Nasal polyposis
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chapter 8

GENERAL DISCUSSION
AND FUTURE PERSPECTIVES
General discussion and future perspectives

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic disease which has a significant negative impact on the quality of life (QoL) and brings along high costs because of high medical resource usage and high societal costs (1, 2). Despite decades of research on the pathophysiology and treatment of CRSwNP, still a group of patients remain symptomatic under current state-of-the-art medical and surgical treatment (3). In order to keep improving our treatment for patients with CRSwNP, we need to critically assess our current therapeutic options and gain more insight in the pathophysiology of CRSwNP. This thesis has investigated multiple aspects of this serious disease to try and better the life of our patients.

Nasal polyposis during a lifetime

The prevalence of CRSwNP is estimated around 10% in Europe and the United States, however it is difficult to estimate because of the need for endoscopic evaluation (2, 4). Suggested is that the prevalence of CRSwNP increases with age with the highest prevalence rate seen around the sixth decade of life and the lowest prevalence up to 40 years old (5, 6). In children CRSwNP is rare and is thought to be associated with cystic fibrosis (CF). We were not able to identify any data about the natural course of the disease and it was always thought that CRSwNP is a lifetime chronic disease. CRSwNP can be treated and controlled with medication and surgery, however there is still a revision rate of around 20% in adults and surgical success rates in children with CRSwNP are not exactly known (3, 7). Therefore a frequently asked question of patients with recalcitrant CRSwNP is if and when their disease will finally stop. Therefore we wanted to know if CRSwNP has a standard active period of disease duration and extinguishes by itself.

In chapter 7 we showed for the first time that the active disease duration of CRSwNP in patients is relatively constant at about eleven years, regardless of the age of onset. This was determined based on the need for FESS as an objective measurement of active disease and could be a first indication that CRSwNP is a self-limiting disease.

Many studies have looked at prognostic factors for failure of FESS, and it is thought that age could influence the objective outcomes of FESS, showing better endoscopic outcomes in elderly patients (8). These results could be influenced by our findings that the activity of CRSwNP decreases when patients get older. A strength of our study is the wide variety of different ages at time of surgery, thereby presenting the results of a very representative mixed group. A limitation of this study was our decision to adopt the need for FESS as a sign of active disease. Ideally, these results would be compared with nasal symptom scores and nasal endoscopy scores before and after surgery. Another potential limitation could be the tertiary setting which could be a group of more severe patients with potential a worse outcome. A recent study also in tertiary care showed that 40% of the patients were uncontrolled and only 20% really were
controlled (9). Furthermore, our results should be validated in the future in a larger cohort of patients with CRSwNP.

Recently Hopkins et al. showed that delayed surgical intervention for CRSwNP is associated with a higher need for postoperative care than when patients undergo FESS in the first 12 months after diagnosis (10). Combining this knowledge to our findings, in the future it would be very interesting to try to indicate the ideal timing of surgery in comparison to optimal medical treatment in patients with CRSwNP. Thereby our study group designed a randomized-controlled trial to investigate whether two regularly applied treatment strategies, namely FESS in addition to drug treatment or drug treatment alone, differ in generic and disease-specific QoL and to establish the presumed superiority of FESS. Also a comparison to cost-effectiveness will be made (11). Hereby we hope to find out which patients exactly to operate and when, to improve the outcome of FESS and reduce recurrence rates.

In children CRSwNP has a severe impact on the quality of life of both children and their parents and can be very difficult to treat (12). The consensus is that surgical intervention should be considered in paediatric patients with CRSwNP when maximum medical therapy has failed (13).

In chapter 5 we showed that FESS is a very effective and safe treatment in children with CRSwNP even in children with CF. Overall QoL has significantly improved in 78% of the patients at long-term follow-up, especially in the domain of nasal symptoms. In total 14% of the children needed a revision and there were no complications.

