Antibiotic therapy for an ENT specialist

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ABSTRACT: The study dedicated mainly to general practitioners of ENTs discusses the principles of antibiotic therapy of the most common diseases that this specialty deals with, namely acute tonsillitis and throat inflammation, acute otitis media (AOM), and acute sinusitis. The most common errors in the antibiotic therapy of these diseases are also presented. The basic antibiotic in streptococcal pharyngitis is and remains oral penicillin administered for 10 days. The basic antibiotic, if it is needed, in AOM and acute sinusitis is amoxicillin in high doses. The most common mistake in antibiotic therapy is to start it with macrolides, especially azithromycin, a "comfortable" antibiotic but with the greatest strength of stimulating drug resistance to all macrolides. Another condition that has been highlighted due to frequency and in this case completely unnecessary antibiotic therapy is subglottic laryngitis in which the basis of treatment are systemic steroids, inhalation adrenaline and possibly inhaled steroids. Practical advice on this type of symptomatic management has been presented.

KEYWORDS: antibiotic therapy, laryngology

Antibiotics constitute one of the greatest discoveries in medicine. However, exponential growth in antibiotic resistance was observed in recent decades due to the drugs being used for no reason in viral infections, treatments lasting too long and employing doses being too small and, last but not least, antibiotics being used e.g. in animal farming.

The problem has become an important and difficult challenge for medicine today due to the real threat that an efficient weapon against bacterial infections would be lost and all consequences of this fact would have to be faced [1].

For us, physicians pursuing their ENT practice in an outpatient setting, it is particularly dangerous to live in the false belief that antibiotic resistance is something that belongs to the hospital world as antibiotic resistance is observed increasingly often not only in nosocomial, but also in community-acquired infections.

We must be aware of the fact that the more frequently the antibiotics are prescribed, the faster is the rise in the resistance. Excessive use of antibiotics, not no mention their misuse, is due to the lack of expertise or will to differentiate a viral infection from a bacterial one.

With this regard, mastering information provided in Table I may be particularly useful.

WHEN AND HOW TO USE ANTIBIOTICS IN THE ENT PRACTICE

Most common mistakes

Pharyngitis

Most mistakes are made in relation to the treatment of pharyngitis.. Many of us seem to forget that most pharyngeal infections, regardless of patient's age, are of viral origin. Viral infections account for 70–85% of cases of acute pharyngitis and tonsillitis in children above the age of 3 as well as for 90–95% of cases of the disorder in adult patients [2, 3]. The remaining 15–30% of pediatric infections and 5–10% of adult patient infections are caused by group A beta hemolytic streptococci (GABHS) (Streptococcus pyogenes), other bacterial species being an extreme rarity [4, 5].

Bacterial origin of acute pharyngitis and tonsillitis (APT) may be indicated by sudden, acute onset of the disease, strong throat pain accompanied by difficulty in swallowing, fever (>38°C) and, in some cases, nausea, vomiting, and abdominal pain. Manifestations seen in physical examination include vivid-red pharyngeal mucosa and tonsillar swelling, vivid-red, swollen palatine uvula, palatine mucosal ecchymoses, fibrin coating in tonsillar crypts, tongue coating followed by scarlet, raspberry tongue, submandibular lymph node enlargement and tender-

Tab. I. Clinical differentiation of viral and bacterial respiratory tract infections.

INFECTION	SYMPTOMS SUGGESTING VIRAL ETIOLOGY	SYMPTOMS SUGGESTING BACTERIAL ETIOLOGY	SUPPLEMENTARY INVESTIGATIONS
Acute pharyngitis	Runny nose Cough	No cough or runny nose, submandibular lymph node enlargement	Streptococcal pharyngeal swab Rapid Group A streptococcal antigen test
Acute otitis media	Duration < 48 hours	On improvement 48 hours after onset Infection in infants below < 1 year of age High fever and vomiting in children	Routinely not required
Acute sinusitis	Duration < 7 days	Symptoms not resolving within 10 days Symptoms worsening within 5–7 days Facial pain and swelling	Routinely not required
Acute subglottic laryngitis	Viral etiology in most cases	Not to be considered	Not required

ness, or, in some cases, skin rash resembling that observed in scarlet fever. Three scales were developed to estimate the probability of streptococcal etiology of APT, with Centor/McIsaac scale being the most applicable one in pediatric as well as adult patients (Tab. II). Total score is indicative of potential need to introduce antibiotic therapy and order microbial diagnostic examinations. 0–1 points: no action required; 2–3 points: bacterial screening (swab or rapid test) recommended; 4 points: antibiotic therapy, possibly with simultaneous diagnostic examination; discontinuation of antibiotic therapy recommended in case of negative results.

