Dynamics of the respiratory tract flora in the first years of life: a comparative analysis between infants / children with cystic fibrosis and healthy controls.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON39211

Source
ToetsingOnline

Brief title
Respiratory flora dynamics in children with CF.

Condition

- Other condition
- Hepatobiliary neoplasms malignant and unspecified
- Respiratory tract infections

Synonym
bacterial colonisation in children with cystic fibrosis;

Health condition

metagenomics, resistomics (feces, nasopharyngeal)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: o.a. WKZ-onderzoeksfonds;verdere funding zal worden aangevraagd bij oa. CF stichting

Intervention

Keyword: cystic fibrosis, microbiomics, pathogens, resistomics

Outcome measures

Primary outcome

We expect in-depth knowledge about nasopharyngeal colonization dynamics and species interaction in young healthy children and children with CF, as well as the sequential relationship with clinical respiratory symptoms in infants with CF. Besides we aim to unravel the effect of antibiotic treatment on divergence of the natural protective microflora in relation to disease progression as well as it*s effect on the evolution of the resistome and resistance in respiratory pathogens in this young population. Lastly we want to determine the mucosal immune response (antibody development) against common respiratory pathogens in children (e.g. pneumococcus) in relation to colonization and vaccination in this patient group.

Secondary outcome

We will collect saliva samples to investigate the mucosal immune response in relation to natural boosting by pneumococcal colonization and childhood vaccinations in children with CF compared to controls (saliva IgA and IgG).
In the present drSNUIT study we observe events of nasopharyngeal recolonization

with the same pathogen, therefore we intend to investigate the correlation between (re)colonization and species-specific local antibody responses in saliva (local IgA-production). It is interesting to know if nasopharyngeal colonization elecits protective antibody levels against recolonization

Study description

Background summary

Nasopharyngeal colonization establishes soon after birth. By 6 months of age, frequent encountered potential pathogens in the nasopharynx are S. pneumoniae, H. influenza, M. catharralis and S. aureus. Upper airway tract colonization is dynamic and often balanced; dysbalance is associated with diseases such as acute otitis media, sepsis and meningitis.Competitive pathogen interactions (e.g. between S. pneumoniae and S. aureus) are present in the upper airways but are still hardly understood.Host- and environmental factors such as day care attendance, age, immunity, viral infections, 7-valent pneumococcal conjugate vaccine and antimicrobial agent use have been shown to modify colonization.
Children with cystic fibrosis (CF) are known to acquire respiratory tract infections very early in life, in particular with S. aureus, non-typable H. influenzae and P. aeruginosa. P. aeruginosa infection is a major determinant for morbidity in CF. Pulmonary inflammation is observed already in the first months of life; it is still debated whether inflammation occurs independently before pathogen colonisation. In patients diagnosed by newborn screening, broncho-alveolar specimens from the first months of life discovered pathogens in 20 % of patients, the majority being asymptomatic. Pulmonary infection in CF patients follows upper respiratory tract colonization, among others in the sinuses.Unlike in healthy children, only scarce data are available for nasopharyngeal colonisation since majority of CF studies focus on the lower airways. Nasopharyngeal specimens from CF patients detect most common pathogens concomitantly present in the lung; there is an extra diagnostic yield with respect to upper respiratory tract colonizing pathogens.
In CF, competitive interactions within the microbial flora seem to be an important determinant for respiratory exacerbations. In healthy children, P. aeruginosa colonization occurs infrequently, and is increased in presence of respiratory viruses. In contrast, in CF patients viral upper respiratory tract infections are clearly associated with lower respiratory tract morbidity and increased risk for initial P. aeruginosa infection. Synergisms within the microbial flora may cause renewed virulence of P. aeruginosa in a chronic infection condition, leading to increased inflammation and respiratory exacerbations.

The quality and quantity of the complete respiratory flora in healthy children and children with CF is largely unknown because of limitations in current microbiological methods, leaving possible windows of treatment opportunities unnoticed. Molecular targeting of pulmonary specimens manifested much more colonizing species in CF patients than conventional cultures; not taking into account colonization rates in the upper airways.
To gain more understanding about microbial colonization profiles, interactions, the impact of use of antibiotics and respiratory viral infections and risks for subsequent pulmonary disease in children with CF, it is necessary to begin at the start and to unravel the microbial colonization profiles from a very early age. Modern high-throughput molecular techniques can facilitate detailed analysis of microbial profiles and -shifts, which was impossible until now using conventional culturing techniques.
Since antibiotic treatment in CF patients may affect the microbiome and resistance, we also will collect faeces for evaluation of flora and resistome.
Amendement 2:
The pneumococcal conjugate vaccine is recommended in infants with CF and currently included in the national infant immunization schedule for all newborns, though the immunogenicity and protectivity of this vaccine hasn*t been tested in this patient group. Recently we showed that saliva IgG levels correlate well with systemic IgG antibodies (Rodenburg et al., under review) .
CF patients may have an altered attenuated antibody response to pneumococcus for several reasons; due to a lot of antibiotic use, organisms are eradicated before a natural antibody response can be generated or vaccine responses can be boosted. The abnormal airway secretions in CF and overgrowth of the respiratory epithelium by other organisms may also impair the ability to recognize and mount an appropriate antibody response to pneumococcus and CF patients may have an attenuated IgG2 response to encapsulated organisms.
We will collect saliva samples to investigate the mucosal immune response in relation to natural boosting by pneumococcal colonization and childhood vaccinations and in relation to vaccination in children with CF compared to controls (saliva IgA and IgG).
Amendement 3:
Amendement 3: (see separate reference list 3)
Since January 2011, a persistent large number of different types of micro-organisms has been discovered in the respiratory samples of both the control and CF patients, aged under 18 months. In literature, correlations have been found between bacterial community profiles and clinical disease markers (2,3,5). Bacterial community complexity was inversely correlated with patient age, presence of P. aeruginosa and antibiotic exposure, and was related to CF genotype. In the current study, untill the age of 18 months, we observed no substantial differences in diversity between control and CF patients. This might be due to the fact that 1) the microbiome is still establishing at this very young age and 2) the antibiotic use is still low in both groups, antibiotics which are essential in the decrease of diversity. Therefore , we believe we need to follow these children for a longer period of time to gain more understanding about microbiome diversity in relation to age and

