males in the total cohort was 7.5 years compared to females 8.6. In 26 (47.3%) of the cases, a CT was performed, and two cases also had an MRI. A postseptal orbital or intracranial complication was verified in 22 of the children that had radiology. At inclusion, all children but one had redness and/or swelling around the eyes as clinical signs of preseptal cellulitis. Twelve had surgery due to complications to ABRS and their median age was 7.9. The number of cultures, viral swabs, Phadiatop tests and immunoglobulins obtained in the cohort are displayed in Table 2.

In ten cases, between one and six doses of oral antibiotics had been administered before admission (Flucloxacillin, Phenoxymethylpenicillin or Amoxicillin/clavulanic acid). In this group of ten children, five had growth of *S. pyogenes* in at least one nasal or surgical culture; five had surgery; the average number of days with worsening symptoms before admission was 2.2 compared to 1.6 days in the remaining cohort; four children tested positive for viral nasopharyngeal PCR and the average CPR at admission and peak CRP during admission were 86 and 89 compared to 74 and 86 in the remaining cohort, see details in supplement Table S2.

In the analysis of the 26 CT and MRI images, four cases had only preseptal cellulitis (Chandler 1), five had orbital cellulitis (Chandler 2), 13 had a subperiosteal abscess (Chandler 3) and two had an orbital abscess (Chandler 4). Two children had an intracranial complication. One case had a small intracranial abscess in addition to the orbital subperiosteal abscess, and another had meningitis and osteitis (osseous complication) in the skull base.

Bacterial cultures

In 20 cases (36.4%), at least one of the same type of bacteria was found in both the nasopharyngeal and middle meatus culture, (Figure 1). Both types of cultures were taken in 48 children.

In nine individuals, the MM culture was positive for bacterial growth while the NPH culture was negative (16.4%). In five individuals, the MM culture was negative and nasopharyngeal culture positive (9.1%). One child had different bacteria growing in the two cultures and both were negative in 13 cultures (23.6%). Data was missing in seven cases. In 39/48 cases where both NPH and MM cultures were obtained, the cultures were

Table 2. Descriptive data of total cohort, prospective study of hospitalized children with acute bacterial rhinosinusitis in Stockholm 2017-2020, n= number of admissions.

Admissions, n	55
Gender, % males	67
Median age, years	7.6
Mean age, years (SD)	7.8 (4.3)
Mean CRP, mg/L, at admission	75.8
Mean CRP, mg/L, peak value	86.1
Mean WBC, x10^9/L, peak value	13.8
Mean ESR, mm (missing, n)	55.5 (34)
CT/MRI, n	26
Surgery, n	12
Nasopharyngeal culture, n (missing)	50 (5)
Nasal middle meatus culture, n (missing)	52 (3)
Surgical site culture, 16s DNA test, n (missing)	12 (0)
Surgical site culture, tissue, n (missing)	11 (1)
Surgical site culture, swab, n (missing)	9 (3)
Blood culture, n (missing)	51 (4)
Viral nasopharyngeal PCR swab, n (missing)	53 (2)
Phadiatop test, n (missing)	48 (7)
Immunoglobulins, n (missing)	47 (8)

taken at approximately the same time. Maximum time between the two cultures were 24 hours (4 cases).

In the 20 children where the NPH and MM cultures had at least one bacteria in common, *S. pyogenes* was found in six cases; *H. influenzae* was found in four; *S. pneumoniae* in two; *H. influenzae* and *S. pneumoniae* in one; *S. pyogenes* and *S. aureus* in one; and *Moraxella* in six cases, see Figure 1 and Table S1. The most common bacteria in MM cultures was *S. pyogenes*, while the most common bacteria in surgical cultures was *S. milleri*. Among the NPH cultures there was a more even distribution of bacteria, primarily *S. pyogenes*, *H. influenzae*, *S. pneumoniae* and *Moraxella*. 36 of 52 MM cultures taken (69.2%) had growth of at least one type of bacteria. 27 of 50 NPH cultures taken (54%) had growth of at least one type of bacteria.

