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REVIEW ARTICLE

Intranasal steroid therapy – EPOS 2020

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ABSTRACT:

Introduction: Due to their strong, multidirectional anti-inflammatory activity, intranasal glucocorticoids are the mainstay of treatment in rhinosinusitis, including acute rhinosinusitis, chronic rhinosinusitis, and chronic rhinosinusitis with nasal polyps, as well as allergic rhinitis. Owing to its high systemic safety and high anti-inflammatory efficacy, mometasone furoate – a new-generation intranasal glucocorticoid – was approved in 2019 as an over-the-counter (OTC) medication for Polish patients diagnosed with allergic rhinitis. Scientific societies and expert groups recommend the use of intranasal glucocorticoids in a much broader range of indications. In February 2020, an updated version of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) was published.

Aim: This article discusses the role of nasal glucocorticoids in regimens used in the treatment of nasal sinusitis as published in EPOS 2020 with Polish country-specific realities being taken into account.

KEYWORDS: corticosteroids, EPOS 2020, rhinosinusitis

ABBREVIATIONS

ARS – acute rhinosinusitis
CI – Confidence interval
CRP – C-reactive protein
CRS – chronic rhinosinusitis
EPOS – European Position Paper on Rhinosinusitis and Nasal Polyp
GRE – Glucocorticoid response element
MFNS – Mometasone furoate nasal spray
NARES – Nonallergic rhinitis with eosinophilia syndrome
NCSs – nasal corticosteroids
OTC – Over-the-counter
PoSLeNN – Polish Standards for the Treatment of Rhinitis
RARS – recurrent acute rhinosinusitis
RCTs – randomized control trials
Rx – Recipe
SPCs – summaries of product characteristics
UACS – Upper airway cough syndrome

INTRODUCTION

The prevalence rates of rhinosinusitis are continuously rising; in most countries, the disorder has become a significant health problem. Acute rhinosinusitis (ARS) has a one-year prevalence of 6–15% and is usually the consequence of a viral infection [1]. Chronic rhinosinusitis (CRS) affects 5–12% of the population [1].

DEFINITION OF RHINOSINUSITIS ACCORDING TO THE *EUROPEAN POSITION PAPER ON RHINOSINUSITIS AND NASAL POLYPS* (EPOS 2020) [1]

Rhinosinusitis in adults is characterized by:

- two or more symptoms, one of which should be either:
  - nasal blockage/swelling/congestion or
  - nasal discharge (anterior/posterior nasal drip):

and

+/– facial pain/pressure;
+/– reduction or loss of smell

and/or

- endoscopic signs of:
  - nasal polyps, and/or
  - mucopurulent discharge primarily from the middle meatus and/or
  - edema/mucosal obstruction primarily in the middle meatus

and/or

- CT changes:
  - mucosal changes within the ostiomeatal complex and/or sinuses.

The clinical definition of rhinosinusitis in children is virtually the same as in adults with the only exception of cough being included in the criteria instead of smell reduction/loss.

For epidemiological studies and general practice, the definition is based on symptomatology, usually without ENT examination or radiology [1].

NASAL CORTICOSTEROIDS

Nasal corticosteroids (NCSs) are the primary, most effective group of medicines used in the treatment of allergic rhinitis and chronic rhinosinusitis with nasal polyps [2]. As per the summaries of product characteristics (SPCs), modern NCS registered in

Poland for the treatment of these disorders include intranasal sprays containing mometasone furoate or fluticasone propionate. A fluticasone furoate product is registered only for the treatment of allergic rhinitis while fluticasone propionate nasal drops (Nasule) are registered for the treatment of nasal polyps.

According to the PoSLeN (Polish Standards for the Treatment of Rhinitis, 2013) document [2], nasal corticosteroids can also be used off-label for:

- rhinitis caused by intolerance to non-steroid anti-inflammatory drugs;
- non-allergic rhinitis with eosinophilia syndrome (NARES);
- drug-induced rhinitis (rhinitis medicamentosa) caused by the abuse of topical decongestants;
- chronic rhinosinusitis without nasal polyps;
- upper airways cough syndrome (UACS).

