

Rhinosinusitis: clinical-based phenotyping

Desiderio Passali¹, Luisa Maria Bellussi¹, Francesco Maria Passali², Giorgio Ciprandi³

¹ International Federation ORL Societies (IFOS), Rome, Italy; ² ENT Department, University Tor Vergata, Rome, Italy; ³ Allergy Clinic, Casa di Cura Villa Serena, Genoa, Italy

Abstract. *Background and aim* Rhinosinusitis (RS) is a common disease and is currently classified into two main types: acute RS (ARS) and chronic RS (CRS), which in turn includes CRS with or without nasal polyps. Different guidelines consider this classification. However, in clinical practice, other phenotypes exist. *Materials and methods* This article revised the recent literature on this topic. *Results* The current article would propose new clinical-based phenotyping of RS, including the following clinical phenotypes: simple catarrhal RS, Acute RS, acute bacterial RS, severe (complicated) acute RS, chronic RS, and recurrent chronic RS. Treatment strategy should be tailored considering the clinical phenotype and could include phytomedicines, intranasal non-pharmacological remedies, and local bacteriotherapy. *Conclusions* RS requires thorough diagnostic work-up, and the therapeutic approach should be mainly based on appropriate management. (www.actabiomedica.it)

Key words: rhinosinusitis, clinical-based phenotyping, phytomedicine, non-pharmacological remedies, local bacteriotherapy

Introduction

The term rhinosinusitis (RS) was first used in 1947 in a study concerning headaches (1). However, the first mention dates back to a year earlier, with the term “rhinosinusal” used for describing the target organs of a topical compound containing mafenide acetate, an antimicrobial agent (2). The concept of rhinosinusitis became widespread after the first studies by Stammberger, who had demonstrated the pathophysiological relevance of the sinus Ostia by endoscopy (3). The close pathogenetic association between rhinitis and sinusitis was then endorsed by the tomographic documentation, highlighting the almost constant association between infectious rhinitis and sinusitis (4). Hence, for more than 20 years, the term rhinosinusitis has officially entered the medical lexicon, and several guidelines have established diagnostic criteria and treatment options (5-8).

A shared definition of RS in adults contemplates the presence of inflammation of the nose and the

paranasal sinuses characterized by two or more symptoms (one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior rhinorrhea), facial pain/pressure, and hypo/anosmia), and either endoscopic signs (including nasal polyps, and/or mucopurulent discharge, primarily from middle meatus, and/or edema/mucosal obstruction, primarily in middle meatus) and/or CT features (mucosal changes within the ostiomeatal complex and/or sinuses). Conventionally, RS is classified as acute (ARS) or chronic (CRS), based on symptoms duration: <12 or >12 weeks.

From a pathophysiological perspective, ARS is usually caused by infective pathogenic mechanisms, whereas inflammatory events commonly sustain CRS. However, type 2 allergic inflammation may characterize both diseases (9).

From an epidemiological viewpoint, RS is a common condition globally, leading to a significant burden on society regarding healthcare consumption and productivity loss. Acute rhinosinusitis (ARS) has

a one-year prevalence of 6-15% and is usually the consequence of a common viral cold. ARS is usually a self-limiting disease, but serious complications leading to life-threatening situations and even death may occur. ARS, one of the most common reasons for the prescription of antibiotics and proper management, is extremely pertinent in the global crisis of resistance to antibiotics. On the other hand, CRS is a significant health problem and affects 10-12% of the European population (10).