S. milleri was found in the MM culture in three children, the NPH culture was negative in all these cases and none of them underwent surgery. In the total cohort, *S. pyogenes* was the bacteria found in the highest number of admissions (n=16), followed by *Moraxella* (n=12), *S. milleri* (n=11), *H. influenza* (n=10), *S. pneumoniae* (n=8), and *S. aureus* (n=6).

There was a statically significant association between *S. pyogenes* and peak CRP (57.5, p=0.007); a negative association between *H. influenzae* and peak CRP (-38.9, p=0.028) and *S. pneumoniae* and peak CRP (-45.5, p=0.023); and a possible negative association between *M. catarrhalis* and number of days of IV antibiotics (-1.3, p=0.055).

S. milleri was the most common pathogen found in the surgical cultures, see supplement Table S1 for individual results of the different types of surgical cultures. In two cases, there was a match between the pathogens found in surgical cultures and nasal cultures, both showing *H. influenzae* in surgical and MM cultures. The nasal cultures were negative or regarded as contaminated in seven of the 12 children that had surgery, both nasal cultures missing in one case. The broad-range 16S rDNA PCR was negative in one case, while there were more negative cultures and more data missing in the tissue and swab cultures. S. *aureus* was not found in any of the cultures among the children with the most severe complications, grade 3-5.

Four children had positive blood cultures, three for *S. milleri* and one for *S. salivarius*. Of the cases with *S. milleri* in blood, one had the same pathogen found in the MM culture, another had growth of *S. aureus* in the NPH culture, and a third, undergoing surgery, had a negative MM culture. The child with *S. salivarius* in blood had growth of *S. pyogenes* in the MM culture.

Viral nasopharyngeal PCR

Viral nasopharyngeal PCR was obtained in 53 individuals and positive in 28 cases. Influenza A was found in 10 patients, rhinovirus in nine, bocavirus in four, metapneumovirus in two, adenovirus in two, parainfluenza in two, RS in two and one each for coronavirus OC43, enterovirus, and influenza B. Four patients had more than one virus identified. Positive viral PCR was associated with a lower grade of complication (-1.3, p=0.028) and peak CRP (-36.2, p=0.05). Influenza virus was possibly associated with a lower grade of complication (-2.2, p=0.055).

There was a statistically significant association between influenza A/B and *S. pyogenes* in any culture (1.5, p=0.040). In six of the 11 Influenza A or B positive cases (54.5%), *S. pyogenes* was found in at least one culture (3 NPH, 5 MM, 1 surgical). In the total cohort, 16 cases had at least one culture positive for *S. pyogenes* (29.1%). Among these 16 cases, only two patients had a viral infection other than an influenza virus (boca and rhinovirus), seven cases had a negative virus NPH swab, and a virus NPH swab was not obtained in one case. The last admitted case, in March 2020, was the only child tested for Coronavirus SARS-CoV-2 and it was negative. The number of cases with positive viral swabs correlated with the total number of cases in regard to month of the calendar year (Figure 2).

Immunoglobulins

Of the 47 cases where immunoglobulins (IgG, IgA and IgM) were obtained, only one case had a slightly low value of IgG (5.8 g/L, ref 6.1-14.5). Eight cases had elevated IgA levels and four cases had elevated IgM levels.

