Rhinology in review: from COVID-19 to biologicals*

Wytske J. Fokkens[1], Basile N. Landis[2], Claire Hopkins[3], Sietze Reitsma[1], Ahmad R. Sedaghat[4]

[1] Department of Otorhinolaryngology, Amsterdam University Medical Centres, location AMC, Amsterdam, The Netherlands

[2] Department of Otorhinolaryngology, Geneva University Hospitals, Geneva, Switzerland; Faculty of Medicine, University of Geneva, Geneva, Switzerland

[3] Department of Otorhinolaryngology, Guy's Hospital, London, UK

[4] Department of Otolaryngology – Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

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Abstract

We look back at the end of what soon will be seen as an historic year, from COVID-19 to real-world introduction of biologicals influencing the life of our patients. This review describes the important findings in Rhinology over the past year. A large body of evidence now demonstrates loss of sense of smell to be one of the most common symptoms of COVID-19 infection; a meta-analysis of 3563 patients found the mean prevalence of self-reported loss to be 47%. A number of studies have now shown long-term reduced loss of smell and parosmia. Given the high numbers of people affected by COVID-19, even with the best reported recovery rates, a significant number worldwide will be left with severe olfactory dysfunction. The most prevalent causes for olfactory dysfunction, besides COVID-19 and upper respiratory tract infections in general, are trauma and CRSwNP. For these CRSwNP patients a bright future seems to be starting with the development of treatment with biologics.

This year the Nobel prize in Medicine 2021 was awarded jointly to David Julius and Ardem Patapoutian for their discoveries of receptors for temperature and touch which has greatly enhanced our understanding of nasal hyperreactivity and understanding of intranasal trigeminal function. Finally, a new definition of chronic rhinitis has been proposed in the last year and we have seen many papers emphasizing the importance of endotyping patients in chronic rhinitis and rhinosinusitis in order to optimise treatment effect.

Key words: rhinitis, rhinosinusitis, diagnosis, treatment, COVID-19, olfaction

Introduction

We look back at the end of what once will be seen as a historic year. In this first full year with COVID-19, our field has realized the enormous consequences of the pandemic for our profession and for our patients, with often long-term impact of COVID-19 on the sense of smell. On the other hand, the registration of biologicals for the treatment of severe CRSwNP has provided new hope for the improvement in the sense of smell (and quality of life in general) for our patients. These advances—and others discussed herein— will make us remember this year for a long time.

COVID-19 and smell

Post-infectious olfactory dysfuntion (PIOD) anosmia is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% of all cases of smell impairment, with a peak incidence in springtime [(1)]; it was therefore perhaps no surprise to see an increase in cases at the onset of the SARS-CoV-2 pandemic. After early newspaper reports of anosmia in Germany, Korea and Iran, olfactory dysfunction (OD) emerged as a potential marker of COVID-19 in March 2020, with Rhinology being one of the first journals to publish on this topic [(2,3)]. A large body of evidence now demonstrates loss of sense of smell to be one of the most common symptoms of COVID-19 infection with a meta-analysis of 3563 patients published in May 2020 reporting the mean prevalence of self-reported loss to be 47% (95% CI: 36%-59%), ranging from 11% to 84% in the included case series [(4)]. Loss of smell may be the only presenting feature for patients with COVID-19 [(3)], with alteration of sense of smell or taste preceding other symptoms in 20% (95% CI: 13%-29%) [(4)]. These olfactory symptoms were quite distinct from those who suffered olfactory loss in association with the common cold [(5)],

with a relative lack of classic rhinitic-type symptoms. In fact, this unique presentation of smell loss in the absence of other nasal symptoms is one of the most sensitive and specific markers of COVID-19 infection [6]. This important role for smell loss as a sentinel sign of COVID-19 placed our specialty in a position to make major research contributions during the pandemic. Sadly, a number of colleagues also contracted the disease themselves, particularly when PPE was limited during the early stages of the pandemic [7,8]. The high prevalence of olfactory dysfunction has been paralleled by an unprecedented volume of research in a hitherto neglected field, evaluating new testing techniques [9], underlying pathophysiology [10], recovery rates and treatment options.

