Nasal polyposis
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GENERAL INTRODUCTION
Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis (CRs) is a multifactorial chronic inflammatory disease of the nose and paranasal sinuses and is one of the most common chronic health conditions in the world. CRs has a major impact on the quality of life and in its treatment many different clinicians can be involved such as general physicians, otorhinolaryngologists, pulmonologists, pediatricians, allergists and even sometimes neurosurgeons (1, 2). As a consequence of this all CRs places a large financial burden on society as a whole due to frequent doctor visits, the need for repeated surgery, and prolonged use of medication. Moreover, also indirect costs of CRs are very high due to missed workdays and reduced productivity (3-8).

According to the EPOS position paper CRs in adults is defined as inflammation of the nose and the paranasal sinuses for more than 12 weeks, characterized clinically by two or more symptoms, one of which should be either nasal obstruction or nasal discharge (4). Further symptoms include facial pain or pressure and reduction or loss of smell. This should be combined with either endoscopic signs of nasal polyps, mucopurulent discharge or edema in the middle meatus and/or mucosal changes within the ostiomeatal complex or sinuses on CT scan. CRs can be categorized into two different entities, CRS without nasal polyposis (CRSwNP) and CRS with nasal polyposis (CRSsNP). Nasal polyps are grey benign masses filled with inflammatory material, which originate from the anterior ethmoid are descending into the nasal cavity. The difference between CRSsNP and CRSwNP is based on the presence or absence of polyps, with endoscopic findings and/or CT scanning. Many clinical symptoms overlap in both CRSsNP and CRSwNP. However, patients with CRSsNP have more problems with facial pain compared to patients with CRSwNP, whereas patients with CRSwNP show more nasal discharge and decreased sense of smell (9).

Recent epidemiological CRS studies have shown a worldwide incidence between 5-12% (10-12). For CRSwNP the exact prevalence is more difficult to estimate because of the need for endoscopic evaluation. Using postal questionnaires in Finland a prevalence of CRSwNP was reported of 4.3% (13). Using endoscopy, a prevalence of 2.7%-5.5% have been reported (14, 15). When removing the whole naso-ethmoidal block in cadavers, nasal polyps were found in 5 out of 19 cadavers (16). Nasal polyps are more frequently seen in men than in women, elderly and asthmatics and are uncommon under the age of 20 years (13, 17, 18). in children nasal polyps are very rare and it has been reported that the majority of children with CRSwNP also have cystic fibrosis (CF) (4, 19).

ASSOCIATED FACTORS OF CRSWNP
CRS is associated with allergic rhinitis and asthma (20). The prevalence of allergy in patients with CRSwNP has been reported as high as 64%, whereas other studies report
an incidence of allergy in CRSwNP which is comparable to the patients without CRSwNP (21-23). However, these finding have not always been linked to skin prick test results and there might be a selection bias. Conversely, in patients with allergic rhinitis only 0.5-4.5% have found to have CRSwNP, which is comparable to the normal population. Although total and specific IgE are increased in nasal polyps tissue and are related to eosinophilia and severity of eosinophilic inflammation, allergy to aeroallergens does not seem to play an important role (24). Further studies are needed to explore the exact role of IgE production in CRSwNP.

We know that the prevalence of asthma in patients with CRSwNP goes up to 20-60% (25, 26) The presence of CRSwNP in patients with asthma is associated with a higher severity of asthmatic symptoms and asthma seems to be more difficult to control in these patients (27, 28). Especially patients with late onset asthma and high levels of periostin and eosinophilia, often have CRSwNP (29).

Nasal polyps are present in 36-96% of the patients with nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD), formerly known as aspirin intolerance or Samter’s Triad (15, 30-32). This is a combination of NSAID intolerance, nasal polyps and asthma (33). These patients are mainly nonatopic and are more difficult to treat. Recurrence rates of CRSwNP after FESS is much higher and also asthma is more difficult to control (34).