The guidelines recognized two main CRS phenotypes based on endoscopy and computed tomography (CT) findings: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) (7,8). CRSwNP is defined by the presence of nasal polyps and signs and symptoms lasting longer than 8–12 weeks. The CRSwNP overall prevalence is approximately estimated to be 2% to 4% of the general population (8). CRS's main pathogenic characteristic is type 2 inflammation, even though type 1 and 3 may also promote and maintain inflammatory response (11). Treatment options for CRSwNP consist of local or systemic corticosteroids as the first-line choice. If ineffective, there is a need for functional endoscopic sinus surgery. Notably, patients with CRSwNP and comorbid asthma have an insufficient therapeutic response and a high recurrence rate, so the disease is more challenging to treat. In this regard, Precision Medicine is helpful to stratify patients into subgroups and to tailor treatment based on their peculiar pheno-endotypes, such as the so-called Personalized Medicine (12,13).

These phenotype RS patients have obtained great recognition from scientific societies and are applied in clinical practice, especially in third level centers. In reality, this classification seems to be somewhat reductive and not very consistent with clinical reality, as it essentially considers three types: ARS, CRSwNP, and CRSsNP. On the contrary, we believe that a different phenotyping type eminently based on clinical criteria is more useful and faithful to reality.

Moreover, it has to be noted that, in the past years, every accredited ENT journal included one or more papers regarding the “Rhinosinusitis” topic. Each article presented a particular clinical picture, often completely different from others, which fore-

saw a therapy different from others again. This is why the corticosteroids are recommended for some pathological pictures, the antibiotics for others, and nasal washes for others only. Our clinical experience, based on fifty years of clinical practice and on tens of thousands of examined patients, allows us to underline that the umbrella term “Rhinosinusitis” includes several clinical pictures, very different from each other, that require absolutely different considerations and therapies. This is the reason why it seems useful, especially for the young specialists, to propose an apparently simple but fundamental classification for understanding all the clinical picture, justifying the symptoms, and establishing the most suitable therapy.

Materials and methods

The present article revised the literature concerning the debated topic, such as rhinosinusitis.

Results

Based on the discussed and revised background, the present article proposes a new RS classification considering clinical phenotypes observed in the real-world. In this regard, the current proposal entails six clinical phenotypes: simple mucous RS, ARS, bacterial ARS, severe (complicated) RS, CRS, and recurrent CRS.

Proposed classification of RS clinical phenotypes (Table I)
Simple (uncomplicated) catarrhal RS (SC-RS)

The simple catarrhal RS is usually a self-limiting disease that mainly affects children. The primary sign is catarrhal rhinorrhea, such as the presence of wa-

Table 1. Proposed classification of RS clinical phenotypes

SC-RS	ARS	BA-RS
Simple (uncomplicated) catarrhal RS	Acute RS	Bacterial acute RS
Severe RS	CRS	RC-RS
Severe (complicated) RS	Chronic RS	Recurrent chronic RS

tery-seromucous discharge, easily detectable during fiberoptic endoscopy. Tubaric occlusion is a frequent complication. The SC-RS is commonly a consequence of an acute upper respiratory infection, typically of viral nature. Persistence of nasal symptoms, per definition “clear” rhinorrhea, more extended than ten days should be considered a reliable diagnostic criterion (8).

SC-RS, because of its prevalence in children, may be primarily the expression of acute allergy-induced inflammation of the nasal-paranasal sinuses mucosa with an impaired epithelial barrier function. Several *in vitro* studies demonstrated impaired epithelial barrier function and early local immune reaction in allergic subjects. These studies reported decreased expression of tight-junction proteins, including occludin and zonula occludens-1, in cultured epithelial basal cells from allergic patients, and up-regulated expression of intercellular adhesion molecule-1 (ICAM-1), which is the receptor for 90% of rhinoviruses (9). This last feature may predispose allergic subjects to upper respiratory infections.

Even though SC-RS is usually self-limiting and is not severe, the symptoms may last for several weeks.