Interestingly until now data on paediatric FESS in children with CRSwNP are very limited. There are a few studies describing result of FESS in children, but they mainly focus on CRSsNP and report contradictory outcomes (14-16).

Our study shows significant improvement in QoL at long-term follow-up after FESS in children with CRSwNP. These result are comparable to the study from Siedek et al which consisted of 59 (51.3%) children with CRSsNP and 45 (39.1%) of children with CRSwNP (14).

Asthma is commonly associated with CRSwNP in the paediatric population and therefore may influence FESS outcomes. The prevalence of asthma is much higher in children with CRSwNP than in the normal population. In our study the prevalence of asthma was 28% compared to 10% in normal childhood population (17). When analyzing our results we detected a difference in outcome between children with and without asthma. Mean postoperative nasal RSOM score in asthma patients was significantly higher than in children without asthma (p=0.048).

Furthermore in our group of children with CRSwNP who underwent FESS, there was only a small percentage with CF (25%). This was in contrast to an earlier report were the majority of the children with CRSwNP has cystic fibrosis (18). This could mean that the percentage of children with CRSwNP who also have CF, might be lower than we previously thought. We demonstrated in chapter 2 that CF is a predictor for revision surgery. In total 33% of the children with CF needed revision surgery and only 7% of
the children without CF. However even though children with CF have more recurrences, long-term improvement of symptoms after FESS are good and comparable to children without CF. Quality of life has significantly improved, especially nasal symptoms. Other studies have reported also positive outcomes after FESS in children with CRSwNP with CF, but usually length of follow-up was very limited (19-22). If sinus surgery can reduce the need for antibiotics in children with CF remains controversial (23). Because CF is a chronic disease where mucociliary transport is impaired, even after successful surgery children can keep having nasal infections or recurrence of nasal polyps. Therefore there is a more negative attitude of surgeons towards FESS in these children. Our results indicate that sinus surgery in these children is able to improve the QoL in the long-term. Aaneas et al showed an additional purpose of performing extensive FESS in selected patients with CRSwNP and CF. They suggested that extensive sinus surgery combined with intensive follow-up can eradicate pathogenic bacteria from the CF sinuses which theoretically should reduce the frequency of lung infections and thereby pulmonary morbidity (24).

With the emergence of drugs that specifically target the mutations in children with CF, good results have been obtained. Studies with Ivacaftor for example, which targets defective chloride channels, show very good results by improving sinonasal pathology and symptoms of sinonasal disease (25). The development of these new drugs could mean that in the future children with CF no longer develop sinonasal pathology and therefore treatment by an ENT surgeon is no longer needed. However this could take many more years. In the meantime we need to make sure that children with CRSwNP are optimally treated.

Therefore the advice is to treat children with CF not differently than children without CF, but keep in mind that children with CF are more likely to need revision surgery in time. Children with CRSwNP with CF should always be carefully monitored by an ENT specialist.

Pathophysiology and the role of nasal epithelial cells in CRSwNP

The pathophysiology of CRSwNP is very complex and involves many different factors. We know that airways epithelial cells play a well-accepted role in the regulation of local inflammatory processes and innate defense responses. Whether epithelial cells from nasal polyps play a role in the pathophysiology beyond their involvement in the innate immune defense against microbes or as a passive target for local inflammation, is relatively poorly explored.