CRSwNP in children is mainly thought to be associated with cystic fibrosis (CF). CF is a lethal autosomal recessive disorder that is caused by a mutation in the CFTR gene on chromosome 7 which leads to defective chlorine channels. CF has severe impact of the function of the pancreas, lungs and sinuses by the production of abnormal thick mucus and ciliary malfunction (35). In around 1/3 of the children with CF nasal polyps are present and these polyps are generally difficult to treat (36). The prevalence of CRSsNP in adult patients with CF is 63%, and the prevalence of CRSwNP 25%

**PATHOPHYSIOLOGY**

The pathophysiology of CRS is very complex and many different factors play a role. Current therapeutic options for CRS are based on the two phenotypes CRSsNP and CRSwNP. However it remains to be confirmed if all patients with a given phenotype do indeed suffer from the same disease. By better understanding the different underlying pathophysiologic mechanisms, different endotypes can be identified. These so called endotypes may lead to new and better treatment options by targeting specific pathological mechanisms in individual patients. This can even imply that treatment could be based on targeting multiple different underlying mechanisms at once in one patient (37). A first example of this approach would be the currently evaluated approach of targeting IL-5 in eosinophilic CRSwNP patients.

Recently there has been a great progress in understanding the pathophysiology of CRS at the local and systemic level that includes environmental, microbial, genetic, and
iatrogenic factors. Early hypotheses considered only exogenous factors like microbes or fungi, whereas today the focus is more on aberrant interactions between these factors and the host immune system in general and the innate response in particular. Bacteria play a significant role in the development of acute rhinosinusitis (ARS) and it has been hypothesized that CRS evolves from ARS. However, the precise role of bacteria in CRS remains unclear. In Caucasian patients with CRS, Staphylococcus aureus is the most common bacterial pathogen, although in Asian patients the rate of S. aureus is much lower (38). Indeed, different studies have shown that the superantigen of S. aureus could be responsible for the local Th2 responses environment in CRS, leading to a polyclonal IgE production (39). In addition to a concrete role for S. aureus, a potential role for bacterial biofilms has been hypothesized as biofilms are correlated with more severe disease (40). However, it is not known if biofilms damage local tissue or that biofilms are better formed on damaged tissue. Similarly, fungi play a role in allergic fungal rhinosinusitis (AFRS) and have been hypothesized to be important for the pathophysiology of CRS in general. Fungi are found in almost all patients and could trigger local eosinophilia as part of the defense mechanism against fungi. As fungi are also found in most healthy individuals, we should assume deficits in anti-fungal immunity in patients with CRS (41). However, the ineffectiveness of antifungal treatment made the relevance of fungi in the pathogenesis of CRS more controversial (42). In addition to these biological environmental factors, also physical environmental factors can play a role in CRS. A GALEN study showed that cigarette smoke was associated with having CRS in all parts of Europe, just like occupational pollution (10). The role of environmental factors in CRS remains unclear. Neither smoking nor pollution seem to influence the prevalence of CRS (43).

In addition to the effect of various exogenous environmental agents, we now know that we should also consider the contribution of local immune responses. The first part of the innate immunity is the anatomical barrier composed of mucus, epithelium, and the process of mucociliary clearance. These aspects act in unison to prevent easy access to the host. The immune barrier hypothesis proposes that mechanical and innate immune barrier defects are present in CRS, resulting in increased exposure to exogenous factors and uncontrolled innate and adaptive immune responses. Indeed genetic defects responsible for cystic fibrosis that affect the hydration state of the mucus, as well as increased mucus production per se will lead to mucociliary dysfunction (44-46). Although mucociliary dysfunction is present in both forms of CRS, a lower expression of tight junction proteins and an increased susceptibility to exogenous protease degradation suggest that mechanical defects are more common in CRS (47-49).