Post COVID-19 recovery and persistence smell disorders

Many studies have now been performed to evaluate recovery rates from COVID-19-related OD, and the risk factors for persistence by using questionnaires or objective olfactory tests. Early studies using self-reported outcomes suggested very high rates of rapid recovery [11], with a low incidence of persistent deficits at 6 months [12-14]. However, it has become clear that self-reporting likely over-estimates the degree of recovery, in contrast to under-estimating the initial prevalence of olfactory dysfunction, highlighting the importance of objective testing [15]. In a study performed by Boscolo-Rizzo et al. [16] a significant mismatch was found between self-reported olfactory function and psychophysical evaluation; interestingly, of 112 patients with self-reported normal sense of smell at 6 months, only 41% revealed normosmia with UPSIT testing.

A number of studies have now published outcomes at 6 months and beyond. Boscolo-Rizzo has undertaken a case-controlled study, with a mean follow-up of 401 days after the infection, in which 46% and 10% of cases and controls were found to have olfactory dysfunction, with 7% of COVID-19 cases still being anosmic [17]. Given the high numbers of people affected by COVID-19, even with the best reported recovery rates, a significant number worldwide will be left with severe olfactory dysfunction. This large burden of disease will hopefully drive therapeutic advances. Currently, olfactory training is the most commonly used treatment. One small study suggested benefit from combined oral and intranasal corticosteroids, but further evaluation is required [18]. The results of a number of ongoing trials worldwide are eagerly awaited by ENT doctors and patients alike.

Many patients have reported the development of parosmia, typically after a period of 2 to 3 months and often after a period of apparent recovery [19]. Parosmia may have a significant impact on quality of life, and better management of qualitative olfactory dysfunction after COVID-19 remains a significant unmet need.

Not all smell disorders are COVID-19

Even before the COVID-19 pandemic and the associated attention that was suddenly given to smell function, chemosensory disorders were increasingly focused upon by many rhinologists. Rhinology as journal has a long-standing commitment to this field which is reflected by the first descriptions of the currently most used, and best validated olfactory [20] and gustatory tests [21] in Europe and many other parts of the world. Continuous efforts in improving how olfactory, taste and also trigeminal tests should be conducted is reflected by work that revisited controversial issues [22,23] and suggested new ways of testing chemical senses [9, 24-28,]. In order to summarize all these advances, and especially those relating to the assessment and evaluation of chemical senses and disorders, Rhinology has published two seminal position papers on olfactory disorders [29] and methods to assess them [30].

Severe olfactory dysfunction with total loss is very prevalent, estimated to affect between 3-5 % of the general population [31]. Another 10-15 % of the population are affected to a milder extent, suffering from decreased olfactory function. This high prevalence of olfactory dysfunction has been recently confirmed based on large epidemiological studies with over 100,000 subjects and once more points out the importance of chemosensory impairment has in our daily practice [32]. As many studies have now shown that these patients suffer considerably [28,33], the need for effective therapies is great [29]. The most prevalent causes for olfactory dysfunction, besides COVID-19 and upper respiratory tract infections in general, are trauma and chronic rhinosinusitis (CRS) [27,34]. For trauma-related olfactory disorders, no meaningful treatments have yet been identified and there is urgent need for research to focus on therapies for these patients [35-37]. Olfactory training, which has proven to be highly effective in patients with post-infectious olfactory impairment [27,38,39], seems to be only marginally useful after head trauma [40-42]. For CRS-related olfactory impairment, the treatments directed at the underlying CRS, such as topical steroids and endoscopic sinus surgery, provide some benefit to improve olfactory function but unfortunately not all patients experience recovery [43,44]. For these CRS patients with treatment-recalcitrant olfactory dysfunction, there is new hope on the horizon. With the development of the biological treatments [45-47], it is very likely from initial investigations that olfactory function can be further improved [48] without the need of recurrent systemic steroids. However more real-life studies in this field are needed to draw a more comprehensive picture of when and which biological treatment is best used for patients with treatment-refractory olfactory dysfunction [49,50].