Similarly, the document titled "Standards for the Management of Non-Nosocomial Respiratory Tract Infections" recommends the use of NCS in post-viral acute rhinosinusitis in adults [3].

NASAL CORTICOSTEROIDS: THE MECHANISM OF ACTION [2]

The mechanism of action of nasal corticosteroids involves the drug molecule binding the cytoplasmic CS receptor (CSR) which, after being transported into the nucleus, binds the GRE sequence which can be found in numerous gene promoters, thus affecting the expression of respective genes. There are five mechanisms responsible for molecular influence of corticosteroids on gene expression [2]:

1. direct activation of gene transcription;

2. direct repression of gene transcription;

3. indirect repression of gene transcription (by means of competitive binding with transcription factors);

4. induction of the transcription of transcription factor inhibitors;

5. destabilization of selected gene mRNAs to increase the rate of their degradation.

Nasal corticosteroids inhibit the expression of numerous genes involved in inflammation such as IL1β, IL2, IL3, IL4, IL5, IL8, IL13, IL16, IFNγ, GMCSF, CSF, and TNF. Corticosteroids inhibit the expression of MHC class II molecules on dendritic cells, monocytes and macrophages, thus reducing their antigen presentation ability; they also inhibit the expression of adhesion molecules and chemokines (e.g. MIP-1α, MCP-1, GRO-α/CXCL1, eotaxins, TARC/CCL17, RANTES) and reduce the release of eosinophils from the bone marrow while also inhibiting their survival (induced by GM-CSF, IL-5, IL-3), inducing their apoptosis. Corticosteroids increase the production of reactive oxygen and nitrogen species; they also reduce the secretion of mucus and the development of inflammatory edema [2]. The process of blocking mucus production is linked to corticosteroids inhibiting the expression of MUC-2 and MUC-5a genes. Corticosteroid-induced sealing of blood vessels is mediated by increased expression of ZO-1, β-catenin and F-actin proteins. In addition, nasal corticosteroids are strong vasoconstrictors, thus reducing the edema and effusion. Corticosteroids have no effect on the innate immune response mechanisms. The clinical anti-inflammatory effect of nasal corticosteroids is generally considered to develop over several days starting from first administration while the vasoconstrictive effect is usually observed as quickly as within 2 to 20 minutes after the medication is taken [2].

Due to their biological availability and the appropriate concentration within the effector tissue, nasal corticosteroids are markedly superior to oral preparations. Direct application onto the mucous membrane of the nose translates to increased local efficacy. Owing to their high affinity to the receptors at the administration site, the anti-inflammatory effect of NCS is not associated with systemic adverse reactions. The fraction of the dose making its way into the gastrointestinal tract (as a result of ingestion following local administration) is biotransformed during the first liver passage before entering systemic circulation [2].

No atrophic lesions or signs of epithelial damage were observed in the assessment of nasal mucosa subjected to long-term, systematic exposure to topical steroids. Adverse effects are generally limited to unpleasant local reactions such as irritation, sneezing, bleeding, burning within the nose, dryness within the frontal parts of the nasal cavity, or scratchy throat. The incidence of these adverse reactions is comparable to those observed for placebo [2].

ACUTE RHINOSINUSITIS – MANAGEMENT AS PER EPOS 2020

Acute rhinosinusitis in adults is characterized by two or more symptoms, one of which should be either:

- nasal blockage/swelling/congestion or
- nasal discharge (anterior/posterior nasal drip)

and

+/– facial pain/pressure;
+/- reduction or loss of smell (cough in children);

and duration of <12 weeks, with symptom-free intervals if the problem is recurrent. The diagnosis may be made on the basis of a physical examination during a personal visit by phone [1].

RECURRENT ACUTE RHINOSINUSITIS (RARS)

ARS can occur once or more than once in a defined time period. This is usually expressed as episodes/year but with complete resolution of symptoms between episodes.

Recurrent acute rhinosinusitis is defined as ≥4 episodes per year with symptom-free intervals [1].