Pharyngeal swab culture remains a gold standard in microbial diagnostics of streptococcal APT. The culture allows to perform antibiotic susceptibility testing. Only macrolide antibiotics have to be taken into account in the testing, since no resistance of group A streptococci to beta-lactams was observed. Antibiotic susceptibility testing is warranted in patients with the history of hypersensitivity to cephalosporins or type I hypersensitivity reactions to any other beta-lactam antibiotic. Rapid immunoenzymatic assays are also used in diagnostics.The idea behind the use of antibiotics in APT is to eradicate the microbial pathogen and to prevent any complications of untreated bacterial infection. Notably, virulence of S. pyogenes is extinguished 24 hours after effective antibiotic therapy has been initiated.

Oral phenoxymethylpenicillin is the antibiotic of choice in streptococcal APT:

- In adults and children with body weight of above 40 kg: 2,000,000–3,000,000 IU/day in 2 split doses for 10 days; in children with body weight below 40 kg: 100,000–200,000 IU/kg/day in 2 split doses for 10 days;
- In cases of non-compliance or difficulties with oral administration of antibiotics, intramuscular benzathine benzylpenicillin: in adults and children with body weight above 40 kg: single dose of 1,000,000 IU; children with body weight below 40 kg: single dose of 600,000 IU.

Adjusted APT treatment in patients with a history of hypersensitivity to penicillins (excluding immediate-type reactions) and in Streptococcus pyogenes carriers:

- cefadroxil administered once daily for 10 days at a dose of:
  – In adults and children with body weight of above 40 kg: 1 g in children with body weight below 40 kg; 30 mg/kg
- Cefalexin: twice a day for 10 days at a dose of:
  – adults: 500 mg p.o. twice a day;, children with body weight below 40 kg: 25–50 mg/kg/day; children with body above 40 kg 25–50 mg/kg/day (max. 1000 mg/day).

With regard to macrolides, current guidelines [1] allow their use only in patients with immediate hypersensitivity to beta-lactams, at doses listed in Table III.

Another challenge for an ENT practitioner consists in the treatment of recurrent APT which may be caused by broadly understood lack of efficacy of the previous episode of treatment, including patient non-compliance, treatment duration being too short, inappropriate choice of drug, presence of beta-lactams-producing pathogens, as well as reinfection from a repeated exposure [1]. Recommended treatments of recurrent pharyngitis are presented in Table IV.

Besides redundant antibiotic therapy, the most common mistake in the treatment of pharyngitis is the use of macrolides as first-line drugs, since an increasing number of Polish streptococci is resistant to these drugs (in 2015, about 15% of *S. pyogenes* strains were resistant to macrolides (www.korld.edu.pl); today this percentage is approaching 20%) [1, 6]. Azithromycin, while considered to be very convenient in use, is simultaneously, due to its unique pharmacokinetics and pharmacodynamics, the strongest stimulator of resistance, and is therefore particularly not recommended [7]. Azithromycin is very shortly available at sufficient concentrations within the extracellular

matrix providing the environment for GABHS as well as other bacteria such as pneumococci, hemophilic bacilli, Moraxella, etc. (in contrast to long intracellular availability accounting for large volume of distribution). As a result, long periods of drug concentrations being maintained at just above MIC result in a long selection window facilitating development and proliferation of resistant strains.

A similar, albeit slightly better situation is observed for clarithromycin, roxithromycin and the best but the least commonly used erythromycin. Nonetheless, these antibiotics also lead to the development of resistant species, with the likelihood of their efficacy being gradually reduced over time. One should always keep in mind that 100% of S. pyogenes strains are still, in manner unchanged for many years, susceptible to penicillin [8, 9, 10]. One should also remember that only penicillin had been proven to prevent rheumatic fever [11, 12].