In addition to direct changes in the barrier function, epithelial cells are also thought to contribute actively to the pathogenesis of CRS at multiple levels. First of all, epithelial cells produce antimicrobial compounds like lysozyme, lactoferrin, defensins, and cathelicidins as well as reactive oxygen and nitrogen species that can be upregulated during active infection (48, 49). Traditionally a major role for the detection of potential
pathogens was given to the presence of toll-like receptors on innate and adaptive immune cells (50). Recently, taste receptors have emerged as an interesting new players in the regulation of innate immune defenses (51). Among other cells, ciliated epithelial cells express taste receptors that are able to respond to a variety of bitter products secreted by potential pathogens. This response induces local inflammation, increased mucous clearance, and antimicrobial peptide secretion. Indeed, mutations in the bitter taste receptors have been linked to increased susceptibility to infection in multiple diseases including chronic rhinosinusitis (51).

Another way by which epithelium may contribute to pathogenesis of CRS is through the regulation and activation of innate lymphoid cells. This hypothesis was triggered by a very exciting notion that the recently discovered innate lymphoid cells (ILCs) could be key players in the pathogenesis of CRSwNP and asthma (52, 53). ILCs are related to T cells but do not express the CD3 antigen receptor. Instead ILCs react directly to “danger signals” and produce an array of cytokines that direct ensuing immune responses. ILCs are a family of effector cells that are important for protection against infiltrating pathogens and restoration of tissue integrity. Three major subsets have been defined on the basis of their phenotype and functional similarities to helper T cells. Group 2 ILCs (ILC2s) are known to produce type 2 cytokines, especially IL-5 and IL-13, and are activated by cytokines from epithelial cells such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are also associated with type 2 inflammatory responses. ILC2s numbers are highly elevated in nasal polyp tissues contrary to ILC1s and ILC3s numbers that are diminished (52-54). Although the precise roles of ILCs in CRS are still under investigation, it is clear that inhibition of ILC function represents a potential target that could provide novel treatments for CRS.

TREATMENT

Considering the complex pathogenesis of CRS, it is not surprising that effective pharmacotherapy requires a broad approach where most evidence has been accumulated for corticosteroids and antibiotics. With the realization that multiple endotypes of CRSsNP and CRSwNP may exist it is perhaps not surprising that we should even consider tailoring treatment to individual patients. Precision Medicine represents a novel approach in medicine, embracing 4 key features: personalized care based on molecular, immunologic and functional endotyping of the disease, with participation of the patient in the decision-making process of therapeutic actions, and taking into account predictive and preventive aspects of the treatment. Implementation of Precision Medicine into clinical practice may help to achieve to stop the epidemic of allergies and chronic airways diseases we see worldwide (55, 56).

The goal of CRS treatment is to achieve and maintain clinical control so that patients do not have symptoms at all or that the symptoms are not bothersome. If possible this should be combined with a healthy or almost healthy mucosa. According
to the EPOS evidence based guidelines, the management of CRSwNP includes nasal saline irrigation, topical or systemic steroids, and (long-term) antibiotics (4).

Nasal irrigation

Given that in CRS inflammation occurs at the interface of mucosa with the external environment suggestive of a dysfunctional host-environment interaction, it only seems logical to target the exogenous agents acting at this interface that drive the secondary inflammatory mechanisms (57). Nasal saline irrigation is an easy and effective way of cleaning the nose, thereby improving mucus clearance, enhancing ciliary beat activity, removal of antigen, biofilm and inflammatory mediators. It should be used as a supplement to other treatments. The evidence suggests that there is benefit of daily, large-volume (150 ml) saline irrigation with a hypertonic solution when compared with placebo (58). Several additions to the nasal saline irrigation have been investigated and proven effective, such as sodium hypochloride (NaClO), Xylitol and baby shampoo (59-61). Also topical corticosteroid droplets can be combined with nasal saline irrigation for a more effective treatment, by better reaching the sinus.