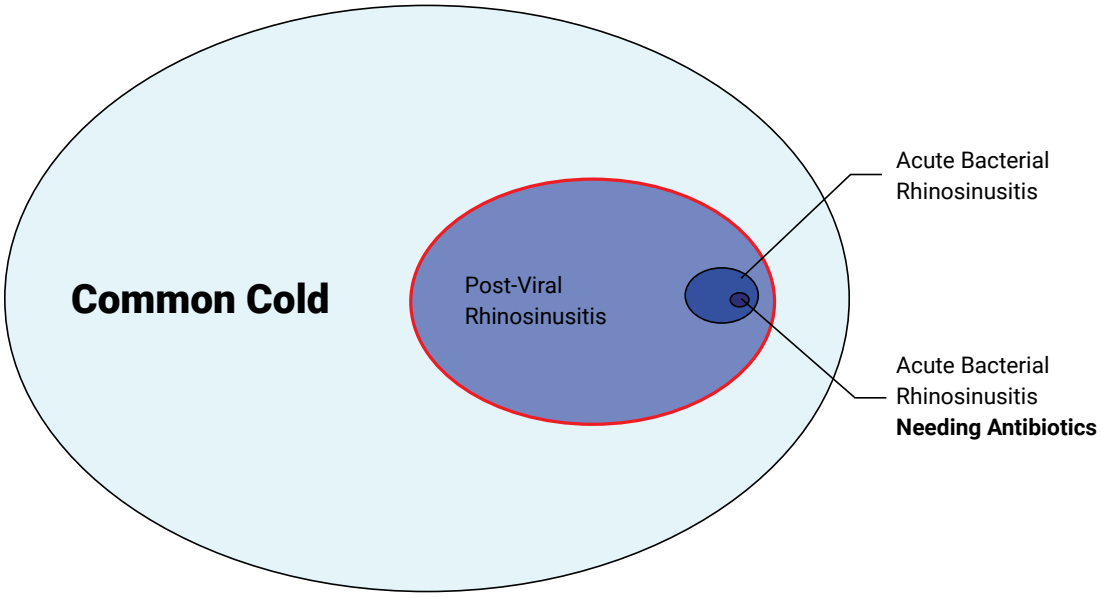


Fig. 1. The prevalence of different types of acute rhinosinusitis as per the EPOS 2020 [1] (adapted by the authors). Acute rhinosinusitis prevalence, common cold vs acute post-viral rhinosinusitis vs. acute bacterial rhinosinusitis vs acute bacterial rhinosinusitis requiring antibiotic therapy. Post-viral acute rhinosinusitis, for which nasal corticosteroids are indicated, has been marked in red.

In addition, the following definitions are provided:

1. Common cold, or acute viral rhinosinusitis with the duration of symptoms of <10 days;

2. Acute post-viral rhinosinusitis, with the duration of symptoms of >10 days (less than 12 weeks), or symptoms increasing after 5 days;

3. Acute bacterial rhinosinusitis defined by at least three of the following symptoms/signs:

   - discolored mucus;
   - severe local pain;
   - fever >38°C;
   - raised CRP/ESR;
   - 'double' sickening [1].

COMMON COLD

Referring to a Cochrane meta-analysis, the authors highlight that the current evidence does not support the use of nasal corticosteroids for symptomatic relief from the common cold despite the fact that some reports pointed at therapeutic effects of interventions including the use of these drugs. However, it should be noted that the authors of the meta-analysis have pointed at the need to validate this treatment in trials with higher statistical power [4].

ACUTE POST-VIRAL RHINOSINUSITIS

The role of nasal corticosteroids is different in the case of persistent symptoms, i.e. in the case of acute post-viral rhinosinusitis. The authors of EPOS 2020 analyzed all studies published in and after the year 1990 and conducted in patients who fulfilled the criteria of post-viral acute rhinosinusitis. Included in the analysis were double-blind placebo-controlled randomized trials assessing the effects of nasal corticosteroids in any form (spays, drops). The results of the studies included in the meta-analysis were quite discrepant. The treatment was assessed for its effects on the duration of symptoms and patients quality of life as well as in terms of its safety profile. Of the 8 studies included in mate-analysis, five were the trials assessing the effects of nasal corticosteroids alone [5–9] and three were the trials evaluating the effects of nasal corticosteroids being added to antibiotic treatment (which had proved inefficient as a standalone intervention). No significant difference was demonstrated in the meta-analysis between nasal corticosteroid and placebo treatments, although significant heterogeneity was observed in the outcomes. Some studies reported nasal congestion being reduced in the nasal corticosteroid group compared to placebo albeit no meta-analysis was conducted with this regard. The authors draw attention to the pharmacoeconomic aspect of nasal steroid therapy. Mometasone furoate nasal spray (MFS) treatment was compared to amoxicillin and placebo. Quality-adjusted life-year (QALY)-based calculations revealed that MFNS treatment reduced disease-related costs compared to amoxicillin or placebo [10],