In chapter 6 we performed expression profiling on epithelial cells from CRSwNP patients and healthy controls. We showed that 27 genes were significantly different between healthy individuals and patients with CRSwNP. Many of these genes could be linked to pathogenic mechanisms in neoplasm formation and cell cycle control. Hereby we have contributed to the notion that epithelium could play a substantial role in the formation of nasal polyps.
There have been many genomics related studies looking at the contribution of individual genes in CRS (26-28). This type of research is relatively easy to perform as DNA of all cell types is the same, even though expression profiles will be different between cell types. A relatively small contribution of individual genes was found, which is not so strange as multiple genes are likely to interact. Moreover it might well be that CRSwNP encompasses potential different endotypes, so that not all patients suffer from the same genetic disease. To circumvent these issues we opted for expression profiling of nasal epithelial cells. This means more work as you need to do expression profiling for this single cell type as whole tissue expression profiling runs into the problem of potential difference in cellular makeup of the tissue. To reduce all possible relevant factors that could influence our results, we included no patients with any auto-immune disorder or other relevant comorbidities, and allergic and asthma status was established in all patients. It still remains very difficult to interpret differences between healthy epithelial cells and epithelia of CRSwNP, because in active disease the epithelium is exposed to many inflammatory triggers that could affect the expression profile. Therefore we have tried to mitigate some of these aspects by limited culturing of the epithelial cells rather than analyzing the expression profile in situ or directly after isolation. This approach may have undocumented effects on the expression profile, although this allows us to obtain pure epithelial cells. The advantage of this approach is that we are able to look at stable differences in epithelial cells whereby we can get a summary view of what has gone wrong in the cell.

Our data discovered at least one process that is nearly impossible to find by genomics only: the involvement of epigenetically regulated genes. We detected two genes that are only expressed from the maternal inherited chromosome and not from the paternal copy, CDKN1C and ASCL2. The most interesting of these genes is probably the deregulated tumour suppressor gene CDKN1C (29). This gene has been linked to multiple forms of cancer, and mutations in this gene underlie Beckwith-Wiedemann Syndrome which is characterized by abundant colon polyp formation (30). The possible involvement of pathological processes regulated by imprinted genes will affect interpretation of genomic studies that investigate CRSwNP as such studies will only consider the presence or absence of specific single nucleotide polymorphisms (SNPs) and not whether or not the genes with the SNPs are expressed.

Another process that seems important in the pathogenesis of CRSwNP is neurogenic inflammation. Neurogenic inflammation has been studied in relationship to inflammation and neoplasm formation, but it has not yet been considered in CRSwNP. Neurogenic inflammation centers around acetylcholine that traditionally has been investigated in the interaction of neurons with down-stream targets like smooth muscle cells, macrophages and other inflammatory cells (31). Recently it has become clear that also epithelial cells produce and respond to acetylcholine and that this could play a role in neoplasm formation (32, 33). In this respect it was remarkable that we
were initially able to detect a deregulated expression of SLURP1 in the epithelia of patients with CRSwNP. SLURP1 acts as a potential negative regulator of acetylcholine receptor mediated signalling due to its high affinity for this receptor (32). Besides SLURP, also LYNX1 (or SLURP2 as it was previously known) and SLC44A4 were deregulated thereby highlighting the link with neurogenic inflammation. The precise role of epithelial-centred neurogenic inflammation is not yet fully established, but one aspect seems to focus on signalling between adjacent epithelial cells and inflammatory cells in the nasal cavity. The link between epithelium and neuronal processes we have observed in our data set may be part of a more general mechanism. Activation of the TRPV1 receptor on neurons by capsaicin could be part of the mechanism by which capsaicin is able to suppress symptoms in idiopathic rhinitis and CRSwNP (34, 35). However the recently described deregulated expression of this receptor on epithelial cells of asthmatics suggests a potential involvement of an epithelial centred pathway (36). As TRPV1/capsaicin also effects acetylcholine signalling it would be interesting to explore this link further.

Our data shows two types of epithelium in patients with CRSwNP and this would be hard to find with genomics as well. These two different types of epithelia cannot be linked to any differences in atopic state of the patient or the level of inflammation. This shows that allergy seems to be an epiphenomenon and that the epithelial differences we have previously observed in allergic rhinitis do not play a common role in CRSwNP (37, 38).

