Research Results in Pharmacology

Research Results in Pharmacology 6(2): 77–83
UDC: 616-08-035
DOI 10.3897/rrpharmacology.6.54570

Review Article

Modern approaches to the treatment of chronic polypous rhinosinusitis

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Academic editor: Tatyana Pokrovskaya ♦ **Received** 21 April 2020 ♦ **Accepted** 10 May 2020 ♦ **Published** 24 June 2020

Citation: Bairashevskaia AV, Kytko OV, Vasil`ev YuL, Kashtanov AD (2020) Modern approaches to the treatment of chronic polypous rhinosinusitis. Research Results in Pharmacology 6(2): 77–83. https://doi.org/10.3897/rrpharmacology.6.54570

Abstract

Introduction: Today, chronic polypous rhinosinusitis (CPR) occupies a special place among otolaryngological diseases, the incidence rate of which increases every year. To date, the main causes of chronic polypous rhinosinusitis are *Staphylococcus aureus* and anatomical abnormalities.

Diagnostics: Knowledge of a universal algorithm for the diagnosis of this disease, consisting of the collection of anamnesis, endoscopic examination of the nasal cavity, computed tomography of the paranasal sinuses, anterior active rhinomanometry and bacteriological determination of the microbial spectrum, allows diagnosing chronic polyposis rhinosinusitis in time, and, as a consequence, to prescribe a treatment.

Treatment: This review describes conservative therapies, including antibiotics and glucocorticosteroids. Today, the main task of doctors is to find the most effective method of administration of glucocorticosteroids to achieve the maximum effect. One of these methods is the introduction of the drug with the help of nebulizer, as in this case, the drug will remain in the perirhinal cavity for a long time and have the maximum effect due to the directed action only in the area of the pathological process.

Features of chronic polypous rhinosinusitis in childhood: It should be noted that children under 12 years of age due to the formation of the paranasal sinuses at different stages of ontogenesis will be characterized by different forms of chronic polyposis rhinosinusitis. That is why they should be known and taken into account when making a diagnosis and prescribing a treatment.

Conclusion: Today, the frequency of chronic rhinosinusitis increases exponentially, which makes the question of the modern approach to its treatment the most relevant. It is possible that additional research in this area will solve the issue of searching for both the optimal path of therapy and treatment of CPR in children.

Keywords

chronic polypous rhinosinusitis, glucocorticosteroids, nebulizer, antibiotics, paranasal sinuses.

Introduction

Chronic polypous rhinosinusitis (CPR) is an inflammation of the mucous membrane of the paranasal sinuses and the nasal cavity, leading to recurrent growth of polyps and characterized by a long course of disease (McCann et al. 2016; Ramakrishnan et al. 2016). According to statistics, the global prevalence of chronic rhinosinusitis is 11.81±5.81%, with a minimum of 1.01% in South Korea and a maximum of 57.6% in India (Shamkina et al. 2019).

In Russia, the average CPR prevalence rate was about 5% (Pestova et al. 2018).

The main causes of CPR according to (Ramakrishnan et al. 2015; Tomassen et al. 2015; Cope et al. 2017; Pestova et al. 2019; Sharma et al. 2019; Viswanatha 2019; Carretero-Vicario et al. 2020; Kennedy and Gerber 2020) are:

1) Bacterial nature:
- Streptococcus pneumoniae;
- Haemophilus influenzae;
- Moraxella catarrhalis;
- Streptococcus pyogenes;
- Staphylococcus aureus;
- Chlamydias;
- Mycoplasmas;

2) Fungal nature:
- Candida;
- Aspergillus;
- Penicillum;
- Alternaria;
- Rhizopus;
- Absidia;

3) Anatomical abnormalities of the osteomeatal complex;
4) Secondary immunodeficiency and/or allergies;
5) Persistent viral infection, such as:
- Rinovirus;
- Adenovirus;
- Respiratory syncytial;
- Parainfluenza virus;
- Coronavirus, etc.

6) Genetic factors (Association of allelic genes HLA-DRB1, -DQA1, -DQB1).