The authors of EPOS 2020 suggest that nasal corticosteroids effectively reduce the severity of symptoms in adults suffering from post-viral rhinosinusitis while having no effect on the quality of their lives. The authors of EPOS 2020 suggest that nasal corticosteroids should be recommended for the treatment of this disorder in order to reduce the severity of symptoms [1].

No sufficient study data are available on the effect of nasal corticosteroids on acute post-viral rhinosinusitis in children. The EPOS 2020 experts had identified two studies which assessed the use of nasal corticosteroids on top of antibiotics. Both studies

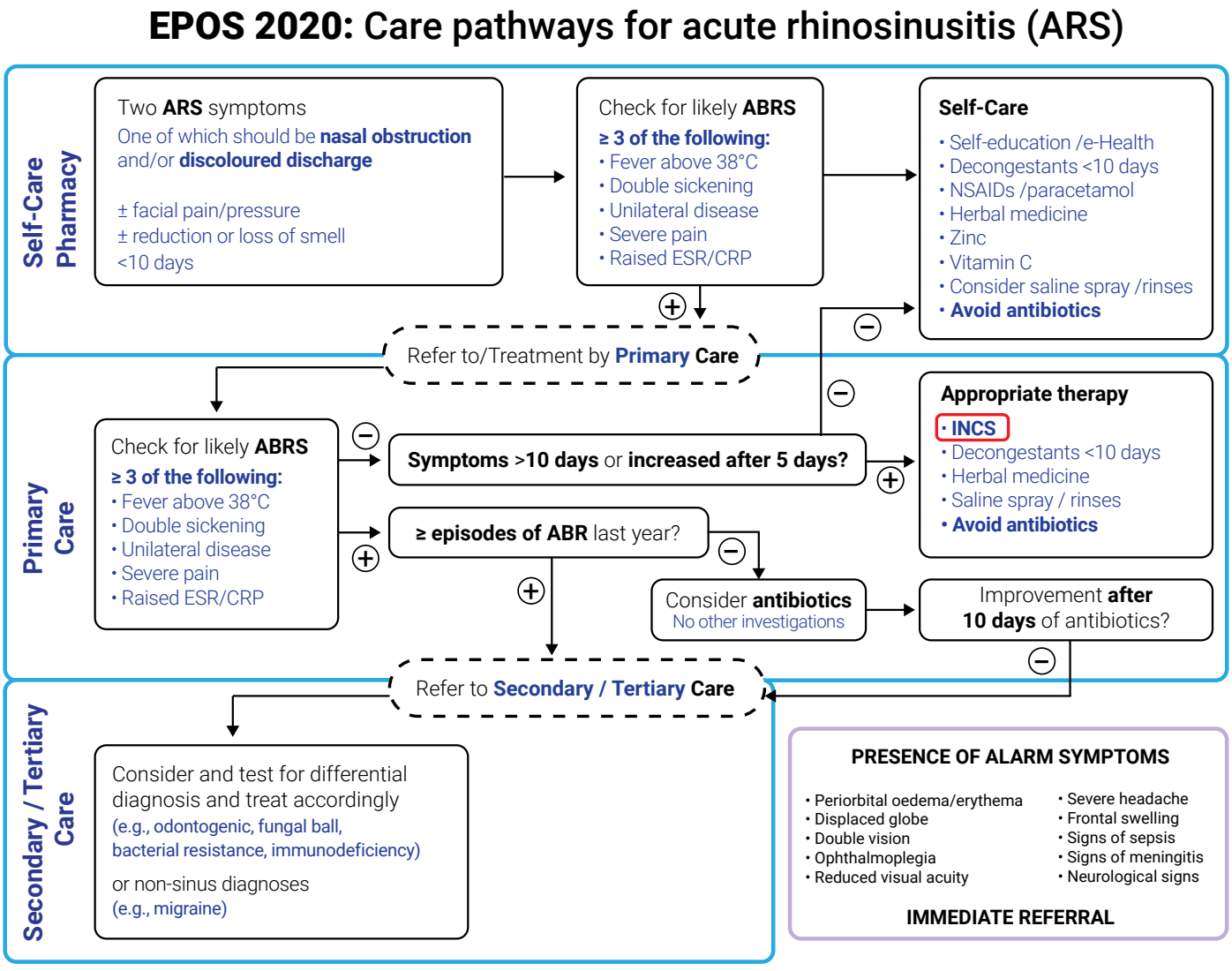


Fig. 2. Care pathways for acute rhinosinusitis [1]. Adapted by the authors. Nasal corticosteroids are marked in red boxes.

found a significant impact of nasal steroid therapy on the reduction of symptoms of acute post-viral rhinosinusitis in children. Due to insufficient quality of the evidence, the EPOS2020 steering committee could not prepare indications on the use of nasal corticosteroids in children with acute post-viral rhinosinusitis.

The authors of both the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) [1] and the PoSLeN (Polish Standards for the Treatment of Rhinitis 2013 [2] and the Standards for the Management of Non-Nosocomial Respiratory Tract Infections 2017 [3]) recommend the use of nasal corticosteroids in acute post-viral rhinosinusitis in adults.

Chronic rhinosinusitis (CRS) with or without polyps in adults is characterized by two or more symptoms, one of which should be either:

- nasal blockage/swelling/congestion or
- nasal discharge (anterior/posterior nasal drip):

and

+/– facial pain/pressure;
+/– reduction or loss of smell;

and the duration of ≥12 weeks [1].

A key difference in the EPOS 2020 definition as compared to the EPOS 2012 definition is the lower importance of phenotype-based classification into chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps. More emphasis was placed on the endotyping of the disease. The new classification distinguishes between localized (usually, albeit not necessarily unilateral), and diffuse (always bilateral) disease. Both of these types can be further divided into subtypes with type 2 inflammatory response or non-type 2 inflammatory response. However, the authors point out that no suitable biomarkers are available at the moment for easy differentiation of these subtypes (conclusions from large studies on the use of monoclonal