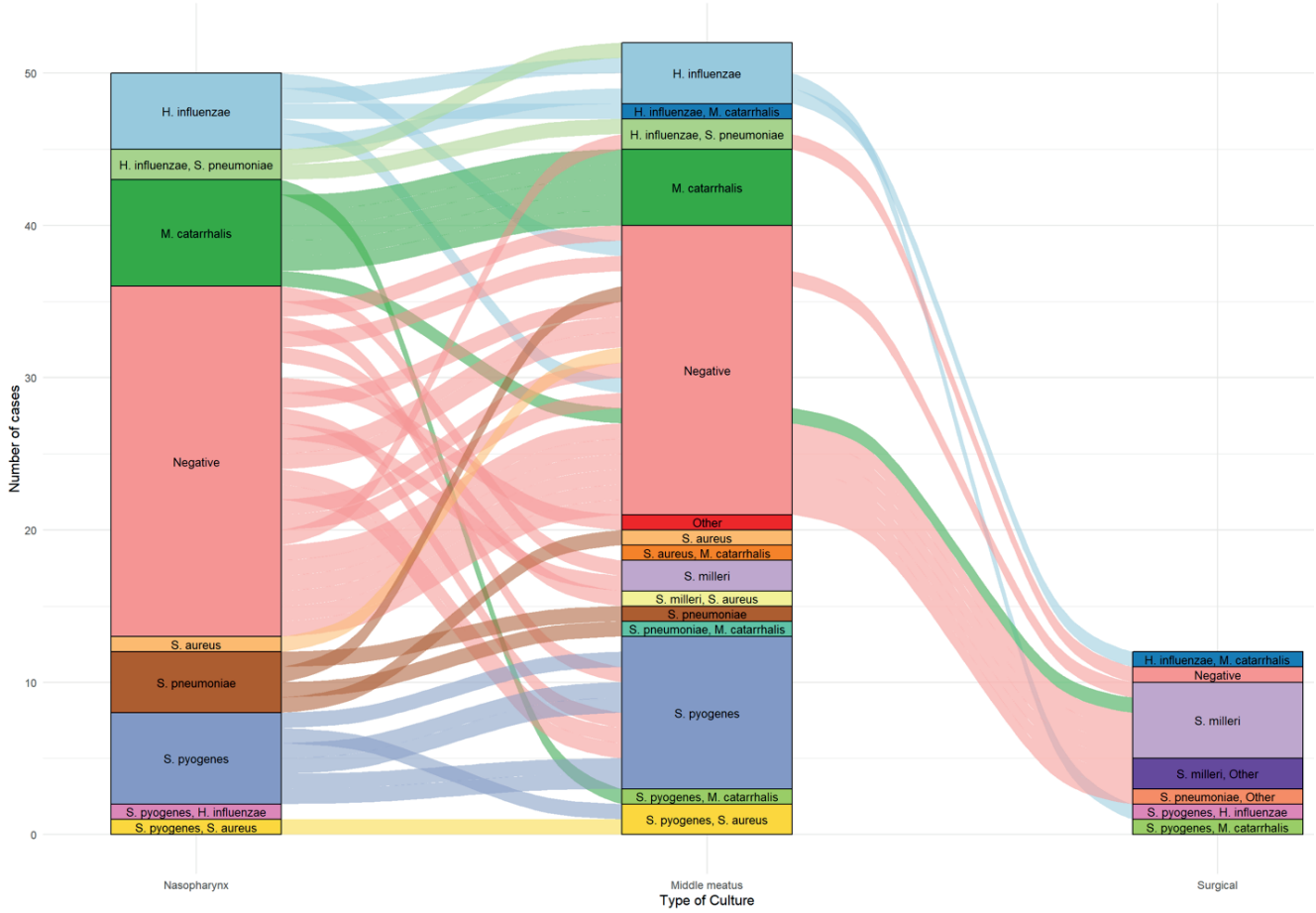

Figure 1. The results of bacterial cultures from nasopharynx, nasal middle meatus and surgical site, in cases included in prospective study of hospitalized children with acute bacterial rhinosinusitis in Stockholm 2017-2020. The results of the different sites of each case are connected by lines between the columns.

Allergy sensitization test

Of the 48 cases with obtained Phadiatop test, 14 were positive (29%). The mean age for the children with a positive test was 11.5 years, median 12.0 years. The allergy sensitization test was possibly associated with a higher number of days with IV antibiotics (1.2, p=0.052).