The most frequent causes are Staphylococcus aureus and anatomical anomalies (Dennis et al. 2016).

Diagnostics

A single algorithm has been proposed for the diagnosis of CPR, including the collection of patient complaints and anamnesis, endoscopic examination of the nasal cavity to determine the prevalence of the polyposis process, computed tomography of the paranasal sinuses to assess the severity of their lesions, anterior active rhinomanometry to assess the respiratory function of the nasal cavity and bacteriological determination of the microbial spectrum of the paranasal sinuses (Eremenko 2017).

Yet there is no exact mechanism for the pathogenesis of the development of CPR. According to one theory, Staphylococcus aureus superantigens affect the local IgE production, causing an inflammatory process that leads to the development of polyposis (Nakatsuji et al. 2017; Paylush et al. 2018). But there is also another theory based on the presence of colonies of microorganisms in the form of biofilms on the mucous membrane, which lead to sensobilization to TNF-α, destruction of the epithelium and the formation of polyps (Kirdeeva and Kosjakov 2017; Kartush et al. 2019). In any case, the patient has edema caused by retention of tissue fluid and accumulation of metabolic products (Jossé 2019). This is due to changes in microcirculation in the area of the middle nasal passage (vasomotor reactions), narrowing of arterioles and a decrease in the number of functioning capillaries (Ho et al. 2018; McHugh et al. 2018; Smith and Alt 2020). The inflammation induced by CPR occurs by the mechanism of Th2-inflammation and is associated with the synthesis of IL-5, IL-4, IL-13, IL-32, thymostromal lymphoprotein and IgE. At the same time, the second type of inflammatory reaction, which is characterized by TGF-β expression, tissue neutrophilia, activation of dendritic cells and tissue fibrosis, leads to chronic rhinosinusitis, which occurs with purulent inflammation in the paranasal sinuses, but without the polyp growth.

Previously, the most common method of treating this type of rhinosinusitis was surgery, but now doctors try to adhere to conservative methods of treatment, which include systemic antibiotics, antileukotrienovye drugs, monoclonal antibodies, and intranasal glucocorticosteroids (Bachert et al. 2016; Tharakan et al. 2018; Jankowski et al. 2019).

There are several stages during CPR (Table 1).

With a long course of the disease or improper treatment of CPR, rhinogenic complications may occur. They can be divided onto (Opoku-Buabeng and Lartey 2017):

1) Intracranial:
- arachnoiditis;
- extradural abscess;
- subdural abscess;
- meningitis;
- brain abscess;
- thrombosis of the sinuses of the dura mater;

2) Orbital (Ting and Hopkins 2018):
- periostitis;
- subperiosteal abscess;
- edema of the eyelids and eye tissue;
- abscess of the eyelids;
- phlegmon of the eye socket;
- retrobulbar neuritis

3) Rhinogenic sepsis.

Treatment

The oldest methods of the treatment of CPR are surgery and laser technologies. However, due to the high risk of injuries from these methods, conservative therapy (with antibiotics and glucocorticosteroids) is now used (Bulfamante et al. 2019).

Treatment of CPR should begin with the eradication of the pathogen, considering the resistance of the micro-

Table 1. The Main Symptoms That Occur at Different stages of the Development of CPR (DeConde et al. 2017; Kartush et al. 2018; Oakley et al. 2018; Orgain and Harvey 2018; Tsetsos et al. 2018).

Stage	Symptoms
Stage 1 (persistent diffuse edema of the mucous membrane in the middle nasal passage)	Slight nasal congestion, difficulty breathing through the nose (may be inconstant)
Stage 2 (polyps are within the middle nasal passage)	Persistent congestion, mucous discharge from the nose, decreased sense of smell
Stage 3 (polypose changes of the mucous membrane on the medial surface of the middle nasal concha)	Breathing through the mouth, a sharp decrease in the sense of smell, mucous or purulent-mucous discharge from the nose, nasal twang
Stage 4 (the presence of polyps in the general nasal passage)	Constant breathing through the mouth, headache and rapid fatigue, speech distortion due to pronounced nasal twang

organism and the pharmacological effect of antibiotics (Feshchenko et al. 2016; Grayson et al. 2019; Iqbal et al. 2020). Currently (according to the Eurasian Clinical Recommendations 2016, which are still currently), antibiotics used for the treatment of infectious diseases of the upper respiratory tract are usually divided into 3 lines of therapy (Song et al. 2019):