Given the recent discovery of innate lymphoid cells (ILCs) as potential new players in the pathogenesis of CRSwNP, perhaps we would have expected to find differences for cytokines important for ILC2 development (TSLP, IL25, IL33) (39). Type 2 innate lymphoid cells (ILC2s) secrete type 2 cytokines which protect against parasites but also are able to contribute to a variety of inflammatory airway diseases. In patients with CRSwNP highly elevated levels of ILC2s were found in nasal polyps tissue (39). It was shown that indirect collaboration of the epithelium with ILC2s in patients with CRSwNP results in shaping of type 2 immunity in the nose (39). However there was no real difference found at baseline between healthy and disease. The exact role of ILCs is still under investigation, but this could be very interesting as potential treatment target in the future.

For the future we would have to look further into the differences and new processes we have detected. For example it would be interesting to investigate other cells like fibroblasts. In addition to epithelial involvement in CRSwNP, it has been suggested that the interaction between nasal epithelium and the myofibroblasts could resemble the interaction between bronchial epithelium and smooth muscle cells (40, 41). This link might help explain the higher prevalence of CRSwNP in asthmatic patients (42, 43). Preliminary data show that nasal epithelial cell conditioned medium (ECCM) stimulates fibroblasts and that diseased fibroblasts seem to be stimulated more strongly. Furthermore recombinant SLURP is able to activate fibroblasts in vitro which
is interesting given the potential role of neurogenic inflammation in the pathogenesis of CRSwNP.

In conclusion, it still remains difficult to determine cause and effect in the interpretation of differences between epithelia of healthy individuals and patients with CRSwNP, however they do seem to point towards new processes that play a role in the pathophysiology of CRSwNP.

**Advances in surgical tools for CRSwNP**

Different operating technique and tools in FESS have evolved over the years and nowadays surgeons tend to choose a more custom approach based on the extent of the disease and comorbidities (44). In FESS surgical techniques have been refined and new instruments introduced. Besides traditional instruments, such as the cutting and non-cutting Blakesley forceps, nowadays the microdebrider (shaver) is widely used. The microdebrider was introduced in FESS in 1992 and is a powered rotary shaving device, which originally was used in arthroscopic surgery (45).

Even though the microdebrider is well known, there was lack of evidence from comparative studies focusing on operating time, blood-loss, and user friendliness between traditional instruments and the microdebrider. In chapter 3 we demonstrated that operating patients with CRSwNP with the microdebrider on top of traditional instruments is safe and very time efficient. Operating with the microdebrider was quicker mainly because it improves visualization due to the continuous suctioning and thereby no need to repeatedly exchange instruments in the nose each time. Furthermore we found that the user-friendliness of the microdebrider is very high, which means surgeons find it easier to operate patients with CRSwNP with the microdebrider than without. Sauer et al previously showed a significant higher operating time when a microdebrider was used (46). An essential difference with our study is that in the study from Sauer et al only the microdebrider was used, instead of the microdebrider on top of traditional instruments. Therefore making it sometimes harder to perform certain maneuvers like removing cells from the lamina papyracea or skull base, which is not very realistic. This could explain why in this study a longer operating time was found on the side were only the microdebrider could be used.

In our study we did not find any difference in intraoperative blood loss. In a retrospective study from 1996 however, a reduction of blood-loss was found when using the microdebrider (47). This might be because the microdebrider removes the mucosa in smaller pieces resulting in higher blood-loss per cm³, which is then compensated by the shorter operating time when the microdebrider was used. Earlier claimed advantages of the microdebrider on postoperative healing were not confirmed by our study. There was no difference found in recurrence rate with a follow-up of 3 months. In a recent study performed by Tirello et al., a significant lower recurrence of CRSwNP with traditional instruments compared to the microdebrider was found,
however they found a higher incidence of synechia formation with a follow-up of 13 months (48). A limitation of this study was that only one instrument was used on each side, and that the same side of the nose was always operated with traditional instrument and the other side with the microdebrider. This could also influence the outcome, because when the surgeon is right handed, the right side of the nose sometimes can be more difficult to reach.