Dividing the cohort into a surgery and non-surgery group, six of the 12 (50%) children in the surgery group, and 8 of the 36 children (22%) in the non-surgery group (7 missing) had a positive Phadiatop test. Median and mean age in the surgery group was 7.9 and 9.0, and 7.5 and 7.4 in the non-surgery group. In the group of children with a CT/MRI verified postseptal complication, 10 of 22 (45%) had a positive Phadiatop test (2 missing), the median age was 10.1 and mean age was 9.7. Among the children that had either only a preseptal cellulitis on CT/MRI or did not have CT/MRI performed, 4 of 26 (15%) had a positive Phadiatop test (5 missing). The median age was 5.7 and mean age was 6.3.

In five of the six children that had surgery and a positive Phadiatop test, S. milleri was found in surgery cultures. Out of the four children that had verified airborne allergy before admission, Phadiatop test was missing in two cases. Five of the cases with a positive Phadiatop test had a positive viral swab (36%), see Table S1.

Discussion

In this prospective cohort study of 55 hospitalized children with complications due to acute rhinosinusitis, MM cultures were positive for bacterial growth to a greater extent and showed a different display of bacteria compared to the NPH cultures. We found positive associations between *S. pyogenes* and peak CRP, and negative association between *H. influenzae* and *S. pneumoniae* and peak CRP. Surgical cultures were dominated by growth of *S. milleri* and broad-range 16S rDNA PCR provided a higher number of positive results compared to traditional swab and tissue cultures. Interestingly, *S. milleri* was not found in the nasal cultures in the children that had undergone surgery, and 50% of the nasal cultures were negative. Half of the cohort had a positive viral swab and there was an association between any virus and a lower grade of complication and lower peak CRP. We

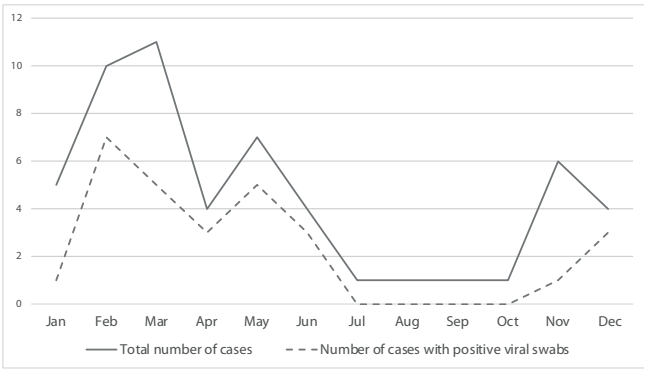

Figure 2. The total number of cases and number of cases with positive viral swab divided into month of admission, January through December, prospective study of hospitalized children with acute bacterial rhinosinusitis in Stockholm 2017-2020.

found an association between influenza A/B and *S. pyogenes* in any culture. Allergy sensitization was possibly associated with a higher number of days with IV antibiotics.