Consequently, active treatment is advisable. Mucoregulators, nasal lavages, and glycyrrhizin could be safe and fruitful options in children with SC-RS. The mucoregulatory drugs have a different mechanism from that which characterizes mucolytics; they act not directly on the mucus but on the cells that produce it (the so-called mucipar cells); the phlegm may therefore be more watery and less sticky or have less adhesiveness; even, in this case, its elimination will be much easier. Among the most well-known mucoregulators, such as mucolytics and fluidifies, should be mentioned ambroxol, bromhexine, and carbocysteine (14). Nasal lavage, using isotonic or hypertonic saline solution, removes secretions, decongests nasal mucosa, and moisturizes the nose (15). Hyaluronic acid is also indicated to repair the damaged nasal mucosa and restore physiological hydration (16). Glycyrrhizin derives from licorice roots, exerts relevant anti-inflammatory and immune-modulating activities; in particular, glycyrrhizin scavengers HMGB-1, an alarmin involved in the inflammatory cascade events

(17). Topical administration of nasal spray containing eutrophic vitamins, including A, E, and H) could help repair nasal mucosa (18).

Acute RS (ARS)

The acute RS is usually a consequence of upper respiratory infections, namely the common cold, when clinical features persist more than ten days. The main symptoms are nasal obstruction, rhinorrhea, mainly anterior and mucopurulent-purulent, and mild facial pain is frequently associated. ARS is usually self-limiting and not complicated. Thus, antibiotics are useless and harmful. The most convenient medications are intranasal corticosteroids, antihistamines, decongestants, and nasal lavage (19-21). Intranasal corticosteroids significantly dampen inflammation, mainly concerning the mucosal edema, which blocks sinus Ostia, promoting sinus inflammation and infection; a short course (2-3 weeks) could be sufficient to improve RS. Antihistamines could be useful when sneezing, itching, and watery rhinorrhea are predominant symptoms, and overall if the patients suffer from allergic rhinitis. Decongestants, preferably non-adrenergic agents (such as mannitol), promptly relieve the perception of blocked nose. For example, a medical device contains glycyrrhizin and mannitol to reduce inflammatory edema. Nasal lavage with isotonic or hypertonic saline solution is very useful in removing secretions, decongests the nasal mucosa, and allowing nasal patency. Phytotherapy may also be fruitful in the management of ARS patients. Several compounds could be used, including eucalyptus, mint, pine, thyme, and niaouli and their extracts, specifically essential oils (22). These substances can give prompt relief by promoting the drainage of the paranasal sinuses' cavities while exercising an important antimicrobial activity necessary to resolve the infection, resulting in relapses and complications. Especially in the form of essential oil, these plants are mainly used externally, primarily through nebulizations and diffusion into the environment, allowing the improvement of respiratory function and disinfection of the air in environments with a high risk of infection, essential for effective prevention. In this regard,

there are some medical devices with this positioning. A multicomponent phytomedicine (Sinupret Forte) contains dry extracts of gentian root (*Gentiana lutea*), primula flowers (*Primula veris*), elderflowers (*Sambucus nigra*), sorrel herb (*Rumex acetosa*), and verbena herb (*Verbena herba*). This compound has many activities, including antiviral, antibacterial, secretomotor, secretolytic, and anti-inflammatory. In this regard, a recent study compared Sinupret Forte with intranasal fluticasone furoate in sixty patients with ARS (23). The study demonstrated that the phytomedicine was effective and safe.

Bacterial acute RS (BARS)

Bacterial acute RS is typically caused by the so-called “Infernal trio,” such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. The main symptoms are fever, mucopurulent rhinorrhea, facial pain. If not adequately cured, BARS may be a severe disease, potentially associated with complications, mainly concerning the neighboring structures (orbit and central nervous system), up to be life-threatening. The treatment necessarily entails antibiotics, injecting, local and/or systemic corticosteroids, and decongestants (24,25). The bacterial infection must be stopped immediately to avoid dangerous complications. Anti-inflammatory treatment, such as corticosteroids, promptly reduces mucosal edema allowing the drainage of purulent secretions from the sinus to the nasal cavity. Decongestant agents, including α -adrenergic drugs, are quicker than corticosteroids in increasing nasal patency. Phytotherapy may have an ancillary role in improving mucosal restoration (26).