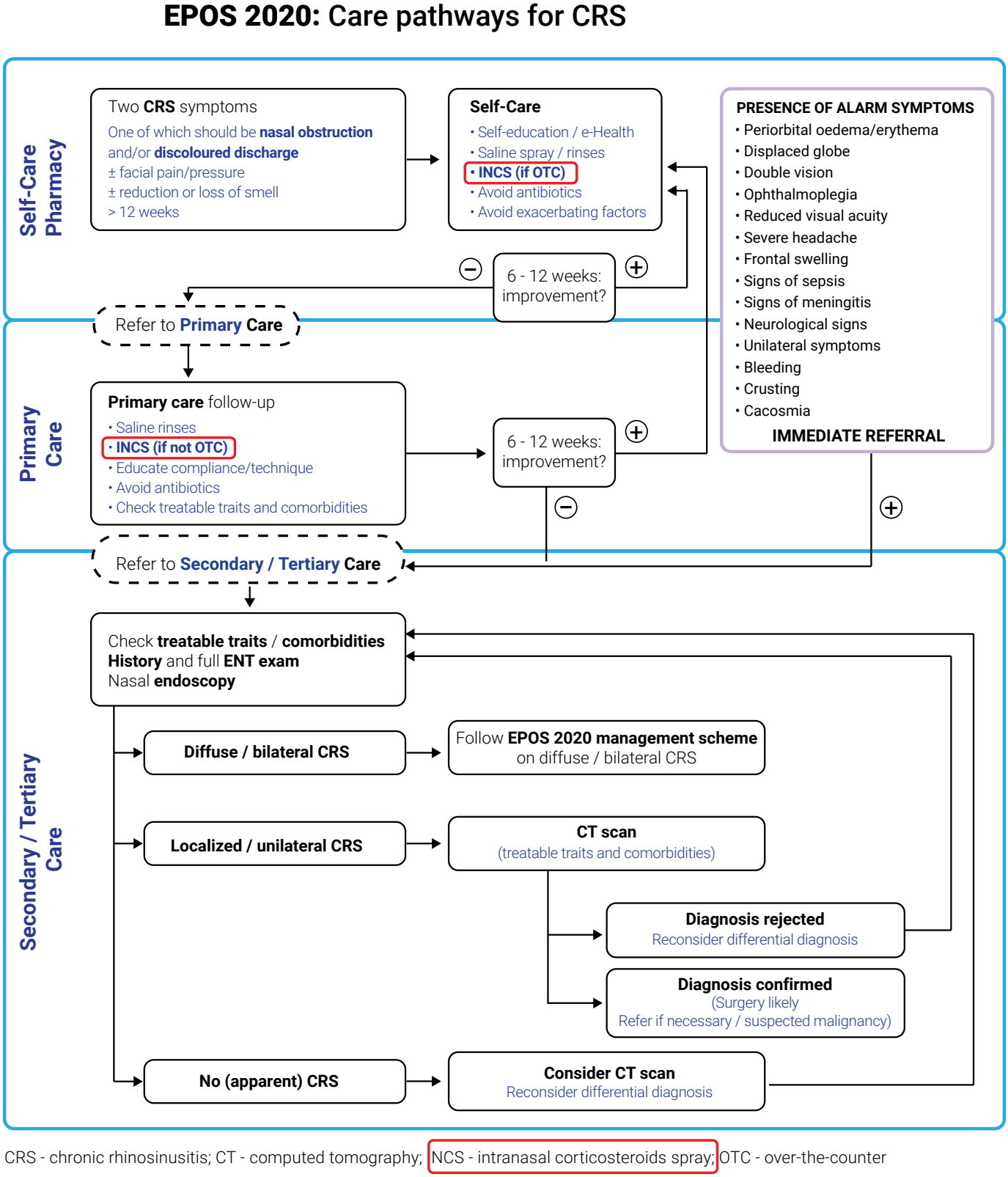