The MM and NPH cultures were coherent in 60%, either regarding growth of the same bacteria, or both negative for bacterial growth. The finding that a larger percent of the MM cultures were positive for bacterial growth and had a different display of bacteria than the NPH cultures may be a significant finding from a clinical point of view. It indicates that a sample from the middle meatus may increase the likelihood of obtaining a culture that represents the causative bacteria. A similar association has previously been shown in adults [13]. There are also studies of adults and one in children that have demonstrated that culture swabs from the middle meatus (the area between the inferior and middle turbinate where the maxillary, ethmoid and frontal sinuses drain) provide a representative bacterial profile when compared to sinus punctures [14, 15].
The value of NPH cultures in children have sometimes been questioned due to children's rich nasopharyngeal bacterial flora. Since the coherency with MM cultures is relatively high according to our data, we would argue that a NPH culture is better than no culture at all. Nasal bacterial cultures from the children that presented with complications requiring surgery were negative for bacterial growth (or contaminated) in 58%. In only two of 12 surgery cases, the same pathogen as in the surgical cultures was found in the nasal cavity, both showing *H. influenzae*. The dominant bacteria in surgical cultures was *S. milleri* (58%). This is in line with many other studies [16-18]. *S. milleri* was only found in three nasal (MM) cultures from children in this study, none of which needed surgery. *S. milleri* is a group of bacteria commonly found as a commensal organism of the mouth and gastrointestinal tract, and not part of the nasal flora [19, 20]. The negative nasal cultures in the surgery cases could indicate that there is no drainage from the sinuses to the nasal cavity in these cases, which may partly explain the development of more severe complications. Furthermore, the dominance of *S. milleri* in surgical cultures but not in corresponding nasal cultures may indicate that *S. milleri* is not the initial pathogen but is established after initial infection when an abscess is formed.
S. pyogenes was the most common bacteria found in nasal cultures in our cohort. When analysing the subgroup of ten children that had received oral antibiotics before admission, *S. pyogenes* was found in 50% (29% of total cohort). In this subgroup, 50% also required surgery, even though the given antibiotic was correct according to the bacterial findings in the nasal cultures of those children. In the statistical analysis, we found associations between different bacteria and the outcome peak CRP. *H. influenzae* and *S. pneumoniae*, and possibly *M. catarrhalis*, were associated with a lower peak CRP. *S. pyogenes* was associated with a higher peak CRP.
In a study from 2018, the nasopharyngeal microbiome in children up to five years old was characterized with 16S rRNA amplicon sequencing technique [20]. The results showed that the nasal microbiome is simple in structure, and that it can be divided into profiles where one single bacterial genus dominates, including *Moraxella*, *Streptococcus*, *Corynebacterium*, *Alloiococcus*, *Haemophilus* and *Staphylococcus*. The microbiome profile changes with age and during upper respiratory infections. In the study, *Streptococcus* (predominantly *Pneumococci*), *Haemophilus* and *Moraxella* dominated during acute respiratory infections, which also could explain why these are important pathogens in bacterial rhinosinusitis. Interestingly though, *S. pyogenes* was only very sparsely found in the nasal microbiome and *S. milleri* was not found in the nasal microbiome at all [20].
The broad-range 16S rDNA PCR test provided a higher number of positive results compared to traditional swab and tissue cultures. Although there was missing data in the swab and tissue cultures, it seems that broad-range 16S rDNA PCR test should be recommended in all cases because of higher sensitivity.

A positive viral swab was found in 53% of the cohort and the seasonal curves of total number of admissions and number of admissions with virus positive swabs followed each other. However, we found that a positive viral PCR was associated with a lower grade of complication and peak CRP, and that influenza virus possibly was associated with a lower grade of complication. An explanation could be that the individuals with a positive viral PCR were at an earlier stage in the pathophysiological pathway. Respiratory viruses have been shown to trigger mucosal responses that lead to post viral acute rhinosinusitis and ABRS [11]. Despite screening for multiple different respiratory viruses, 47% in our cohort did not show evidence of a viral trigger. Viruses have varying shedding duration [21-24] and the low viral finding in our study could be explained by that the virus had already disappeared. Another possible explanation could be the absence

of a viral trigger and rather a change in the nasal microbiota that takes place prior to the debut of acute respiratory infection symptoms described in the nasal microbiome study [20]. Only a few studies have investigated if any specific virus is associated with ABRS, and to our knowledge, no study have looked at a potential relationship between virus and complications to ABRS. One prospective study found a positive correlation between the presence of rhinovirus and *Moraxella* during an upper airway infection and the risk of acute bacterial rhinosinusitis in children up to three years old [25]. We found a statistically significant association between influenza A/B and *S. pyogenes* in any culture. This is in line with the studies supporting that influenza virus is associated with *S. pyogenes* infection [26-30]. The molecular process involved in influenza induced secondary bacterial infection is not fully understood, but examples of studied interactions have been a decrease in the immune cells ability to take up and kill bacteria due to influenza virus, and an influenza-virus induced alteration of the gene expression of *S. pneumoniae* to enhance spread of the bacteria in the mucosa have been presented [31], and reduced bacterial attachment [26].