Literature on complications of the use of powered instruments in FESS is limited. There is no available literature indicating an increased complication rate, besides some case reports describing potentially dangerous complications (49, 50). In our study no difference was found in complications rate between traditional instrument and the additional use of the microdebrider. Because in our study the microdebrider was used by both experienced surgeons as well as surgeons in training (under supervision), we can conclude that the microdebrider is safe to use.

Since the introduction of the microdebrider in FESS, modifications like different sizes and angles have been made so that the microdebrider could be integrated in different types of surgery as well, like larynx surgery, turbinate reduction, supraglottoplasty and choanal atresia repair. Similar advantages of the microdebrider have been found comparable to the use of the microdebrider in FESS. For example in larynx surgery nowadays the microdebrider is widely used and studies have shown that the use of the shaver requires less operating time than the CO2 laser and therefore can be cost saving (51, 52). In turbinate reduction no differences were found in postoperative healing between the microdebrider and traditional instruments (53). These results confirm our thoughts on the advantages of the microdebrider in FESS.

In conclusion, these results are encouraging and show that it could be worthwhile to invest in a microdebrider, saving operating time and retaining good results. The use of the microdebrider could also bring along higher costs, because blades are disposable and sometimes more than one blade is needed per operation (47). Therefore in the future to optimize surgical management more randomised controlled trials are needed, to evaluate the effectiveness and extensiveness of surgical treatment. An analysis of the cost-effectiveness of the use of the microdebrider should be performed, taking into account all different aspects such as operating time, cost of the disposable blades and general costs of healthcare around the operation.

Perioperative medical management of CRSwNP

Local and systemic corticosteroids are included in the initial treatment of CRSwNP to reduce inflammation, but also can be used preoperatively, intraoperatively and postoperatively in patients with CRSwNP undergoing FESS. About the role of corticosteroids in FESS there are several studies, but they report conflicting results about their perioperative role in the improvement of symptoms and polyp scores. Currently, the choice what to use is very doctor specific, and depends more on their personal preferences rather than evidence.
In chapter 4 we performed a systematic review and meta-analysis of randomised controlled trials for operative outcomes which demonstrated that operation time and estimated blood loss were significantly lower, and surgical field quality was significantly better in the local and/or systemic steroid group compared to the non-steroid group (54, 55). There was no difference in postoperative pain scores when intraoperative corticosteroids were used. The postoperative use of corticosteroids was shown to significantly improve endoscopic scores, but there was no significant difference in symptom scores when corticosteroids were used (56-59). The use of corticosteroids was not associated with an increased risk of sinusitis. There was a reduced recurrence rate when postoperative corticosteroids were used in patients with CRSwNP, however this role is unclear in patients with CRSsNP (56).

Because of their anti-inflammatory effect, topical corticosteroids are used in the treatment of CRS (60). A recent Cochrane review reported a beneficial effect of intranasal corticosteroids compared to placebo or no treatment on symptoms and nasal blockage especially in patients with CRSwNP (61). When the effects were assessed of the different types of intranasal corticosteroids in patients with CRS there was insufficient evidence found that one steroid is more effective than another, nor that effectiveness of a spray differs from that of an aerosol (62). Another Cochrane review showed that when a short course of systemic corticosteroids is used as an adjunct therapy to intranasal corticosteroids there might be an improvement in symptom severity, polyp size and condition of the sinuses when assessed using CT scans (63). However, it seems unclear whether these beneficial effects of oral corticosteroids are sustained beyond the short follow-up period (up to 30 days) as there are no longer follow-up data available. When we specifically look at the use of corticosteroids after FESS, we find a previous systematic review on the use of topical corticosteroids after FESS which reports a significant improvement of symptoms, endoscopic scores and lower recurrence rate (60). However, these authors only summarized the results of different studies and did not perform a meta-analysis. In the recent EPOS 2012 systematic review on the role of corticosteroids after FESS, topical corticosteroids were recommended for patients with CRSsNP and both topical and systemic corticosteroids for patients with CRSwNP (13). In this review patients with CRSwNP with previous sinus surgery responded better to topical steroid treatment than without sinus surgery in polyp size reduction, but there was no difference in improvement in symptoms between the two subgroups. In contrast to our review where we included only patients who underwent FESS, here were also patients included with just a history of polypectomy which might influence this result positively.

