

ПРИНЦИПЫ МЕДИКАМЕНТОЗНОГО ЛЕЧЕНИЯ ОСТРОГО БАКТЕРИАЛЬНОГО РИНОСИНУСИТА: ОТ ДОКАЗАТЕЛЬНОЙ МЕДИЦИНЫ К ПРАКТИКЕ

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Проблема лечения острого риносинусита (ОРС) в связи с широкой распространенностью является крайне актуальной. По данным статистики, заболеваемость ОРС составляет от 6 до 15% населения и не имеет тенденции к снижению. Эти цифры обусловлены высокой частотой острой респираторной вирусной инфекции (ОРВИ), которая напрямую способствует развитию риносинусита. Однако, несмотря на то, что практически каждый человек переносит от 2 до 5 эпизодов ОРВИ в год, из них только 0,5-2,0% осложняются острым бактериальным риносинуситом (ОБРС). При таком низком проценте бактериальной инфекции в 80% случаев назначаются системные антибактериальные препараты, что усугубляет проблему бактериальной резистентности в современном мире. Основная сложность в определении тактики лечения ОБРС заключается в отсутствии достоверных методов дифференциальной диагностики вирусной и бактериальной этиологии заболевания. По причине невысокого уровня чувствительности и специфичности ни один из дополнительных визуализирующих методов диагностики ОБРС, таких как рентгенография, ультразвуковая диагностика, компьютерная томография не используется рутинно в амбулаторных условиях. Таким образом, основным методом дифференциальной диагностики вирусного и бактериального ОРС по-прежнему остается анализ клинических данных, что приводит к высокой частоте диагностических ошибок и полипрагмазии.

На сегодняшний день на фармакологическом рынке существует большое количество групп препаратов для лечения ОБРС. В выборе тактики лечения западные коллеги опираются, в основном, на требования доказательной медицины. Российские ученые помимо принципов доказательной медицины учитывают патогенетические закономерности развития болезни. В статье представлены различные группы препаратов для лечения ОБРС. Некоторые из них пока не могут удовлетворять требованиям доказательной медицины, но включены в Российские стандарты и применяются для терапии ОБРС.

Ключевые слова: острый риносинусит, бактериальная инфекция, доказательная медицина.



PRINCIPLES OF DRUG THERAPY FOR ACUTE BACTERIAL RHINOSINUSITIS: FROM EVIDENCE-BASED MEDICINE TO PRACTICE

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The problem of treatment of acute rhinosinusitis (ARS) is extremely important due to high prevalence of the disease. According to statistical data the ARS affects from 6% to 15% of population and does not show any tendency to reduction. These figures are associated with a high rate of acute respiratory viral infection (ARVI) which directly leads to rhinosinusitis. But, however, despite the fact that practically every individual experiences from 2 to 5 episodes of ARVI every year, only 0.5-2% of them are complicated with acute bacterial rhinosinusitis (ABRS). Despite this low percentage of bacterial infection, in 80% of cases systemic antibacterial treatment is prescribed which further worsens the problem of bacterial resistance in the world. The main difficulty in determination of therapeutic approach to ABRS is associated with absence of reliable methods of differential diagnostics of viral and bacterial etiology of the disease. Because of low sensitivity and specificity, none of additional visualization methods of ABRS diagnosing such as radiography, ultrasonography, computed tomography, can be used as a routine laboratory method. Thus, the main method of differential diagnostics of viral and bacterial ARS remains analysis of clinical data which leads to a high rate of diagnostic errors and to polypragmacy.

Nowadays there exists a wide range of medications for treatment of ABRS in the pharmacological market. The choice of therapeutic approach by our international colleagues is mostly based on the requirements of evidence-based medicine. Russian scientists, besides evidence-based medicine principles take into account the pathogenesis of the disease.

In this article different groups of medications for treatment of ABRS are presented. Some of them do not meet the requirements of evidence-based medicine so far, but they are included to the Russian standards and are used for management of ABRS.

Keywords: *acute rhinosinusitis, bacterial infection, evidence-based medicine.*

The problem of treatment of acute rhinosinusitis (ARS) is important in otorhinolaryngology. In Russia inflammation of paranasal sinuses (PNS) is the leading cause for referral for medical help [1]. According to

European standards EPOS 2012 the incidence of ARS among population is 6 to 13% and does not show any tendency to reduction [2].

By etiopathogenesis and severity of clinical manifestations of the nose and PNS

there are distinguished ARVI, acute postviral rhinosinusitis (APVRS) and acute bacterial rhinosinusitis (ABRS) [2]. However, ARS of bacterial origin develops only in 1-2% of cases of ARVI and only in 0.5-2.0% of patients with APVRS [3].

The main difficulty in diagnosing ABRS consists in the absence of reliable methods of differential diagnosis of viral or bacterial etiology of the disease which is of primary significance for defining a therapeutic approach. Because of low sensitivity and specificity none of visualization methods such as radiography, ultrasonography, computed tomography can be used as a routine method of laboratory examination in outpatient clinics [4]. For diagnosing ABRS the following temporary criteria are proposed:

- persistence of symptoms of the disease for more than 7-10 days;
- appearance of the “second waves” of symptoms after the 5th day of the disease [2,4].