Not all nasal senses are olfaction: Nobel prize for TRPVI and TRPM8 importance for intranasal trigeminal function

The Nobel prize in medicine of 2021, awarded to David Julius and Ardem Patapoutian (https://www.nobelprize.org/prizes/medicine/2021/summary) who discovered the receptors for temperature and touch, clearly highlights the importance of theses senses.

The last few years have seen an substantial increase in studies investigating the often neglected chemical sense that is intranasal trigeminal function [51,52]. It had been known for over a decade that the perception of nasal obstruction depends not just on mechanical factors but also on the detection of airflow that is mediated by trigeminal innervation of the nasal mucosa [53-55]. To which extent this also reflects in clinical complaints has been speculated, but until recently very little data existed [56,57]. Recently, Migneault-Bouchard et al. [58] showed that trigeminal function appears to be more informative than mechanical resistance in patients with treatment refractory nasal obstruction, and Bischoff et al. [59] published data suggesting that intranasal trigeminal function predicts satisfaction after septoplasty. Taken together, these reports strongly suggest that rhinologists should consider assessment of trigeminal function, especially in patients potentially being prone to develop paradoxical nasal obstruction after surgery, a condition commonly coined as empty nose syndrome [60,61].

Advances in chronic rhinitis

Definition and diagnosis; epidemiology

Chronic rhinitis (CR) was defined for a long time as the presence of at least two nasal symptoms for at least 1 hour per day for more than 12 weeks per year. However, this definition lacked an evidence-based foundation. For that reason the epidemiological definition of CR was recently redefined as the presence of at least one nasal complaint present for at least 3 weeks per year [62]. CR can be categorized into allergic (AR) and non-allergic rhinitis (NAR) [62-67].

The prevalence of CR in the general population is 40% (of which a majority is NAR) and it has recently been described that AR and NAR have distinct seasonal patterns with AR being more prevalent in spring/summer and NAR being in autumn/winter. The most common NAR phenotypes are idiopathic and rhinitis medicamentosa, followed by occupational, smokers' ,hormonal, gustatory and rhinorrhoea of the elderly [62] . The high prevalence of rhinitis medicamentosa has also recently been shown to be correlated with the presence of local inflammation, anxiety and habitual smoking [68].

The diagnosis of rhinitis–and more specifically NAR— is primarily based on symptomatology and the presence/absence of sensitisation measured by skin prick testing of serum specific IgE measurements [30].

For the diagnosis of CR it is important to exclude other diseases involving the nose and sinuses like CRS, septal deviation [69] and other anatomical changes like turbinate hypertrophy [69-73] and even OSAS [74,75]. Although this may be obvious, in the last year COVID-19 has shown us how difficult it can be for patients with CR or CRS and their surroundings to discriminate their daily symptoms from concomitant conditions like COVID-19 [76] . The complex anatomical structure of the nasal guides the airflow throughout the nasal cavities and anatomical or inflammatory changes can modify this environment with negative consequences Computational fluid dynamics, although at the moment still too expensive and laborious for routine use, may become a viable diagnostic tool in the future for studying nasal physiology [77-80].

Nobel prize for TRPV1 and TRPM8 – role in nasal hyperreactivity

The Nobel prize discovery of TRPV1 and TRPM8 has also greatly enhanced our understanding of nasal hyperreactivity [81-83].

The stimulation of the TRPVI receptor with Cold Dry Air (CDA) has been shown to be an excellent way to measure nasal hyperreactivity [66,84,85] and treatment of NAR with capsaicin has shown to reduce nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis [86]. In the past years, It has been increasingly clear that hyperreactivity occur in all forms of sinunasal disease [87-91]. However, it is unclear, at the moment, whether the TRPVI receptor (overexpression) is the cause in all these forms of hyperreactivity.