Besides steroids, perioperative management can include the use of antibiotics. A Cochrane review from 2016 reported very little evidence that systemic antibiotics are effective in patient with CRS (64). There was only moderate quality evidence of a modest improvement in disease-specific quality of life in adults with CRSsNP receiving 3 months of macrolides (64). Three months after the end of the treatment
this effect was gone. On the use of preoperative antibiotics is very limited evidence. The current consensus is that in patients with acute infection prior to surgery, preoperative antibiotics can be useful by reducing inflammation and thereby improving the surgical field (13, 65). Experts’ opinion on the postoperative use of antibiotics is that 7-14 days is advised, however the evidence for this choice is very limited (13, 65). Both amoxicillin-clavulanate and macrolides have shown improvement in endoscopy scores, but especially in patients with CRSsNP (66, 67). Only in patients with CF specific antibiotics (tobramycin) play a role in the treatment of bacterial rhinosinusitis and postoperative outcomes of FESS (68).

Even though our review included some potential biases, like the inclusion of a very mixed group of patients with both CRSsNP and CRSwNP and a wide variability in agents used, dose, route and duration, we have attempted to bring together the best evidence on this subject available. Based on current available evidence preoperative use of corticosteroids is advised to reduce operative time and blood loss. There are limited studies on the use of intraoperative corticosteroids regarding symptom scores, but there seems to be no benefit. More studies should be performed to assess this further in the future. Postoperative use of corticosteroids is advised to improve endoscopic scores and reduce recurrence rate in CRSwNP. However, most studies are limited to small sample size and for the future there are large RCTs required which better analyze the long term outcomes and recurrence rates.

New treatments for severe bilateral CRSwNP

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. Considering the complex pathogenesis of CRSwNP, it is not surprising that a broad approach can be effective. With the realization that CRSwNP consists of different endotypes, a tailored treatment should be considered. These endotypes can be defined by distinct pathophysiologic mechanisms that correspond with different biomarkers and could help us identify new treatment targets.

The development of biologicals is progressing over the last years and several studies have been performed which reported good results in patients with allergic diseases and asthma (69). For CRSwNP several studies have been performed with different antibodies, like anti-IgE, anti-IL-5 and anti-IL-4 receptor alpha (70-72). All these studies have shown positive clinical effects and show very limited side effects.

Given the fact that in Europe and the US most polyps are characterized by a Th2 inflammatory pattern with cytokines IL-4, IL-5, IL-13, eosinophils and IgE involved, these Th2 cytokines could be targets for therapeutic intervention. Mepolizumab, a humanized anti-interleukin (IL)-5 antibody, is as new treatment of nasal polyposis. Mepolizumab reduces eosinophil counts and is approved for the treatment of severe
eosinophilic asthma (73). A randomized double-blind trial in 2011 demonstrated the efficacy of mepolizumab in reducing the size of nasal polyps (74). This study was in a small patient group and consisted of 2 single intravenous injections of mepolizumab or placebo with a follow-up of 8 weeks. Therefore it is interesting to find out if mepolizumab in a larger population with more injections could also reduce the need for surgery in patient with CRSwNP.

In chapter 2 we report on a large randomised, double-blind, placebo-controlled, multicenter, multinational (Belgium, the Netherlands, and United Kingdom) trial to determine whether mepolizumab could reduce the need for surgery in patients with severe, recurrent bilateral nasal polyps on topical corticoid therapy. This Phase II study based on a composite endpoint of reductions in endoscopic nasal polyposis score and nasal polyposis severity VAS score, demonstrated a statistically significant reduction in the proportion of patients eligible for surgery 4 weeks after the last dose at week 25 in the mepolizumab group compared with placebo. These results were supported by clinically significant improvement of symptoms and QoL SNOT-22 scores in the mepolizumab group compared with placebo. These results suggest that mepolizumab can improve the QoL and may reduce the need for surgery for patients with refractory CRSwNP.