Infectious Diseases Society of America (IDSA) proposes the third criterion: beginning of the disease with the evident symptoms (fever > 39°C and purulent nasal discharge) persisting within 3-4 days after the onset [5]. Thus, the analysis of clinical data still remains the main method of differential diagnosis of viral and bacterial ARS. Here, an important criteria is duration of the disease.

Improvement of the therapeutic approach to patients with ABRS still remains an actual and unsolved task because of a wide spread of the given pathology and difficulty of identification of the etiological factor, and on the basis of clinical symptoms the correct diagnosis can be made only in 50% of cases [3,6].

According to EPOS 2012 document, from the point of view of evidence-based

medicine only systemic antibiotics, peroral glucocorticosteroids (GCSs) in combination with antibiotics, intranasal GCSs (InGCSs) and nasal douching with saline are recommended for treatment of acute rhinosinusitis of bacterial etiology (that is, they have the highest level of evidence Ia and the level of recommendation A) [2]. Here, the nasal douching is attractive due to its harmlessness, it is undoubtedly used in combined treatment, but practically is not considered a monotherapy for ABRS. In the meanwhile Russian otolaryngologists rely on Russian regulations in their practical activity, and besides clinical recommendations, are guided by standards of rendering medical assistance established by Ministry of Health of Russian Federation. And in this case the evidenced effectiveness of treatment, moreover the results of treatment published in the International guidelines, recede into the background.

Taking into account the above, the aim of the present work was to analyze and generalize information about the main groups of medications used in treatment for ABRS.

It is clear that in treatment for any bacterial disease including ABBR, the leading remedy is systemic antibiotic therapy indicated in severe and moderately severe infectious process [7-9]. Due to difficulties in identification of etiology of ABRS and absence of reliable additional diagnostic methods, systemic antibiotic therapy in most cases is prescribed empirically, that is, on the basis of the suggested structure of a causative agent [8]. At present, taking into account etiological factor and antibiotic resistance, most promising medications for treatment of ABRS in Russia are amoxicillin, amoxicillin clavulanate, 14-, 15-, 16-member macrolides and respiratory fluoroquinolones [8,9]. Even despite a high frequency of spontaneous reco-

varies in more than 50% of cases, it is recommended to administer antibiotics in ABRS which accelerates the recovery [10]. However, much importance is given to criteria of identification of patients with evident clinical symptoms, with increased concentration of C-reactive proteins and accelerated ESR. Necessity of earlier administration of antibiotic therapy is emphasized in case of proven bacterial nature and severe course of the disease to prevent probable complications and progression of the process into a chronic form.

At the same time in non-severe cases of ABRS watchful waiting is admitted – delayed administration of antibiotics after 5-7 days of persistence or worsening of symptoms with the adequate symptomatic therapy [8]. This approach is especially justified taking into account a high rate of spontaneous recoveries from this nosology. It was found that delayed antibiotic therapy in case of a non-severe non-complicated course of ABRS does not promote development of complications and progression into a chronic form [5,11].

Undoubtedly, ABRS is an infectious disease, but at the same time it is an inflammatory condition of mucosa of the nasal cavity and of paranasal sinuses accompanied by a bacterial infection. There exists an opinion that control of inflammation may alleviate many symptoms of rhinosinusitis and also facilitate elimination of the infectious agent [12]. So, does it mean that ABRS can be cured without antimicrobial therapy, just by management of inflammation? It is an argumentative issue. But, nevertheless, it is known that acute rhinosinusitis even of bacterial origin in most cases passes away by itself without any treatment, not saying a word about antibacterial treatment. According to the data of placebo-control study, frequency of spontaneous recovery is rather high and

ranges within 50-70% [13]. Research was conducted that showed that treatment of non-severe forms of ABRS with antibiotics has no advantages over placebo treatment [14]. So, there exists a possibility to facilitate recovery from acute bacterial rhinosinusitis using anti-inflammatory therapy.

In view of the above, of extreme importance in treatment for acute bacterial rhinosinusitis is action on the key processes of inflammation of the mucous membrane of the nasal cavity and paranasal sinuses. Medications possessing a pronounced anti-inflammatory effect are GCSs. They suppress all stages of the inflammatory process. On the basis of evidence of their effect they are widely indicated for ARS of any etiology [2,4,6]. Their systemic application is disputable whereas topical preparations are used ubiquitously. At present systemic GCSs are rather rarely used in ARS and are practically not used in Russia. Steroid phobia in our country both in patients and in doctors is probably associated with numerous side effects of steroid therapy. However, the majority of these undesirable drug-related reactions are associated with long-term therapy of chronic infections, while short sessions not longer than two weeks are sufficiently safe [15]. These preparations are mostly used in severe forms of ABRS to reduce the evident inflammation and pain syndrome [2,15].