The percentage of children in the total cohort with verified sensitization for airborne allergies was in line with what has been found in population-based studies of children in the Stockholm area [32, 33]. A positive allergy sensitization test was possibly associated with a higher number of days with IV antibiotics. There is conflicting evidence in literature whether allergic rhinitis is a risk factor for acute rhinosinusitis [34-36], and only a few studies include children [8, 37]. In one study, the authors found an increased risk of lower respiratory infections in children with allergic sensitization [20]. There is evidence for an association between allergy and chronic rhinosinusitis in adults [38], but there are few studies on children, and the results are ambiguous [39-42]. To our knowledge, there is no study of the relationship between acute rhinosinusitis with complications and sensitization to airborne allergies. The children with a verified sensitization to airborne allergies in this study were overrepresented in the group of children that had CT verified postseptal complication and/or surgery. Although they had a higher median age than the total cohort, and therefore should have a higher prevalence of sensitization to airborne allergies, the finding that 45-50% of them were sensitized seems higher than expected compared to studies in a normal childhood population in Stockholm [32, 33]. The immunoglobulin results in this study did not show any deficiencies, and the previous identified diseases in the cohort was in line with what can be found in the normal population.
The greatest strength of this study is that it is a prospective study of a rare condition, with systematic gathering of cultures from different sites including bacterial DNA as well as clinical data. The limitation of the study is that the sample size is small and some data are missing, which limits the interpretations that can be made. Furthermore, the diagnosis and degree of postseptal complication could not be made in the cases that did not undergo a CT.

Conclusion

In conclusion, there seem to be differences in the patterns of bacterial growth in nasopharyngeal, middle meatus and surgical cultures in children with complications to ABRS. Presence of certain viruses and sensitization to airborne allergies seem to play a role in the development of complications to ABRS. Larger prospective studies are needed to fully understand the role and potential interplay of microbiome, pathogenic bacteria, viruses and airborne allergy.

Authorship contribution

SHD led the group and acquired the data; analysed and interpreted the data; wrote the manuscript draft; and critically revised the manuscript. All authors contributed to study conception and design; analysed and interpreted the data; participated in writing the manuscript draft and critically revised the manuscript.

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Conflict of interest

No conflict of interest exists.

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List of abbreviations

ABRS: Acute bacterial rhinosinusitis; CRP: C-reactive protein; CT: Computed tomography; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; ESR: Erythrocyte sedimentation rate; IV: Intravenous; MM: Nasal middle meatus; NPH: Nasopharyngeal; MRI: Magnetic Resonance Imaging; PCV: Pneumococcal conjugate vaccine; WBC: White blood cell count

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Individual data for whole cohort, prospective study of hospitalized children with acute bacterial rhinosinusitis in Stockholm 2017-2020, sex (M=male, F=female), days with intravenous antibiotics (IV AB), results from Phadiatop test and viral PCR, and results of cultures from nasopharynx (NPH), nasal middle meatus (MM), blood and surgical site (surgical).