Endotypes of CR including local allergic rhinitis

It can be difficult to discriminate between different forms of CR [92]. Recently a first attempt of cluster analysis has been tried although one can envision that in due time better biomarkers will help us in our daily practice [66,93-95].

In recent years a number of papers have evaluated the phenomenon of local allergic rhinitis (LAR), defined by the presence of allergen-specific immunoglobulin in the nasal mucosa of patients with non-allergic rhinitis (NAR) [65,96]. The prevalence of local allergic rhinitis has been reported to vary greatly [65].

One of the reasons might be that LAR is mainly found in NAR patients who think they have an allergy (and are seen by allergists), another reason might be the difference in availability of nasal corticosteroids [97,98] (being OTC or prescribed by GP), a very effective treatment of LAR.

Treatment of CR

The treatment of CR of course largely depends on the endotype. For AR a new algorithm has been proposed [99] emphasizing the importance of control of symptoms in CR. CR is an extremely

costly disease due to the high prevalence and large number of patients with uncontrolled disease [100]. The mainstay of treatment of inflammatory forms of CR are local corticosteroids [97,101,102]. In the treatment of CR, azelastine has an increasingly prominent role. This drug that originally was classified as an antihistamine has been shown to be effective in some forms of NAR and in a combination preparation with local corticosteroids it has been shown to be very effective in control of disease in AR [103,104].

Advances in chronic rhinosinusitis

Another subject that has had a tremendous amount of interest in the past year is CRS and especially new treatment options in CRSwNP.

Chronic rhinosinusitis (CRS) is one of the most common inflammatory conditions of the upper airway, affecting up to approximately 10% of the population around the world [43,105,106]. Research continues to show that CRS has a great negative impact on the patient [107,108] in addition to costing society billions of euros every year [109,110].

Pathophysiology of CRS

In the last several years, a number of advances have been made in our understanding of the pathophysiology of CRS and the consequent downstream impact to patients' quality of life (QOL). Recent multiomic approaches applied to CRS have revealed novel insights into the pathophysiologic mechanisms of CRS. Gene expression in the sinonasal mucosa continues to show a dominant role for inflammatory responses [111-113] that may be quite heterogeneous from patient-to-patient [114] as well as increasing importance for the role of mucosal stromal cells and tissue remodeling response [115], all of which seem to be processes intrinsic to the patient and the mucosa [116]. More recently, single cell gene expression studies have also revealed distinct populations of epithelial cells and lymphocytes uniquely contributing to CRS pathophysiology [117,118]. Transcriptional changes have largely been validated by proteomic studies [119-121] as well as cellular and histologic studies of sinonasal mucosa which have highlighted not only importance of inflammatory dysregulation, but tissue remodeling in CRS pathophysiology [122-126]. There is even increasing evidence for neurogenic modulation sinonasal inflammation through direct neural input and solitary chemosensory cells [127,128]. Multiomic characterization of CRS pathophysiology also extends beyond the host to include the microbiome [129,130] with the most recent studies showing that there are common alterations in the sinonasal microbiome of CRS patients found throughout the world [131].

Supported by the aforementioned multiomic approaches, endotypes of CRS—although potentially quite numerous—have been shown to be broadly characterized as being dominated by type-2 inflammation or not [92,120,121]. In fact, the most recent guidance from the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps is that primary inflammatory CRS be classified based on whether the patient's disease is due to type-2 inflammation or not, rather than using phenotypic classifications such as the presence of nasal polyps [43]. Endotyping of CRS based on the dominance of type-2 inflammation, which includes eosinophilic inflammation, has been especially shown to be predictive of response to corticosteroids as well as outcomes after endoscopic sinus surgery [132-136]. Moreover, molecular characterization of CRS endotypes has also allowed for identification of novel biomarkers, for example to identify patients with NSAID-exacerbated respiratory disease [137] or more precisely predict response to specific treatments [138]. Beyond the underlying host specific characteristics, increasing work has shown that environmental factors may also influence the development and persistence of CRS. Recent work has shown that factors such as air pollution as well as occupational exposures may contribute to the CRS disease process [139-141]. Even food exposures are have been recently identified as potential modulators of the CRS disease process [142].