Corticosteroids

Topical intranasal corticosteroids, in the form of either spray of droplets, are the most common choice of treatment for CRSwNP (62). Corticosteroids act on two different types of intracellular glucocorticoid receptors (GRα and GRβ), which results in promoting anti-inflammatory and repressing pro-inflammatory gene transcription (63). This is how corticosteroid suppress the inflammatory response of the nasal mucosa, thereby improving nasal congestion, facial pain and nasal blockage and also improving drainage of the osteomeatal complex. Based on several randomized controlled trials intranasal corticosteroids are highly effective especially in mild disease (62). They show very few side effects, besides a chance of local irritation of the nose (64).

In more severe disease a short-term course of systemic corticosteroids can be prescribed (65). Short courses of oral corticosteroids in patients with CRSwNP show an improvement in Quality of Life (QoL) (66). Systemic corticosteroids are more effective, but also have a higher risk of side effects, like weight gain, adrenal suppression, osteoporosis and steroid induced diabetes mellitus (64). In general a maximum of three courses a year of oral corticosteroids is considered safe. Also the postoperative use of corticosteroids has a significant effect on the recurrence of polyps (67). Even though there is evidence of effectiveness of corticosteroids, still a substantial number of patients remain refractory to corticosteroid treatment. In general patient with eosinophilic nasal polyps respond better to corticosteroid treatment than neutrophilic polyps (68).

Antibiotics

Even though short-term antibiotics are frequently prescribed, there is no substantial evidence for the effectiveness in CRSwNP. There are two placebo-controlled trials with
short-term course of antibiotics in CRSwNP. In a double blind, placebo-controlled study by Van Zele et al, a 1-week-course of methylprednisolone was compared to 3 weeks of doxycycline and placebo in patients with CRSwNP. This study showed a significant effect of oral methylprednisolone and doxycycline on the polyp size, nasal symptoms, and mucosal and systemic markers of inflammation (69). Another study by Schalek et al compared oral anti-staphylococcal antibiotics to placebo after endoscopic sinus surgery. No significant results were obtained for the antibiotic group for symptom-specific and endoscopic scores, as well as quality of life (70). Studies on long-term use of antibiotics in CRSwNP demonstrate some effect on polyp size and patient symptoms without proper quality of life data.

Therefore the role of antibiotics in the treatment of CRSwNP seems to be small. Only in acute exacerbations short-term antibiotics can be effective, if combined with a bacterial culture from the middle meatus. For treatment with long-term antibiotics (macrolides) there are data supporting a moderate effect, but one should always be aware of the potential risk of developing bacterial resistance (71).

**Biologicals**

When patients with CRSwNP are refractory to current medical treatments, there are very limited treatment options available beyond FESS. Therefore there is a need for new and better medical treatments focusing on the underlying pathophysiological mechanisms of CRSwNP. The development of biologicals is rapidly progressing over the last years and several studies have been performed which reported good results in patients with allergic diseases and asthma (72). For CRSwNP several studies have been performed with different antibodies, like omalizumab (anti-IgE), reslizumab (anti-IL-5) and dupilimab (anti-IL-4 receptor alpha and interfering with both IL-4 and IL-13 pathways) (73-75). All these studies have shown a positive clinical effects and show very limited side effects.

**Sinus surgery**

If patients do not respond to optimal medical therapy, currently no other therapies are available which means that the polyps have to be surgically removed (76). History of surgical treatment for CRSwNP goes as far back as the time of Hippocrates around 400 BC. Hippocrates is not only known as the ‘father of medicine’, also as the ‘father of rhinology’. He first described a surgical method for removing nasal polyps by pulling a rough sponge on a string through the nasal canal. He also used a hot iron passed through the nostrils to cauterize polyps (77). In the years after, polypectomy has further evolved and nowadays functional endoscopic sinus surgery (FESS) is the technique of choice in sinus surgery. The goal of FESS is to restore normal ventilation and mucus drainage of the paranasal sinuses and to resect irreversibly changed mucosa. Overall FESS is a frequently performed and safe procedure and there are data suggesting there is only a 1% chance on major complications and 5-6 % on minor complications.
The efficacy of FESS is demonstrated in several studies but there still is a revision rate of around 20% (78). Therefore nasal irrigation in combination with nasal steroids is a very important part of postoperative management of CRSwNP (79).