Case no	Sex	IV AB (days)	Age (years)	Phadiatop	Viral PCR	NPH	MM	Blood	Surgical
1	F	7	12,0	neg	neg	neg	*S. milleri, Parvimonas micra* (cont)	neg	
2	M	2	10,7	pos	neg	neg	neg	neg	
3	M	2	2,4	neg	neg	*H. influenzae, S. pyogenes*	missing	neg	
4	M	2	6,9	neg	neg	missing	*M. catarrhalis, S. aureus*	neg	
5	M	5	13,5	missing	neg	missing	*S. pyogenes*	S.salivarius	
6	F	1	3,6	missing	missing	*M. catarrhalis*	*S. pyogenes, M. catarrhalis*	neg	
7*	M	4	2,8	neg	Influenza A	missing	Missing	neg	*S. pyogenes, M. catarrhalis, Corynebacterium* species (cont), *Dolosigranulum pigrum* (cont)
8*	M	1	1,6	neg	Boca	*S. pyogenes*	*S. pyogenes*	neg	
9*	M	2	8,8	neg	neg	neg	*S. pyogenes*	neg	
10	M	2	8,7	missing	Influenza B	*S. pyogenes*	*S. pyogenes, S. aureus*	neg	
11	M	1	8,6	missing	Adeno, RS	*H. influenzae*	neg	neg	
12	F	5	13,1	pos	neg	neg	neg	neg	*S. milleri*
13	M	2	12,6	pos	Influenza A	*S. pneumoniae*	*S. pneumoniae*	neg	
14	M	2	7,8	missing	neg	neg	*Staphylococcus epidermidis* (cont)	neg	
15	F	2	8,8	pos	Influenza A, Metapneumo	*S. pyogenes, S. aureus*	*S. pyogenes, S. aureus*	neg	
16	F	1	11,0	neg	Rhino	*M. catarrhalis*	*M. catarrhalis*	missing	
17	F	3	3,4	neg	Influenza A	*H. influenzae, S. pneumoniae*	*H. influenzae*	neg	
18	F	2	3,3	neg	Boca, Metap-neumo, Rhino	neg	*S. milleri, S. aureus*	missing	
19	F	3	3,2	neg	Parainflu-enza 1	neg	missing	neg	
20	F	3	10,8	pos	Influenza A	*H. influenzae*	*H. influenzae*	neg	
21	M	4	6,3	pos	neg	*S. pyogenes*	*S. pyogenes*	neg	
22	F	2	2,3	neg	Corona OC43 HKU1	*H. influenzae, S. pneumoniae*	*H. influenzae, S. pneumoniae*	neg	
23	M	4	7,3	pos	neg	neg	neg	neg	*S. milleri*
24	F	5	11,4	pos	missing	missing	neg	S. milleri	*S. milleri, Koagulas-negativ staphylococcus* (cont)
25	M	4	14,2	pos	neg	neg	Skinflora (cont)	neg	*S. milleri, Propionibacterium acnes* (cont)