As antibiotics are burdened by resistance and unlike eliminating bacterial biofilm, BARS recurrence is possible (27). In this regard, microbiota dysbiosis is a frequent risk factor (28). Therefore, the preventive strategy includes local bacteriotherapy, such as administering “good” microbes hindering pathogens (29).

Severe RS (complicated)

Severe RS is usually BARS, not adequately and timely treated. Ocular, bone and cerebral complica-

tions are present in patients with severe RS. The main symptoms are fever/hyperpyrexia, pain, and neurologic symptoms, including sensory clouding. Antibiotic therapy is mandatory and should be targeted against the causal microbe. Careful imaging, CT, associated with the endoscopic procedure, are the mainstay work-up in severe RS patients. Lab exams should include blood count, C-reactive protein, and pro-calcitonin assay.

Chronic RS (CRS)

CRS is defined when symptoms persist for more than 12 weeks and are usually mild and affecting the nose. The main imaging feature is the muddy sinus. Chronic rhinosinusitis may present as chronic rhinosinusitis without nasal polyps (CRSsNP), chronic rhinosinusitis with nasal polyps (CRSwNP), and allergic fungal rhinosinusitis.

In patients with CRSsNP, antibiotics should not be prescribed, but anti-inflammatory drugs are beneficial, mainly concerning topical corticosteroids (30). Mucoregulators could be suitable to improve secretion removal and to restore a physiological mucociliary clearance. Antihistamines could be indicated in allergic patients. As the persistence of inflammation could be a risk factor for respiratory infections, local bacteriotherapy may be a reliable option. Local bacteriotherapy is the administration of “good” microbes that interfere with the pathogens’ colonization in upper airways.

Recurrent CRS

Recurrent CRS is relatively common and consists of the relapse of acute RS in a patient with CRS. The cause could be bacterial or viral. The symptoms include both ARS and CRS clinical features. The treatment should be tailored considering the clinical status.

As said, this phenotypic classification of CRS deliberately does not include CRSwNP and comorbid asthma, characterized by a high recurrence rate and an inadequate response to corticosteroids treatment for which endotype characterization and the need for targeted treatment against specific inflam-

matory biomarkers represent the new frontier of pharmacological research for this complicated and disabling pathology.