Topical corticosteroid therapy has been widely used for a long time in treatment for acute rhinosinusitis including bacterial ones. An intranasal glucocorticosteroid (InGCS) certified for treatment of ARS in Russia is mometasone furoate (MF). Even long-term application of MF is proven to be safe, and its use is not associated with systemic steroid side effects [16,17]. It was shown by research that use of MF in ARS not only normalizes

mucociliary activity and stimulates repair processes, but also enhances the effect of antibacterial treatment [18]. InGCSs produce an evident anti-inflammatory effect realized through transactivation of glucocorticoid-dependent anti-inflammatory genes and transrepression of pro-inflammatory genes. These processes lead to inhibition of pro-inflammatory cytokines (interleukins-1,3,4,5) [16]. Therapy with InGCSs gives a clinically significant reduction in the inflammation with improvement of drainage and ventilation of the paranasal sinuses and increase in clearance of infectious agents. These effects directly reduce the main symptoms of RS associated with inflammation including nasal congestion, rhinorrhea and facial pain [12,19].

In view of the fact that ABRS is pathogenetically associated with production of a large quantity of secretion that accumulates in the inflammation focus and supports the pathological process, much importance in treatment of patients in our country is attached to mucoactive preparations. Currently in treatment for ARS mucolytics are actively used that reduce viscosity and elasticity of secretion through breakage of intra- and intermolecular disulfide bonds of acidic mucopolysaccharides [20]. Most commonly N-acetylcysteine is used that also possesses mucoregulatory activity increasing secretion of less viscous mucins by goblet cells which reduces adhesion of bacteria to cells of the ciliary epithelium of the mucous membrane of the airways due to enhancement of mucociliary clearance [21].

There exists a significant discordance in the opinions concerning application of mucoactive therapy. Russian otorhinolaryngology does not accept an absolute denial of pathogenetically justified use of mucoactive

therapy in ABRS by European colleagues which is evidenced by absence of this therapy in the international recommendations EPOS 2007 and 2012. This is first of all associated with the fact that EPOS was primarily oriented exclusively on evidence-based medicine whereas at the present moment there does not exist any reliable method that could experimentally confirm effectiveness of mucoactive drugs. Here, international scientists rely only on the data of research (double blind, placebo-controlled, randomized) and ignore the clinical experience in treatment for sinusitis, and according to EPOS 2012 no research of such level has been conducted on adult patients that could permit to make a conclusion about benefits of application of mucoactive drugs in ABRS [2]. On the contrary, Russian authors indicate the necessity to use complex treatment of acute rhinosinusitis [22]. Besides, a number of these preparations are included into Russian clinical recommendations on treatment for ARS [9,23].

As to topical (local) antibiotic therapy, the situation here is not that clear as with use of InGCSs. A question of local application of antibiotics in therapy of ABRS is arguable [18,19]. They are not recommended by international documents EPOS and IDSA, however, in Russia in treatment for ARS preparations are used that contain substances of local antibacterial effect [2,5,9]. In Russian Federation antibacterial drug framycetin is registered for treatment of inflammatory diseases of the nasal cavity and of paranasal sinuses, and also a combined medical drug which, besides antibacterial effect due to neomycin and polymyxin B, also possesses anti-inflammatory and vasoconstriction effects due to dexamethasone and phenylephrine. However, because of absence of evidence base, these drugs are used in treatment for ABRS to a

limited extent as an additional remedy.

Much argument exists around application of nasal decongestants in ABRS. Among them the most popular are oxymetazoline and xylometazoline. According to EPOS they can be indicated only for application in the region of the medium nasal meatus, while use of sprays and nasal drops is not recommended because this can lead to rebound syndrome with enhancement of nasal obstruction [[2]. However, topical vasoconstriction preparations may in the shortest time significantly reduce edema of nasal mucosa, restore nasal breathing and patency of natural junctions of paranasal sinuses which produces a pathogenetically favorable effect on the course of ABRS. We think that one should not forget about the doubtless benefit of short sessions of application of vasoconstriction medical drugs. These drugs, opposite to the international recommendations, are included into Russian clinical recommendations and are used in combinations with other medical drugs for treatment of ABRS with the proven effectiveness [23].

All topical pharmacological prepara-

tions for treatment of ABRS whether sprays or drops, produce a limited effect only in the nasal cavity [24]. This may probably be the main cause of low popularity of topical non-hormonal therapy of ABRS in the international medicine. In opposition to this, Russian otolaryngologists were always interested in therapy of rhinosinusitis with the application point being nasal mucosa. Hence, a wide variety of topical preparations in Russian clinical recommendations.

In summary it should be noted that nowadays there exist many groups of medications for treatment for acute bacterial rhinosinusitis. Some of them so far do not meet the requirements of evidence-based medicine, but they are included into Russian clinical standards and are successfully used for management of acute bacterial rhinosinusitis with good clinical results. Probably, this factor is a cause for a lower antibiotic resistance in comparison with the international parameters [8,25]. Besides principles of evidence-based medicine, it is also important to take into account pathogenetic laws of disease development.

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Дополнительная информация
[Additional Info]

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