Another not uncommon mistake consists in amoxicillin being used in the treatment of streptococcal pharyngitis. Although amoxicillin is effective against the streptococcal strain, its spectrum is too broad and therefore unnecessarily stimulates the resistance of bacterial species quite commonly prevalent within the nasopharynx, particularly in pediatric patients; these include S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, or Staphylococcus aureus.

Another common mistake consists in using co-trimoxazole as a mild antibiotic agent since the drug has no efficacy against GABHS [1]; in addition, it is currently inefficient against most other supradiaphragmatic infections, with the exception of *Pneumocystis Pneumonia.*

Attempts at treating streptococcal pharyngitis with amoxicillin and clavulanic acid are a sign of complete miscomprehension on the side of the physician. As GABHS do not produce beta-lactamases, their inhibition is absolutely unnecessary while creating a risk of adverse events and resistance resulting in our losing future possibilities for using an antibiotic tool of well-established efficacy.

With regard to cephalosporins, although eradication efficacy was demonstrated for cefuroxime axetil [13, 14, 15] to even exceed that of penicillin, the use of an antibiotic characterized by such a wide spectrum and potential for selection of resistant strains of other pathogens in a treatment course lasting four to five days appears tempting yet unjustified.

In fact, in cases of GABHS infections, cefadroxil [16, 17, 18, 19] and cephalexin are the only cephalosporins which may be used in this treatment, albeit not as the first-line antibio-

Tab. II. Centor/McIsaac score of the probability of S. pyogenes infection [4, 5].

PARAMETER	SCORE
Fever of > 38°C	1
No cough	1
Anterior cervical lymph node enlargement	1
Fibrin coating and tonsillar swelling	1
Age of 3-14 years	1
Age of 15-44 years	0
Age of >45 years	-1

tics. Both drugs have the advantage of relatively narrow spectrum, established efficacy and ability of being administered once or twice a day.

Acute otitis media

Acute otitis media (AOM) is also one of diseases frequently treated with unnecessary and misadministered antibiotic therapy. It develops in 50–85% of children below the age of 3 years, with peak incidence between 6 and 12 months [20]. About 30% of AOM patients present for medical consultation; the disorder is the most common cause of medical advices given to patients below the age of 3 [21]. Despite the watchful waiting strategy consisting of symptomatic treatment and follow up being widely propagated [1], these consultations frequently lead to antibiotics being prescribed "just in case".

According to 2016 Recommendations [1] indications for immediate antibiotic therapy in AOM in children include:

- age of less than 6 months;
- high fever and vomiting;
- bilateral otitis media in a child below 2 years of age;
- ear effusion.

Watchful waiting and no antibiotic administration are recommended in the remaining cases of non-complicated AOM.

Due to the important role played in the etiology of bacterial AOM by pneumococci and Haemophilus influenzae (most strains in Poland still remain susceptible to amoxicillin), the first line of treatment should include amoxicillin [1] administered at the following doses:

- adults and children with body weight above 40 kg: 1500–2000 mg every 12 hours;
- children with body weight below 40 kg: 75–90 mg/kg/d in two daily doses.

Tab. III. Dosage of macrolide antibiotics in APT.

ANTIBIOTIC	ADULTS AND CHILDREN WITH BODY WEIGHT OF ABOVE 40 KG	CHILDREN WITH BODY WEIGHT BELOW 40 KG
Erythromycin	0.2–0.4 g every 6–8 h for 10 days	30–50 mg/kg/day in 3–4 split doses for 10 days
Clarithromycin	250–0.4 g every 12 h for 10 days	15 mg/kg/day in 2 split doses for 10 days
Azithromycin	500 mg in a single dose on the first day followed by 250 mg/day on days 2–5	12 mg/kg/day in a single dose on the first day followed by 6 mg/kg/day on days 2–5

Tab. IV. Treatment of recurrent streptococcal pharyngitis.