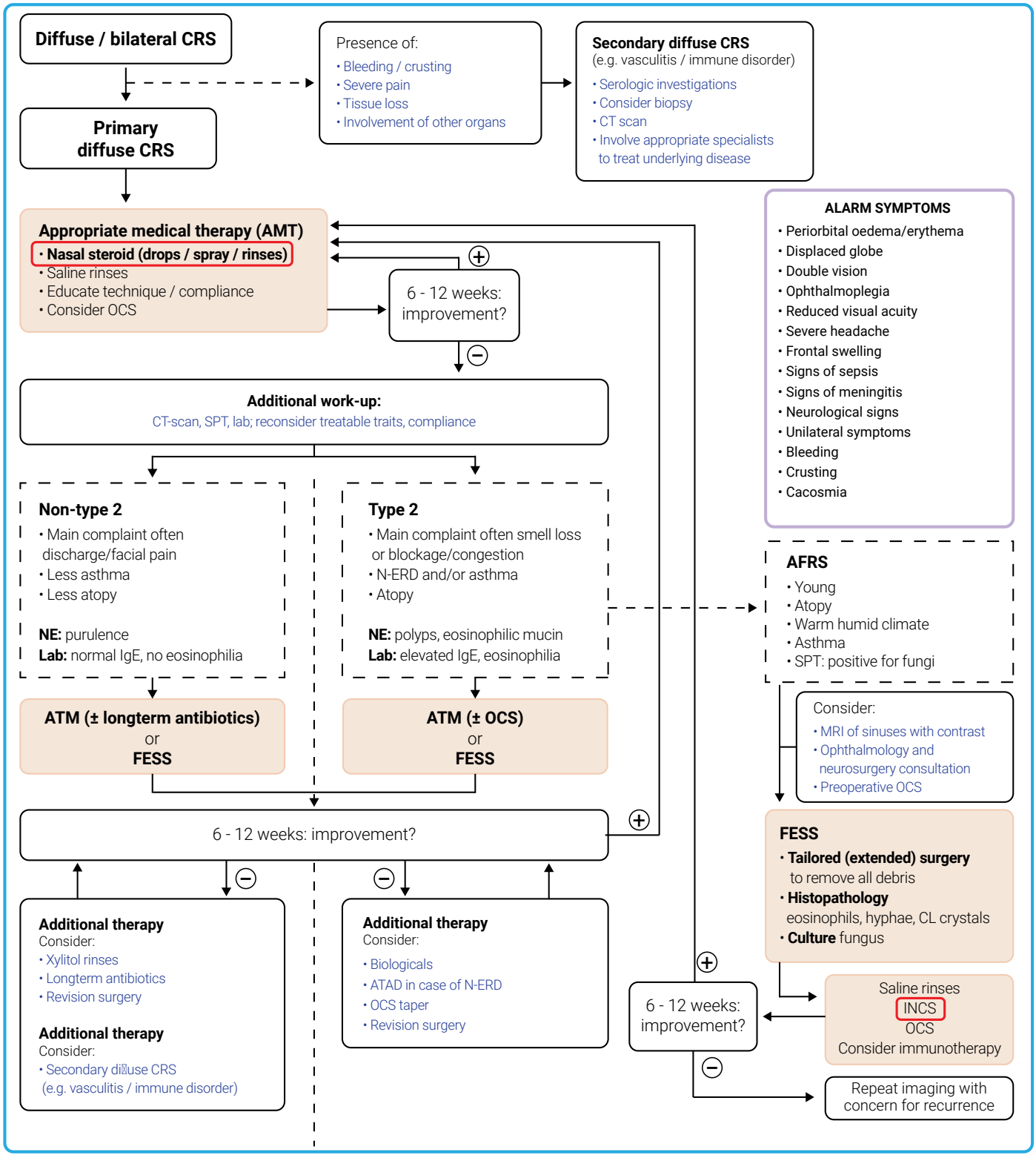