Even though the link between rhinosinusitis and asthma is well established it is interesting to note that FESS has been shown to improve lower airway and reduce medication use for asthma (80). Recently studies in the UK have shown that patients with a surgical intervention for rhinosinusitis five years after the start of the disease had lower Sino-nasal Outcome Test-22 (SNOT-22) QoL scores, greater post-operative healthcare needs, and had a significantly higher prevalence of asthma, than patients treated at earlier time points (81).

AIM AND OUTLINE OF THE THESIS

The general aim of this thesis is to analyze and thereby optimize both existing and new treatments for CRSwNP and to improve our current knowledge about the pathophysiologic mechanisms of CRSwNP.

According to European guidelines current medical treatment of CRS is mostly based on the clinical differentiation of two phenotypes, CRSsNP and CRSwNP(4). Both these phenotypes are likely to have different subtypes (or endotypes) based on the existence of several underlying conditions. These include cystic fibrosis, aspirin-exacerbated respiratory disease (AERD), and also different comorbidities like asthma and allergies. Besides topical and oral steroids, current medical treatment options for CRSwNP exist of treating these different phenotypes with for example intranasal and oral corticosteroids, long-term antibiotics, antileukotrienes, Xolair and nasal saline irrigation. If patients with CRSwNP are refractory to these treatments, there are very limited treatment options available beyond FESS. Even though there is a proven efficacy of FESS, there still is a revision rate of around 20% (78). Because this recurrence rate of CRSwNP after FESS is so high, there is a need for new and better treatments which focus more on the underlying pathophysiologic mechanism as a target for the treatment of CRSwNP.

Just like in severe eosinophilic asthma, most nasal polyps in Caucasians are characterized by prominent local eosinophilic inflammation and high IL-5 concentration as well (82). IL-5 appears to have a key role in the pathogenesis of nasal polyposis. Consequently, IL-5 could be a major target for personalized therapeutic intervention. Previous studies with small numbers of patients have shown that anti-IL-5 treatments, such as mepolizumab (Glaxo Smith Kline), can successfully reduce nasal polyp size (73, 83).

In a clinical randomized double-blind placebo controlled trial in Chapter 2 we assessed the safety and efficacy of mepolizumab in the treatment of severe bilateral nasal polyposis.
When maximal medical treatment fails, FESS is the technique of choice in sinus surgery in patients with CRSwNP. The extent of FESS in the treatment of CRSwNP can vary from polypectomy and infundibulotomy, to opening all the sinuses. In the last few decades surgeons tend to use a more custom approach based on the extent of the disease and comorbidities (84). The specific goal of FESS in patients with CRSwNP is not only to resect irreversibly changed mucosa, but also to re-establish normal ventilation and mucus drainage from the sinuses. This extensive approach improves postoperative drug delivery to the sinuses (85). In the last decades surgical techniques in FESS have been refined and new instruments are introduced. Besides traditional instruments, such as the cutting and non-cutting Blakesley forceps, nowadays the microdebrider (shaver) is widely used (86). This is a powered rotary shaving device, which can resect tissue very precisely while minimizing mucosal trauma. Because the microdebrider supplies continuous suction there always is a bloodless surgical field while operating. This may improve safety because of the increased visibility. But along with the use of powered instrumentation there are reports of higher incidence of serious complications, for example cerebrospinal fluid leaks or orbital injuries. Even though the use of the microdebrider (Shaver) is well known in FESS, there is a lack of evidence from comparative studies focusing on operating time, blood-loss and user friendless between traditional techniques and the microdebrider. In Chapter 3 the use of the microdebrider is compared to conventional instruments in FESS for patients with CRSwNP.