CAUSE	ADULTS AND CHILDREN WITH BODY WEIGHT OF ABOVE 40 KG	CHILDREN WITH BODY WEIGHT BELOW 40 KG
Recurrence due to non-compliance	Benzathine benzylpenicillin 1,200,000 IU in single intramuscular injection	Benzathine benzylpenicillin 600,000 IU in single intramuscular injection
Recurrence due to inefficient penicillin treatment in a S. *pyogenes* carrier	Cefadroxil 1 g once daily for 10 days	Cefadroxil 30 mg/kg once daily for 10 days
Recurrence due to unspecified reason	Clindamycin 300 mg every 8 h for 10 days	Clindamycin 20–30 mg/kg/day in 3 split doses for 10 days

The duration of treatment of uncomplicated acute otitis media may be shortened to 5 days in adults and children above the age of 2 years; in children below the age of 2 years, treatment duration should be 10 days.

Other antibiotics should be used only in the following circumstances:

- delayed type hypersensitivity reaction to amoxicillin: cefuroxime axetil or, in more severe cases, ceftriaxone.
- delayed type hypersensitivity reaction to all beta-lactams or immediate hypersensitivity reaction to any beta-lactam: macrolide.

What are the most common mistakes made with regard to antibiotic treatment of AOM?

In a manner similar to streptococcal pharyngitis, some physicians, including ENT practitioners, still prescribe co-trimoxazole which is basically completely ineffective against basic pathogens involved in otitis media (pneumococci, Haemophilus influenzae, Moraxella catarrhalis). Cases of therapeutic success frequently cited as an argument for continued use of this agent may be currently ascribed solely to the not-so-rare spontaneous resolution of the disease.

Another quite common mistake consists in the treatment being started with macrolides, particularly azithromycin which is considered convenient in application. The activity of macrolide antibiotics against pneumococci and *Haemophilus influenzae* is not too high while selection of resistant strain may be used as a model example.

Another mistake consists in amoxicillin with clavulanic acid being used as the first-line antibiotic. The addition of clavulanic acid to amoxicillin is of no importance in the case of one of the most common causes of AOM, i.e. pneumococcal infection (as pneumococci do not produce beta-lactamases) whereas less than 10% of Polish strains of H. influenzae is resistant to amoxicillin alone [1]. Moraxella catarrhalis, although in nearly 100% of cases being a beta-lactams producing species, is a very rare cause of AOM and there is always time for any potential corrections to the treatment regimen.

Acute rhinosinusitis

Acute rhinosinusitis (previously referred to as acute sinusitis) is an inflammation of nasal cavities and sinuses, characterized by sudden onset and lasting not more than 12 weeks.

Acute rhinosinusitis is caused by viral infections, particularly by infections with rhino- and orbiviruses, RS viruses, influenza and parainfluenza viruses, and adenoviruses. Bacterial infection develops from viral rhinosinusitis in as few as 0.5–2% of cases [22]. In most cases, bacterial rhinosinusitis is caused by S. pneumoniae and H. influenzae [23, 24]. Other microbial strains are responsible for less than 20% of bacterial infections; these include anaerobic bacteria, M. catarrhalis, S. aureus, and non-pneumococcal streptococci [24].

It is assumed and recommended in current guidelines [1] that potential bacterial infection (superinfection) should be considered when rhinosinusitis symptoms are maintained for more than 10 days and when clinical condition of the patient deteriorates after 5 days despite symptomatic treatment.

Therefore, the use of antibiotics in acute rhinosinusitis is recommended only in the following cases:

- *severe course of the disease determined by the intensity of maxillofacial pain and fever of above 39℃;*
- *no improvement after 7–10 days of symptomatic treatment;*
- *symptoms of worsening following earlier clinical improvement;*
- *development of complications.*

The antibiotic of choice in the treatment of bacterial rhinosinusitis is high dose amoxicillin administered over 10 days.

Second-line treatment of acute rhinosinusitis should include amoxicillin and clavulanic acid, particularly following a failure of previous amoxicillin treatment.

In cases of non-immediate hypersensitivity reactions to penicillins, cefuroxime axetil should be used.

In cases of immediate hypersensitivity to beta-lactams, macrolide antibiotics are recommended.

Individual mistakes made with regard to antibiotic treatment of acute rhinosinusitis are the same as in the case of AOM, with antibiotics being misused and administered beforehand even more frequently, particularly in pediatric patients.