Case no	Sex	IV AB (days)	Age (years)	Phadiatop	Viral PCR	NPH	MM	Blood	Surgical
26	M	3	5,3	neg	Parainfluenza 2	neg	*H. influenzae*, *S. pneumoniae*	neg	Neg
27*	F	4	6,0	neg	Adeno	neg	neg	neg	*S. milleri*, *Campylobacter* species, Anaerobic mixed flora, *Parvimonas micra* (cont)
28*	F	2	8,8	neg	neg	*M. catarrhalis*	*M. catarrhalis*	neg	
29	M	2	7,5	neg	Influenza A	*M. catarrhalis*	*M. catarrhalis*	neg	
30	M	3	3,3	neg	Influenza A	*S. pyogenes*	*S. pyogenes*	missing	
31*	M	3	16,0	pos	neg	neg	*Bacteroides fragilis*	neg	
32*	M	6	5,8	neg	RS	*H. influenzae*	*H. influenzae*	neg	*H. influenzae*, *M. catarrhalis*, *Corynebacterium fastidiosum* (cont)
33	M	2	1,5	neg	Boca	*M. catarrhalis*	*M. catarrhalis*	neg	
34	M	1	0,8	missing	Boca	*S. pneumoniae*	neg	neg	
35	M	3	16,4	neg	neg	neg	neg	neg	
36	F	2	5,7	neg	Influenza A	neg	*S. pyogenes*	neg	
37	M	2	13,7	neg	neg	neg	*S. milleri*	S. milleri	
38	M	2	2,7	neg	Rhino	*H. influenzae*	*H. influenzae*, *M. catarrhalis*	neg	
39	F	2	3,8	neg	neg	*S. pneumoniae*	*S. pneumoniae*, *M. catarrhalis*	neg	
40	M	2	1,7	neg	Rhino	*M. catarrhalis*	*M. catarrhalis*	missing	
41	M	3	5,7	neg	Rhino	neg	neg	neg	
42	F	9	16,9	neg	neg	neg	neg	Micrococcus species (cont)	
43	M	5	14,1	pos	Rhino	neg	neg	neg	*S. milleri*, *Prevotella* species, *Fusobacterium nucleatum*, *Staphylococcus epidermidis* (cont), *Staphylococcus lugdunensis* (cont)
44	M	6	12,7	pos	neg	*S. aureus*	neg	S. milleri	
45*	M	2	5,9	neg	neg	missing	*H. influenzae*	neg	*S. pyogenes*, *H. influenzae*
46	M	3	7,8	neg	neg	*S. pneumoniae*	*S. aureus*	neg	
47	M	14	9,6	pos	Rhino	neg	*S. pyogenes*	neg	
48	F	6	8,7	neg	Influenza A	neg	*S. pyogenes*	neg	
49	M	4	10,5	neg	neg	neg	neg	neg	
50	M	3	4,3	neg	Influenza A, Rhino, Entero	*H. influenzae*	neg	neg	
51	M	3	3,6	neg	neg	*S. pyogenes*	*S. pyogenes*	neg	
52*	M	2	13,6	pos	neg	neg	*Propionibacterium acnes* (cont)	neg	*S. pneumoniae*, *Klebsiella oxytoca*,
53	F	3	8,5	neg	Rhino	*M. catarrhalis*	neg	neg	*S. milleri*
54	M	3	4,4	missing	neg	neg	neg	neg	
55*	M	2	7,6	neg	neg	*S. pyogenes*	*S. pyogenes*	neg	

*Cases that had received oral antibiotics before admission

Table S2. Individual results of surgical cultures, prospective study of hospitalized children with acute bacterial rhinosinusitis in Stockholm 2017-2020.

Case no	Days with IV Ab	Ab before admission	Bacterial DNA (16s)	Bacterial tissue culture	Bacterial swab culture
7	4	Phenoxymethylpenicillin 1,5 days	*S. pyogenes, Moraxella, Corynebacterium* species (cont), *Dolosigranulum pigrum* (cont),	*S. pyogenes*	*S. pyogenes, Corynebacterium pseudodiphtheriticum* (cont)
32	6	Phenoxymethylpenicillin 0,5 days	*Moraxella, Corynebacterium* species (contt)	neg	*H. influenzae*
45	2	Flucloxacillin 1 day	*H. influenzae, S. pyogenes*	*S. pyogenes*	*H. influenzae, S. pyogenes*
26	3		Neg	neg	Missing
52	2	Amoxicillin/clavulanic acid 2 days	*S. pneumoniae*	*Staphylococcus epidermidis* (cont), *Propionibacterium acnes* (cont)	*Klebsiella oxytoca, Streptococcus pneumoniae, Staphylococcus epidermidis* (cont), *Propionibacterium acnes* (cont)
53	3		*S. milleri*	*S. milleri*	*S. milleri*
23	4		*S. milleri*	Neg	missing
12	5		*S. milleri*	*S. milleri*	*S. milleri*
24	5		*S. milleri*	*S. milleri*, Koagulas-negative *staphylococcus (*cont)	neg
27	4	Phenoxymethylpenicillin 1 day	*S. milleri, Campylobacter* species, Anaerobic mixed flora	*S. milleri, Parvimonas micra* (cont)	missing
43	5		*S. milleri, Prevotella* species, *Fusobacterium nucleatum*	*S. milleri, Staphylococcus epidermidis* (cont), *Staphylococcus lugdunensis* (cont)	*S. milleri*
25	4		*S. milleri, Propionibacterium acnes* (cont)	missing	*S. milleri*