Fig. 3. Primary care pathway for chronic rhinosinusitis [1]. Adapted by the authors. Nasal corticosteroids are marked in red boxes.

antibodies in the treatment of chronic rhinosinusitis [13]. According to current knowledge, researchers recommend the use of markers such as the phenotype of rhinosinusitis, response to the treatment (oral steroid therapy) and, possibly, of ancillary markers such as the eosinophil counts, periostin levels, or IgE concentrations determined within the serum or tissues [1].



For explanation of (primary and secondary) diffuse CRS see 1.2.3.

AMT – appropriate medical therapy; ATAD – aspirin treatment after desensitisation; CRS – chronic rhinosinusitis; CT – computed tomography; FESS – functional endoscopic sinus surgery; INCS – intranasal corticosteroid spray; MRI – magnetic resonance imaging; NE – nasal endoscopy; N-ERD – NSAID-exacer-bated respiratory disease; OCS – Oral corticosteroids; SPT

Fig. 4. Specialist ENT care pathway for severe chronic rhinosinusitis [1]. Adapted by the authors. Nasal corticosteroids are marked in red boxes.

The authors of EPOS 2020 analyzed all double-blind placebo-controlled trials published after the year 1990. Included in the analysis were only studies involving nasal steroids being administered by any of the delivery methods generally available in clinical practice. The analyses focused on symptoms, quality of life, endoscopy polyp size, polyp recurrence and adverse events. Included in the analysis were a total of 42 studies, including 32 studies conducted in patients with chronic sinusitis with nasal polyps, 5 studies conducted in chronic sinusitis without nasal polyps, and 5 studies conducted in patients with both phenotypes of the disease. Twelve studies assessing the impact of nasal steroid therapy of chronic rhinosinusitis were included in the analysis. The studies which employed the Sinonasal Outcome Test-22 (SNIOT-22) for the assessment of the quality of life were combined in a meta-analysis. The meta-analysis favored nasal corticosteroids over placebo in the improvement of disease-specific quality of life (MD: −5.46, 95% CI: −8.08 to −2.84, P < 0.001; 6 CTs, n = 715) [1]. From the analysis of all studies, it is clear that nasal corticosteroids have a positive effect on disease-specific quality of life as assessed using both general and disease-specific questionnaires. Eighteen studies evaluating symptoms could be combined in a meta-analysis. The meta-analysis favored nasal corticosteroids over placebo in the improvement in symptoms for both symptom score (SMD −0.63, 95% confidence interval (CI): −0.89 to −0.37, P < 0.01; 12 randomized controlled trials (RCTs, n = 1690) and the proportion of responders (RR 0.66, 95% CI 0.59 to 0.73, P < 0.01; 12 RCTs, n = 1646) [1]. The expert-selected studies lacked a common method for the assessment of endoscopy outcomes; however, improvement in endoscopic presentation or reduction in nasal polyps was observed in combined subgroups regardless of the scale used. None of the active substances was shown to be superior to another in the analysis. Both mometasone furoate, fluticasone propionate, and budesonide were superior to placebo while no differences were observed between individual substances. According to the EPOS 2020 experts, the minimum recommended duration of nasal corticosteroid therapy is 12 weeks; however, shorter treatments were found to lead to outcomes similar to those obtained for the recommended duration. The steroid dose and method of intranasal delivery were also analyzed. Although meta-analyzes revealed that higher doses and certain delivery methods appear to have a greater effect on symptoms, direct comparisons are often lacking and such effects cannot be explicitly confirmed.