Acute subglottic laryngitis (croup)

It should be highlighted from the very start: one should nearly completely forget about antibiotics when treating this disease!

Acute subglottic laryngitis, commonly referred to as croup, is an acute viral infection of the upper respiratory tract. Inflammation causes swelling of the mucosal membrane lining the pharynx, larynx, and trachea, which disturbs air flow and is manifested by stridor, cough, and coarse throat. Although subglottic laryngitis is in most cases a self-restricted disease, severe shortness of breath in small children may be life-threatening and thus require urgent treatment.

Symptoms of croup are diagnosed in about 15% of children reporting at practices due respiratory tract infection; annual incidence is estimated at 2–6 cases per 100 children [25, 26]. According to the epidemiological data, subglottic laryngitis is most common in children between 6 months and 6 years of age, with peak incidence at the age of about 2 years [27]. However, isolated cases were reported in both younger children (3 months of age) and adolescents. The disease is prevalent in the fall/winter season, and a predominance of male patients (3:2) has been observed [28].

Since vaccinations against Corynebacterium diphtheriae beca-

me obligatory (delivered together with anti-tetanus and anti-pertussis vaccination as part of DTP vaccine), the etiology of the disease is nearly exclusively viral. One should keep in mind however, that a broader definition of croup, including the disease of bacterial origin (S. aureus, S. pneumoniae, M. catarrhalis, M. pneumoniae), epiglottitis caused by H. influenzae, and even an allergic component, is in use in some studies, particularly in the literature published in English. Current management guidelines pertain only to the disease of viral etiology. It includes parainfluenza viruses (mainly of type I), responsible for nearly 75% of cases. However, symptoms of subglottic laryngitis may be evoked by virtually any viruses attacking the respiratory tract, including adenoviruses, rhinoviruses, enteroviruses, RSV, and flu viruses. One should also keep in mind that measles combined with influenza virus type A may be responsible for severe course of the disease [29].

Diagnosis is made on the basis of clinical presentation only [30]. At the initial stage of the disease (12–72 hours), the predominant symptoms are those of upper respiratory tract infection: elevated body temperature, nasal and sinus mucositis (presence of serous or mucoserous secretion in nasal passages). Next, swelling of pharyngeal, laryngeal, tracheal, and even bronchial mucosa is observed in the course of the disorder. The patency of respiratory tract becomes significantly impaired leading to characteristic symptoms of air flow turbulences. These include coarse throat, inhalatory stridor, harsh coughing, wheezing and shortness of breath, manifested by accelerated breathing rate, visible nasal wing movements and intercostal recession. Symptoms exacerbate at night as well as during cries or anxiety periods.

In most cases, the characteristic clinical presentation is sufficient for the diagnosis, with **no rationale for supportive investigations.** Primary treatment of subglottic laryngitis consists of systemic glucocorticosteroids; their efficacy has been confirmed in numerous randomized clinical studies. Their anti-inflammatory and decongestant activities reduce the swelling within the respiratory tract and lower the risk of recurrent obstruction. It is recommended that each patient presenting with symptoms of croup receives dexamethasone in a single dose of 0.15–0.6 mg/kg body weight. Such a wide dose range is due to the ambiguity of studies on the differences in the efficacy of these doses or, more precisely, on the lack of such differences. Some authors of global guidelines recommend 0.15 mg/kg of body weight – in mild croup, 0.3 mg/kg of body weight in moderate croup, and 0.6 mg/kg of body weight in severe croup. No maximum safe dose of dexamethasone has been established; however, it appears that it should not exceed 8 mg [31]. None of the application routes is superior to the other, with oral and intramuscular administration being equally efficient and the onset of the effect being observed 30 minutes after administration.

Intramuscular route is preferred in case of severe disease accompanied by severe shortness of breath and swallowing disorders, particularly in younger children. This is due only to reasons associated with the reliability of dose administration rather than the efficacy or time to the onset of treatment effect. Oral route is preferred in other cases, for reasons including ease of administration (e.g. in primary health care setting) and low cost. **An alternative for dexamethasone p.o. is provided by prednisone/prednisolone p.o. at a dose of 1 mg/kg body weight.** Clinical studies revealed no need for repeated doses of steroids being administered. If the patient appears to require such repeated administration of the drug, another cause of symptoms should be taken into consideration.