CFTR-genotype. Consequently,
we want to extend the duration of the follow-up part of this case-control study, investigating the dynamics and diversity of the airway-microbiome in children.
In the present study we observe events of nasopharyngeal recolonization with the same pathogen, therefore we intend to investigate the correlation between (re)colonization and species-specific local antibody responses in saliva (local IgA-production)(1). It is interesting to know if nasopharyngeal colonization elecits protective antibody levels against recolonization.

Study objective

Our primary hypothesis is that the process of nasopharyngeal and fecal colonization from birth to childhood differs in quality and quantity between infants with CF and healthy controls and that these differences are related to subsequent respiratory morbidity in patients with CF. The following specific questions will be answered:
1. What is the general nasopharyngeal microbial colonization profile shortly after birth in healthy newborns and infants with CF and how do these profiles change over time during the first years of life?
2. Are clinical respiratory exacerbations preceded by changes in quality or quantity of the nasopharyngeal microbial profile?
3. What are the colonization dynamics before and after acquisition of the most important pathogen in CF, P. aeruginosa?
4a. What is characteristic of the resistome and how does the resistome change over time in gut of CF infants (versus controls) during the first years of life?
4b. What is the effect of prophylactic antibiotics (macrolides) on the respiratory and gut microbiota, in relation to protective flora and recovery
4c. What are the effects of therapeutic antibiotics on the selection and development of resistance in respiratory pathogens in relation to the existing (gut) resistome
4d. What is the role of respiratory viral infections on the respiratory microbiota, in relation to protective flora and recovery
5. What is the mucosal immune response in relation to pneumococcal colonization and vaccination.
6. Is bacterial community complexity inversely correlated with patient age and related to CF genotype?
7. What is the impact of (re)colonization on species-specific local antibody responses?

Study design

This explorative study aims to identify the sequential nasopharyngeal and gut microbial colonization profile in the first years of life of 20 newborns with CF (diagnosed with heelprick screening) and 45 age- and sex-matched healthy controls. Saliva will be collected at the age of 3, 6 and 12 months till the

age of 18 months, thereafter annually in both groups. Nasopharyngeal and fecal samples will be obtained regularly and during respiratoire complaints (voluntarily one month after respiratory complaints) in all children. To identify differences and shifts in microbial flora, high-throughput pyrosequencing will first be performed on 3-monthly samples. Conventional cultures and viral multiplex PCRs will be performed on the nasopharyngeal samples. According to the pyrosequencing outcomes, representative nasopharyngeal bacterial flora CHIPS and/or multiplex PCR will be developed to analyze the remaining samples and to identify the colonization process in relationship to disease on an individual base.

Study burden and risks

New knowledge about nasopharyngeal colonization dynamics and species interaction in childrenwith CF leads to earlier recognition of pathogenic microbial profiles leading to respiratory exacerbations. The final aim of the study is to explore risk factors for respiratory exacerbations and to facilitate monitoring and specific early interventions with respect to colonization with pathogenic microorganisms (eg. P. aeruginosa and S. aureus) in children with CF. In the future, rapid extensive evaluation of colonization status by sensitive and innovative techniques might lead to immediate and proper treatment and subsequent prevention of serious and chronic pulmonary infections. In addition, we feel that detailed studies of the development of resistance in pathogens in relation to the evolution of the human resistome (resistance gene pool as present in the most important gene reservoir, e.g. the gut) will help us in the future to design tailored antibiotic regimes to prevent resistance development in the respiratory pathogens. Finally this study might lead to data regarding vaccinations to common respiratory pathogens like pneumococcus in infants with Cystic Fibrosis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. diagnosis of cystic fibrosis, proven by positive sweat chloride test and DNA-analysis
2. age < 3 months at time of inclusion
3. informed consent of parents/legal guardian

Exclusion criteria

1. Other underlying disease or prematurity (<36 weeks)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	07-03-2011
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	21-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-08-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-09-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32268.041.10