Downstream of the pathophysiologic mechanisms of CRS are the clinical manifestations of CRS, which include chronic sinonasal symptoms, as well as symptoms related to poor sleep, craniofacial discomfort, emotional disturbance and lower airway hyperreactivity or asthma exacerbation [143-147]. These symptoms may differentially impact patients with nasal symptoms most dominantly impacting patients' perception of their disease burden while extra-nasal symptoms dominantly associate with their general QOL [148-151]. Recent work has shown that QOL may be significantly reduced by clinical manifestations of CRS beyond just the associated symptoms of CRS. The ability of CRS to exacerbate comorbid asthma has recently been shown to be one important means for not just reduction of QOL but also asthma-related morbidity [152-154]. The use systemic rescue medications for CRS in the form of oral antibiotics and oral corticosteroids, which may reflect acute exacerbations of CRS or progression of CRS, have now been shown to be independent predictors of decreased QOL as well as validated measures of CRS disease burden [155] that may be used to complement tradition symptom-based CRS outcome measures in determining CRS disease control [156]. Finally, studies continue to show that we learn more about how CRS impacts our patients from talking to them. Qualitative research that focuses on one-on-one or group interviews has revealed novel insights about the impact of CRS as well as what patients need for their care and optimal outcomes [157-159].

Medical treatment of CRS

The cornerstone treatment of CRS remains the application of topical corticosteroids, often administered as a nasal spray. For

nasal spray, much can be gained regarding education on proper administration techniques [98]. Other application methods have been investigated over recent years. In a single-arm prospective study, fluticasone delivered with an exhalation delivery system gave a reduction in SNOT-22 scores of more than 20 points in over 700 patients. There was no control group but many included subjects had been using a conventional intranasal steroid spray before, suggesting that this exhalation delivery system might provide additional benefit in CRS patients [102]. On the other hand, nebulization as delivery system does not seem to give better symptom control than a conventional nasal spray [160]. Some even advocate patient-personalized irrigation strategies based on 3D-printed models of their sinus CT scans [161].

Additional therapies consist, amongst others, of oral corticosteroids and antibiotics. Although the latter are generally not advised for all CRS patients [43], trials are still being performed in subgroups of patients to find those that might benefit from antibiotics. For example, 12 weeks of azithromycin 500mg thrice a week gave a sustained improved of SNOT-22 scores at one year follow-up in a small group of 27 N-ERD patients versus 21 on placebo [162]. Despite the lack of sound evidence for antibiotics in CRS, electronic records show that patients are given them frequently at the primary care level [163]. It has been suggested that the reason antibiotics may be effective for treatment of CRS, is that they help control the local microbiome. However, in a small RCT with 50 CRS patients randomly assigned to oral prednisolone, topical budesonide or oral doxycycline, (and their respective placebos), no treatment seemed to alter the nasal microbiome, despite clear clinical improvement of the disease [164].

Treatable traits in CRS

Physicians treating CRS should be aware of treatable traits. A few should be actively assessed, such as smoking [141], and occupational exposure [139,140]. Furthermore, the presence of N-ERD should be noted [73]. This condition has a high tendency to result in severe, uncontrolled CRS, leaving patients divided between their allergist suggesting more oral corticosteroids and their ENT-surgeon suggesting yet another ESS [157]. Unfortunately, most other treatment options for N-ERD, including diets (e.g., to reduce salicylate contents [142], seem to be of little additional value [165]. Another area of interest is the presence of possible odontogenic disease in CRS patients [166].