In Poland, dexamethasone is available in oral formulation only as 0.5 mg or 1 mg tablets, with no oral suspension products being available. This requires several tablets being swallowed at the same time, which is not accepted by a large part of pediatric patients. On the other hand, oral prednisone, despite being available at convenient dose strengths (1 mg, 5 mg, 10 mg, 20 mg) is particularly bitter in taste. These factors are probably the cause of intramuscular dexamethasone being frequently chosen.

Another key drug used in the treatment of subglottic laryngitis is **nebulized adrenaline (epinephrine)** which should be administered in severe disease at the same time or prior to steroid administration. The onset of adrenaline's effect is observed within 30 minutes from administration (usually after 10 minutes); it is maintained for 2 hours and therefore may be used as a platform for relief being provided until the maximum effect of glucocorticosteroids takes hold. The dose of racemic adrenaline 2.25% is 0.05 ml/kg of body weight (max. 0.5 ml) and should be administered following dilution in 0.9% NaCl. **Adrenaline 1:1000** (L-epinephrine 0.1%), much more available (and much less expensive) in most European countries **should be administered at a dose of: 0.5 ml/kg of body weight (max. 5 ml).** If no improvement is observed, or if symptoms recur, nebulization may be repeated. The requirement of > 2 adrenaline nebulizations is an indication for hospitalization. Adrenaline is a relatively safe drug characterized by short half-life. Most important adverse effects include temporary increase in the heart rate and paleness. The only contraindication consists in cardiac defects involving ventricular outflow tract obstruction (e.g. tetralogy of Fallot).

In Poland, adrenaline is available only as 0.1% L-epinephrine for single administration at a maximum dose of 0.5 ml/kg of body weight (max. 5 ml). The only marketed product consists in 1 ml ampoules (1 mg/ml), and therefore as many as 5 ampoules may have to be used for nebulization.

Nebulized administration of glucocorticosteroids is not superior to systemic administration (studies were conducted using budesonide mostly). It is, on the other hand, burdened by the risk of child's non-compliance and insufficient deposition at target location. The number of possible errors committed in the course of nebulization session (e.g. incomplete mask fitting) may lead to a failure in the delivery of as much as more than one half of the dose. Nebulized glucocorticosteroids are also more expensive. The recommended dose of nebulized budesonide is 2 mg, with time to the onset of drug effect of about 30 minutes. No benefits of repeated administration of nebulized steroid could be demonstrated. Combinations of systemic and inhaled glucocorticosteroids are not supported by scientific evidence and may only increase the risk of adverse effects.

In Polish conditions, 2 mg of budesonide corresponds to 4 ml of nebulization product containing budesonide at a dose of 500 µg/ml (2 containers).

As in the case of all disorders involving increased respiratory rate and fever, dehydration must be always taken into account. **Appropriate supply of fluids is an integral part of the treatment; most patients require only oral hydration.**

If the symptoms are accompanied by elevated body temperature, antipyretic agents such as **ibuprofen or paracetamol** should be used at body weight-adjusted doses.

Passive oxygen therapy is recommended only in patients with severe croup and O2 saturation levels of less than 90–92%.

In individual cases of severe subglottic laryngitis caused by the influenza virus, neuraminidase inhibitors (oseltamivir) may be considered.

Clinical studies and meta-analyses provide no support for non-pharmacological treatment consisting in inhalation of moist air (or nebulized physiological saline solutions). This method, which had been used for more than two centuries, does not improve the condition of the patient in the acute stage of the infection while delivering some subjective benefits in infection-related cough [32]. However, one should keep in mind that home inhalations of steam generated by boiling water is associated with the risk of burns to the patient's skin and respiratory tract.

No sufficient data are available to recommend breathing mixtures of helium and oxygen for a reduction in air flow turbulence within the respiratory tract.

Sedatives, expectorants, or antitussive agents are not useful in the treatment of croup.

Due to the etiology of the disease, **there is no rationale for antibiotic therapy;** this should be particularly highlighted since such "protective" treatment is continued to be offered, including in ENT clinics!

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