The safety profiles of intranasal drugs were also analyzed in 26 out of the 42 studies selected by the experts. All these studies found that nasal corticosteroids were well tolerated and safe. Major adverse events were not reported while minor adverse events (if any) had mild to moderate severity. When data were pooled for meta-analysis, nasal corticosteroids resulted in an increase in the risk of epistaxis compared to placebo (RR 3.49, 95% CI 2.42 to 5.05; 16 RCTs, n = 2021) [1]. Isolated studies pointed to the increased risk of septal lesions. No correlation between nasal corticosteroids and the suppression of the hypothalamic-pituitary-adrenal axis could be demonstrated in any of the 4 studies in which the potential for such a correlation was examined. Importantly, as observed by Leopold et al., nasal steroids did not increase intraocular pressure and did not cause cataract [14]. This was consistent with the data from the systematic review by Ahmadi et al. [15] and is thus of key importance for our everyday practice.

The efficacy of nasal corticosteroids in the treatment of chronic rhinosinusitis was confirmed in numerous studies; it was shown to be safe while reducing the disease symptoms and improving the quality of life. Symptom reduction is greater in the case of chronic rhinosinusitis with nasal polyps as compared to rhinosinusitis without nasal polyps. Nasal corticosteroids were found to reduce the size of nasal polyps and contribute to the prevention of polyp recurrence following endoscopic sinus surgeries.

In conclusion, EPOS 2020 reaffirms the key role of nasal steroid therapy in the management of rhinosinusitis. Corticosteroids are recommended for the reduction of symptoms in post-viral acute rhinosinusitis; as highlighted by authors, they may provide an alternative to the overuse of antibiotics as frequently observed (and proved ineffective) in the treatment of this nosocomial unit. Nasal steroid therapy is the treatment of choice in chronic rhinosinusitis. The EPOS authors recommend appropriate patient education; patients should be able to formulate a suspicion of chronic sinusitis and attempt the self-treatment by means of OTC intranasal corticosteroids. This "therapeutic trial" is recommended over a period of 6 to 12 weeks. Only if no improvement is observed, patients are recommended to present at their primary care physician. This model can be followed when intranasal corticosteroids are available without prescription; since recently, this has also been the case in Poland. However, one should keep in mind that as of the date of this article (June 2020), NCS preparations (of mometasone furoate) registered as OTC medicines in Poland are indicated for physician-diagnosed allergic rhinitis while simultaneously being available on prescription (Rx) in the additional indication of nasal polyps (or, to be scientifically precise, chronic rhinosinusitis with nasal polyps) in adults. The above differences in the statements included in the package information leaflet require appropriate explanation being provided to the patient; physicians should also explain that the applied treatment is based on actual, proven scientific knowledge and recommendations from scientific associations and expert groups.

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