Conclusions

Rhinosinusitis is a multifaceted disease that is commonly observed in clinical practice. Rhinosinusitis requires adequate attention as history, clinical features, and evolution may be significantly different in every patient. Consistently, the treatment should be tailored considering peculiar characteristics. The current paper provides a simple way for a clinical-based phenotyping that may be useful in daily practice.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Fox SL. The use of sulfamylon in rhinosinusitis. *Ann Otol Rhinol Laryngol* 1947;56(4):946-52
2. Elise FC, Montero J. Aetiopathogenesis of rhinosinusal headaches. *Prensa Med Argent* 1946;33:1018-23.
3. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. *Otolaryngol Head Neck Surg* 1986;94(2):143-7
4. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med* 1994;330(1):25-30
5. Bachert C, Pawankar R, Zhang L, et al. ICON: chronic rhinosinusitis. *World Allergy Organ J* 2014;7(1):25
6. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg* 2015;152(2 Suppl): S1-S39.
7. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6 Suppl 1:S22-209
8. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020;58(Suppl S29):1-464
9. De Corso E, Lucidi D, Cantone E, et al. Clinical Evidence and Biomarkers Linking Allergy and Acute or Chronic Rhinosinusitis in Children: a Systematic Review. *Curr Allergy Asthma Rep* 2020;20(11):68
10. Hassan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2) LEN study. *Allergy* 2011;66:1216-23
11. Castagnoli R, Licari A, Brambilla I, Tosca M, Ciprandi G, Marseglia GL. An update on the role of chronic rhinosinusitis with nasal polyps as a co-morbidity in severe asthma. *Expert Rev Respir Med* 2020 (in press)
12. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol* 2019;144:1-12
13. Guilleminault L, Oukel H, Belleguic C, et al. Personalised medicine in asthma: from curative to preventive medicine. *Eur Respir Rev* 2017;26:143
14. Scaglione F, Petrini O. Mucoactive Agents in the Therapy of Upper Respiratory Airways Infections: Fair to Describe Them Just as Mucoactive? *Clin Med Insights Ear Nose Throat* 2019;12:11795506188219
15. Achilles N, Mösges R. Nasal saline irrigations for the symptoms of acute and chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2013;13(2):229-35
16. Pereira H, Sousa DA, Cunha A, et al. Hyaluronic Acid. *Adv Exp Med Biol*. 2018;1059:137-153
17. Ciprandi G, Bellussi LM, Passali GC, Damiani V, Passali D. HMGB1 in nasal inflammatory diseases: a reappraisal 30 years after its discovery. *Expert Rev Clin Immunol* 2020; 16(5):457-463
18. Maiolino L, La Mantia I, Grillo C, Grillo Ct, Ciprandi G. Dystrophic rhinitis: etiopathogenetic mechanisms and therapeutic strategy for functional recovery. *J Biol Reg Hom Ag* (in press)
19. Rot P, Rapiejko P, Jurkiewicz D. Intranasal steroid therapy - EPOS 2020. *Otolaryngol Pol* 2020;74(3):41-49
20. DeBoer DL, Kwon E. Acute Sinusitis. *StatPearls* 2020 Aug 10
21. Shakhova EG. Comparative study of the efficacy of combined nasal, topical drug, and topical decongestants in the treatment of acute rhinosinusitis]. *Vestn Otorinolaringol* 2020;85(4):46-50
22. Pietruszewska W, Bara ska M, Wielgat J. Place of phytotherapy in the treatment of acute infections of upper respiratory tract and upper gastrointestinal tract. *Otolaryngol Pol* 2018;72(4):42-50
23. Passali D, Loglisci M, Passali GC, Cassano P, Rodriguez HA, Bellussi LM. A prospective open-label study to assess the efficacy and safety of a herbal medicinal product (Sinupret) in patients with acute rhinosinusitis. *ORL* 2015;77:27-32
24. Rosenfeld RM. Clinical practice. Acute sinusitis in adults. *N Engl J Med* 2016;375:962-70
25. Brook I. Acute sinusitis in children. *Pediatr Clin North Am* 2013;60:409-24
26. Peri A, Ga eña D, Bara A, Sotirovi J, Peri AV. Herbal Drug EPs 7630 versus Amoxicillin in Patients with Uncomplicated Acute Bacterial Rhinosinusitis: A Randomized, Open-Label Study. *Ann Otol Rhinol Laryngol* 2020;129(10):969-976

27. Wu D, Bleier BS, Wei Y. Current Understanding of the Acute Exacerbation of Chronic Rhinosinusitis. *Front Cell Infect Microbiol.* 2019;9:415
28. Dimitri-Pinheiro S, Soares R, Barata P. The Microbiome of the Nose-Friend or Foe? *Allergy Rhinol (Providence)* 2020;11:2152656720911605
29. Ciprandi G, La Mantia I, Damiani V, Passali D. Local Bacteriotherapy – a promising preventive tool in recurrent respiratory infections. *Exp Rev Clin Immunol* 2020 (in press)
30. Kim DK, Kang SI, Kong IG, et al. Two-Track Medical Treatment Strategy According to the Clinical Scoring System for Chronic Rhinosinusitis. *Allergy Asthma Immunol Res* 2018;10(5):490-502

Correspondence:

Received: 1 December, 2021

Accepted: 17 December, 2021

Giorgio Ciprandi

Via P. Boselli 5

16146 Genova (Italy)

E-mail: gio.cip@libero.it