1. They provide high clinical efficacy and has a minimal effect on the growth of respiratory pathogens. These are the safest drugs for humans.
2. They are active against the main respiratory pathogens. They are used, as a rule, with a high probability of resistance of the main pathogens, with long-term, recurrent infections and in complex clinical situations.
3. They are used in cases of anaphylaxis to penicillin drugs (beta-lactams).

The most used antibiotics, which are characterized by high efficacy and hypoallergenicity, and their mechanisms of action are shown in Table 2.

It should be noted that the above drugs are typical for the treatment of adults, since the question of the use of certain drugs, in particular, a decongestant, in pediatric practice is still open (Bachert and Zhang 2019). Often, instead of decongestants, topical nasal steroids are used to relieve edema in children (from the age of two).

Normally, as is known, the sympathetic nervous system maintains the level of the vascular structure, and the parasympathetic nervous system causes vasodilation, and, therefore, contributes to the blood filling of the mucous membrane and an increase in the amount and a decrease in the viscosity of mucus. In addition to the decongestants (Laidlaw et al. 2019; Morozova et al. 2019), which regulate vascular tone, adrenomimetics can be used: direct and indirect, acting on the adrenoreceptors (α-1,2 and β) (Chong et al. 2020). However, their use is not appropriate if a patient has left ventricular systolic dysfunction, chronic heart failure, thyrotoxicosis and other conditions indicated as contraindications to these drugs.

Talking about preparations of plant origin, it is necessary to mention plant complexes that include limonene, cineol and α-pinene (Table 3). The pharmacological effects of such drugs are well studied, so they are often used in the treatment of CPR (Lin and Kacker 2019):

- mucosecretolytic – to reduce the viscosity of secret due to the break of disulfide bonds, an increase in the frequency of oscillation of cilia of ciliated epithelium, which facilitates the outflow of secretions from the paranasal sinuses;
- anti-inflammatory, due to the neutralization of oxygen OH-radicals, and a reduced synthesis of ethylene and histamine level;
- antibacterial, manifested in bacteriostatic action on the main pathogens (Szaleniec et al. 2019).

It is known that the most potent anti-inflammatory drugs are glucocorticosteroids (GCSs), which inhibit all links in the chain of the inflammatory process. However, to date GCSs are hardly used in CPR due to a large number of side effects.

It is advisable to use intranasal GCSs with a pronounced anti-inflammatory effect, which is achieved either by transrepression of anti-inflammatory genes, or through transactivation of glucocorticoid-dependent anti-inflammatory genes (Fedoseeva and Shilenkova 2019). An anti- inflammatory effect is caused by inhibition of IL-1, IL-3, IL-4, IL-5 (Heffler et al. 2019; Baroody 2020). The therapy by intranasal GCSs reduces eosinophilic infiltration and secretory activity of the glands, which leads to a slowdown in the synthesis of pro-allergic mediators. As a result, the concentration of eosinophils in the focus of inflammation decreases, thus reducing the swelling of the nasal mucosa and the volume of polyps (Poblete et al. 2018). However, this method of treatment has a disadvantage: its effect extends only in the nasal cavity, without reaching beyond it, and, thus, does not enter the paranasal sinuses. This problem can be solved by the inhalation method of intranasal GCSs, the main purpose of which is to act directly at the site of the pathological process with a larger contact area (Hong and Kim 2019). According to (Ito et al. 2019), up to 8% of the drug penetrates into the paranasal cavity and remains there for a long time. Now there are nebulizers available for delivery of medicines, including GCSs, which are actively used in medical practice (Wang et al. 2019). Currently, the development of nebulizers for drug delivery, including GCSs, is very promising and requires additional research. And in the future, nebulizers can replace the antibiotic therapy, the main disadvantage of which is known to be antibiotic resistance, and will improve the treatment of CPR.