Mepolizumab inhibits eosinophilic inflammation, which is present in many nasal polyps (75). In the mepolizumab group was a significant reduction in eosinophil counts at week 25 together with improvement of nasal symptoms and a reduced need for surgery. We did not find any improvement in long function on the other hand in patients with concomitant asthma, even though mepolizumab is an approved treatment for severe eosinophilic asthma. The reason for this could be that in this study only patients with mild or moderate asthmatic disease were included, not with severe eosinophilic asthma.

Not all patients with CRSwNP in this study showed a significant improvement after treatment with mepolizumab. The reason why some patients do not respond to the medicine, remains unclear. There was no difference found between responders and non-responders is VAS scores, QoL, clinical pharmacodynamics, blood eosinophil counts, anti IL-5 levels or comorbidities.

With the improved understanding of the different pathophysiologic pathways of CRSwNP, the treatment options are enhanced. With the arrival of new biologicals, we are challenged to select patients eligible for each specific treatment and predicting their therapeutic response. By the development of different biologicals there is a shift from general medical treatment of CRSwNP to a more target-specific treatment and personalised therapy for patients with certain endotypes in the future.

Concluding remarks
This thesis focused on analyzing and thereby optimizing different treatments and obtaining further insight in the pathophysiologic mechanisms of CRSwNP. We showed
for the first time that the active disease duration of CRSwNP in patients seems to be relatively constant at about eleven years, regardless of the age of onset, and that the epithelium could play a substantial role in the formation of nasal polyps, especially in neoplasm formation and cell cycle control. Furthermore we showed advantages of using the microdebrider in FESS and that FESS is a safe and effective treatment in children with CRSwNP, even if they have CF. By performing a systematic review we can advise the use of preoperative corticosteroids to reduce operative time and blood loss, and postoperative use of corticosteroids to improve endoscopic scores and reduce recurrence rates. And finally we showed that treatment with mepolizumab added daily to nasal corticosteroids might offer a viable alternative to surgery in a selected group of patients with severe, recurrent nasal polyposis requiring surgery.

Even though this thesis has led to an improvement of our understanding of the pathophysiology of CRSwNP and impact of the current treatments, still many gaps remain and treating CRSwNP can be very difficult. To further improve our care for patients with CRSwNP in the future we should focus more on precision medicine (PM). PM is already of major interest in other medical domains such as oncology, allergy and chronic airways disease. PM is a medical model aiming at the customization of healthcare tailored to the individual patients. PM consists of four principles, namely personalised care, prediction of treatment success, prevention of disease and patient participation in the elaboration of the treatment plan (76). The combination of these four pillars is expected to improve treatment outcomes. Most principles of PM can be implemented easily without major costs, such as providing patients with information about the effectiveness of different treatment modalities, informing patients about the impact of CRSwNP on asthma, and preventing progression of the disease and secondary prevention of the onset of asthma (77). However, the implementation of personalised care in patients with CRSwNP, is still in progress. The current knowledge that most nasal polyps are characterized by Th2 inflammatory patterns could be a possible therapeutic target for intervention. However, we are not sure whether Th2 cytokines are the cause or an effect of the disease. With the arrival of new biologicals, we are challenged to select patients eligible for each specific treatment and predicting their therapeutic response. Given the high costs of these new biologicals, improving patient selection by developing specific predictors will be very important to further implement this as a treatment in the future. It will be a great challenge to further investigate the etiology, endotyping, biomarkers and treatment (medical and surgical) of CRSwNP, for us to better understand this disease and develop new and better treatments for our patients.
REFERENCES


38. Vroling AB, Jonker MJ, Luiten S, Brent TM, Fokkens WJ, van Drunen CM. Primary nasal epithelium exposed to house dust