Surgery and post-operative care in CRS

With the first RCT on endoscopic sinus surgery (ESS) with medical therapy versus non-surgical management to be published in the coming weeks [167], the role of ESS in the treatment of CRSwNP has been confirmed. However, there is still a large debate on the extent of surgery. Retrospective (and hence, biased) studies show inconclusive results [168]. However, more extensive surgery may improve delivery of topical medications and more extensive surgery has been associated with lower revision rates [169]. Moreover both high volume, low flow lavages and the use of an exhalation delivery system were shown to give better penetration into the sinuses postoperatively when compared to standard spray in a silicon cast model [170]. These findings underscoring the importance of attention to postoperative topical delivery techniques as well as surgical extent.
With tools now available to quantify extent of past surgery [171], the next steps will be RCTs comparing limited and more extensive approaches [172]. As an example, a prospective, randomized-controlled study comparing functional ESS, radical ESS and radical ESS with Draf III in 81 patients showed better disease control at one year follow-up, but not at five year follow-up in the radical ESS group; addition of Draf III did not give further short-term improvement. However, postoperative medical treatment was not standardized in this study [173]. Certain other surgical variations to ESS, such as the addition of a partial middle turbinectomy or the use of a free nasal floor mucosal graft can help improve QoL as well [174,175]. Interestingly, ESS also seems to improve Eustachian tube dysfunction in CRSwNP as shown by a small prospective study with 57 patients [176].

Perioperative attention should be given to the anaesthetic techniques, as total intravenous anaesthesia was shown in a meta-analysis to provide a better surgical field, reduced blood loss and shorter operative times compared to inhalation anaesthesia [177].

Postoperative care is also a continuing point of debate. In a systematic review and meta-analysis, small advantages of fibrin tissue adhesive over nasal packing were demonstrated. However, the pricing is higher than that of nasal packing which could well be a reason not to implement this strategy [178]. Infiltrating nasal polyvinyl alcohol packs with triamcinolone showed additional benefit in the postoperative recovery [179].

Regarding postoperative antibiotics, some controversy remains. In a double-blind placebo-controlled RCT with 126 patients, the addition of 12 weeks of oral clarithromycin to 2 weeks of oral corticosteroids as post-operative therapy resulted in reduced SNOT-22 and improved endoscopy scores, especially in patients without tissue eosinophilia [180]. These results could not be found in 187 postoperative CRS patients randomized to receive either intranasal fluticasone proprionate or daily clarithromycin for 12 weeks, regardless of polyp or eosinophilia status [181]. The possible benefits of long-term antibiotics should always be weighed against possible disadvantages and complications, although for macrolides, no significant short-term or long-term increased

risks of myocardial infarction could be established in a large database study holding over 66.000 patients [182].

Biologicals for CRS

The field of CRS treatment has evolved largely over the past few years as biologicals have become available. Phase III trials, their post-hoc analyses, and the first real-life data have shown the great potential of biologicals to (rapidly) improve quality of life, reduce disease burden, and alleviate olfactory dysfunction [46,47,50,183,184]. Currently, dupilumab, mepolizumab, and omalizumab are available as add-on treatment for CRSwNP, although data pointing to a preferential treatment are limited [45,185]. Unfortunately, biologicals are as yet not cost-effective due to the high treatment costs [186], and are therefore not available or reimbursed in many countries. It is likely that cost-effectiveness will increase by reducing the costs (e.g., by stepwise interdosage interval prolongation [50], or by selecting those with the largest risk of failing other therapy (e.g., those with N-ERD) [169]. They are now still often identified from groups of patients treated with biologicals for their asthma. For example, one small open study using omalizumab in 16 N-ERD patients versus 16 N-ERD patients receiving aspirin therapy after desensitization (ATAD), reported improvement in 14 of the 16 omalizumab-treated patients. They had a decrease in RSOM-31 scores, accompanied by a reduction of nasal polyp scores [187]. The field desperately needs more real-life data from large groups of patients treated with biological with CRS as the primary indication. These will help the identification of patient groups that would benefit most from biologicals.

Conclusion

A lot has happened in Rhinology in 2021. This review gives an overview of the highlights.

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All authors contributed to the text of this review, reviewed and approved the final text.

Conflict of interest

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Wytske Fokkens
Department of Otorhinolaryngology
Amsterdam University Medical Centres
location AMC
Amsterdam
The Netherlands

E-mail:
w.j.fokkens@amsterdamumc.nl