Table 2. The Mechanism of Action of the Main Medicines Used in CPR (Stevens et al. 2016; Stevens et al. 2016; Van Crombruggen et al. 2016; Alekseenko et al. 2019; Bachert et al. 2020).

Medicine	Mechanism of action
Amoxicillin	Blocking peptidoglycan synthesis and inhibiting b-lactamase
Levofloxacin	Inhibition of DNA-gyrase
Omalizubad	Monoclonal IgG1 antibodies selectively bind to IgE
Decongestant	Activation of adenylate cyclase on the inner surface of the cell membrane

Table 3. The Main Components of Essential Oils and Plant Complex Myrtol and Their Effect on the Human Body (Ferraro et al. 2019; Jin and Chin 2019).

Some components of the drug and essential oils	Action/effect
Cineol	Decongestive, anti-inflammatory, antifungal (effect in case of internal inhalations)
Levomenthol	Antiseptic, decongestive due to the reflex action on the ending of the trigeminal nerve
Racemic camphor	Decongestive, vasoconstricting, antiseptic
Limonene	Anti-inflammatory, antibacterial, antifungal, antiproliferative
Alpha-pinene	Antibacterial, bronchodilator, anti-inflammatory

Features of CPR in childhood

Anatomical features of the structure and development of the paranasal sinuses in children determine, first of all, the localization of the inflammatory process, which can change at different ages (Anamika et al. 2019). In the first 4 years of life, children are most characterized by ethmoiditis, since at this age only the ethmoidal labyrinth is finally formed (in the future, only an increase in its cells can occur) (Jiao et al. 2019). With the formation of maxillary sinuses by the age of 4, the frequency of maxillitis (maxillary sinusitis) increases, which peaks at 5–12 years (Baqueiro-Achach et al. 2019). Before the age of 12, the complete formation of the frontal sinuses also occurs, so the risk of frontal sinusitis increases. After the age of 12, CPR can occur in any paranasal sinus or even in several (Gitman and Peña 2020).

In children, the development of CPR is accompanied by the following features (Pavez et al. 2019; Maurrasse et al. 2020):

1. High frequency of the process;
2. One-type microflora;
3. Occurrence is usually a complication of an acute respiratory viral infection (ARVI);
4. Rapid onset of the pathological process, with a high degree of intoxication and rapid formation of purulent exudate;
5. High risk of the process moving to closely located organs and tissues, in particular, to the meninges, cellular spaces of the neck, orbit, etc.);
6. Frequent relapse;
7. Latent course of disease in adolescence;
8. Development of rhinopharyngitis with the spread of the inflammatory process to the larynx and the underlying respiratory tract, including the development of pneumonia (in young children)

Treatment of children is complex and includes the elimination of inflammation, restoration of patency of the natural ostia of the paranasal sinuses, eradication of the pathogen, prevention of complications, and a local immunomodulatory therapy (by medical prescription) (Maximiliano et al. 2019; Din-Lovinescu et al. 2020). With a severe course of CPR (a large amount of purulence, pronounced general symptoms and general intoxication), the treatment begins with antibacterial drugs. They are also used in young children in cases of a high risk of complications or in the development of rhinogenic complications (Quintanilla-Dieck and Lam 2018; Alejandro et al. 2020).

With complications developing, the child should be immediately hospitalized, and a therapy should be selected in accordance with his/her condition (Levy et al. 2020). In other cases, the treatment is usually started with a symptomatic therapy, since there is no consensus about an antibiotic therapy in childhood (Klimek et al. 2019). This is due to the fact that in some patients with CPR, the pathogen of infection is not detected and that a long-term use of antibacterial drugs can lead to dysbiosis, allergies and other side effects (Drago et al. 2019).

Conclusion

Today, the frequency of chronic rhinosinusitis increases exponentially, which makes the question of the modern approach to its treatment the most relevant. An antibiotic therapy, which has long been the main method of treatment, is inferior to the introduction of drugs using nebulizers. It is possible that additional research in this area will solve the questions of both the optimal path of therapy and treatment of CPR in children.

Conflict of interest

The authors declare no conflict of interest.

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