Corticosteroids are the most common choice of treatment for CRSwNP (62). Corticosteroids are able to suppress the inflammatory response of the nasal mucosa and suppress the productions of pro-anti-inflammatory mediators, cell chemotactic factors and adhesion molecules. They thereby improve nasal congestion, facial pain and nasal blockage and also drainage of the osteomeatal complex (87). Corticosteroids are included in the initial treatment of CRS, but also can be used preoperatively, intraoperatively and postoperatively in patients with CRS undergoing FESS. About the role of corticosteroids in FESS there are several randomized controlled trails, but they report conflicting results. It is not clear what the exact benefits of perioperative use of corticosteroids are regarding postoperative pain, symptoms and wound healing. Furthermore we know that the recurrence rate of CRSwNP after FESS is high and goes up to 15-20 % in adults (78). The exact influence of postoperative use of corticosteroids on the recurrence rate is not known.

Therefore in Chapter 4 we performed a systematic review and meta-analysis of randomized controlled trials. The aim of this study was to systematically review all existing evidence on the role of corticosteroids in patients undergoing FESS. We determined whether preoperative corticosteroids affect operative parameters, intraoperative corticosteroids reduce pain and postoperative corticosteroids affect symptom scores, endoscopic scores and recurrence rates.
Although CRSwNP is rare in children it has a major impact on the QoL and therefore a thorough treatment is needed (88). In adults with CRSwNP FESS is considered to be the treatment of choice when maximum medical treatment fails. Several studies have shown that FESS in adults with CRSwNP is effective and safe with a revision rate of 20%. (78) In children with CRSwNP on the other hand surgical success rates are not known. There are a few studies describing results of FESS in children, but they mainly focus on CRSsNP and data are very limited (89-91). Moreover safety of FESS has only been established in children with CRSsNP in small case series (92, 93). Furthermore in previous literature is described that most children with CRSwNP also have CF (94). There are several studies that show positive outcome after FESS in children with CF, but CF still is a chronic disease of mucociliary transport where even after FESS problems like infections or nasal polyps can recur. Because of this there might be a more negative attitude to perform FESS in children with CF.

Therefore in Chapter 5 we assessed the long-term results of FESS in children with CRSwNP with CF and without CF and determined outcome, symptoms, quality of life and complications.

There is not much known about the etiology of CRSwNP. We know that sinonasal epithelial cells play an important role in the immune response as a passive physical barrier, but the potential role as an active participant in the regulation of local immune responses in patients with CRSwNP is not well explored. In allergic airway disease on the other hand, there is an established awareness of the role of epithelial cells as an active participant in the regulation of local immune responses (95). Epithelial cells are able to detect and respond to environmental signals through a wide variety of receptors. The exact role of epithelial cells from nasal polyps in the pathophysiology of CRSwNP and their involvement in the innate defense against microbes or as a passive target for local inflammation, is relatively poorly explored. Chapter 6 explores the potential contribution of nasal epithelial cells to the pathophysiology of CRSwNP. We performed micro-array expression profiling on epithelial cells from CRSwNP patients and healthy controls to investigate the role of polyp epithelium in the pathogenesis of CRSwNP.

CRSwNP is a chronic disease with a high prevalence estimated more than 10% in Europe and the United States (10, 11). Thereby it results in high costs for society as a whole mainly because of the need for repeated surgery. There are no good data available about the natural course of CRSwNP.

Suggested is that the prevalence of CRSwNP increases with age with the highest prevalence around the sixth decade of life and the lowest prevalence up to 40 years old (14, 96). Reliable data on the exact prevalence of CRSwNP in different age groups are very rare, because of the difficulties in selecting a representative group of
the population and also due to the fact that most studies only used questionnaires and no endoscopic evaluation, thereby missing asymptomatic patients.

Therefore in *Chapter 7* we adopted FESS as an objective sign of active/uncontrolled disease and measured the time between first and final surgical intervention with a follow-up of 10 years. We determined the active disease duration of CRSwNP by looking at the relation between age, total number of times of sinus surgery and age at the time of the first operation ever.
REFERENCES


