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Antimicrobial therapy of upper respiratory tract infections in children

Respiratory tract infections, in spite of great therapeutical successes and progress in diagnosis, still represent a serious medical problem. It is still impossible to treat such infections effectively or eliminate the pathogenic strains causing them.

Among factors responsible for infections the leading one is common and inappropriate usage of extended spectrum antimicrobials. Thereby, the changes in respiratory tract microflora are more often observed. That situation also leads to spread of antibiotic resistant pathogens, and as a consequence, to reduction or elimination of one drug from treatment (1, 8).

It is known that the best stimulus for immune system and prevention from egzogenic infections is the comensal flora. Besides, the upper respiratory tract is settled by opportunistic bacteria, that, in condition of impairment of host defence mechanisms (for example as a result of long lasting antibiotics use), could cause the endogenic infection.

The bacterial aetiologic agents of upper respiratory tract infections, mainly in children, are: *Staphylococcus aureus,* β-haemolytic streptococci of different serological groups – B, C, G, *Streptococcus pyogenes* and opportunistic bacteria, that could be present at pharyngeal physiologic flora: *Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, Moraxella catarrhalis,* G (-) rods from the *Enterobacteriaceae* family and G (+) cocci (2, 3, 9, 13).

Upper respiratory tract infections appear mainly in people with different dysfunctions of the immune system. No wonder, that this kind of infection frequently happens to the children and to the elderly. Impairment of host defence mechanisms may be the result of medical treatment, viral infections and allergies as well as the effect of environmental factors – malnutrition or airborne environmental pollutants (1, 2, 13, 14).

Infection is initiated with breaking of the respiratory tract epidermal barrier, while the host defence mechanisms are impaired. Then, bacterial pathogens adhere to mucous membranes and colonisation ensures. The pathogenic strains possess the ability to pro-

duce extracellular factors (enzymes and toxins) responsible for pathological changes and to produce factors that defect the immune system functions. The host defence mechanism becomes weakened by neutrophils chaemotaxy and phagocytosis inhibiting, impairment of cytokine release and reduction of macrophages functions. Besides, the bacterial outer structure antigen diversity helps them to avoid effective supervision of the host immune system. Those mechanisms let pathogens avoid the eradication from the respiratory tract and responds for infection strengthen (2, 13).

Otherwise, the healthy human organism possesses high resistance to infections that is acquired as a result of constant contact with pathogens. However, in some cases, the antimicrobial treatment is necessary. If antibiotic does not eradicate the invading microorganisms and successfully interrupt the progress of infection, the patient may develop chronic or recurrent disease (2).

Since the first antibiotic – penicillin was discovered by Fleming, there is observed a continuous race among pharmacists searching for new antibiotics and microorganisms, becoming resistant to their effect. The major function of antimicrobials is to inhibit or damage the essential processes for bacterium life, as cell wall biosynthesis, cytoplasmatic membrane synthesis, protein synthesis, nucleic acids synthesis and metabolism or cell energetic metabolism. The appropriate use of antibiotics should be based on the knowledge of the natural history and most likely pathogens responsible for infection and on the knowledge of local trends and mechanisms of antimicrobial resistance. Candidate drugs should also exceed at the site of infection the minimum inhibitory concentration for 90% of each most likely pathogen (2, 8).

Rational treatment is difficult as most of pathogens once susceptible to antibiotics, are now resistant to them. It is the result of widespread use of antimicrobials, whether appropriate or inappropriate (5). It has been documented that bacteria are able to activate several mechanisms of resistance to one drug, and also reveal the resistance to more antibiotics (8). Major mechanisms of bacterial resistance to antibiotics in upper respiratory tract infections include enzymatic inactivation by hydrolysing or modification of antibiotic structure, prevention from getting the site of action by cell membrane and wall impermeability, alteration at the target site or active pumping out of antibiotic from the bacterial cell (2, 8).

The main aim in today's medicine thus should be proper and effective use of antibiotics (5). The common phenomenon, however, is overprescription of antibiotics. That fact concerns mainly children that receive a significant proportion of drugs, even though the resistance to some of them is clearly evidenced. *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* carry the genes for resistance to majority of the antibiotics currently on the market. Among them, 1/3 of *Streptococcus pneumoniae* strains are resistant to penicillin, about 50% of *Haemophilus influenzae* and all *Moraxella catarrhalis* strains produce β-lactamases. Up to 90% of *Staphylococcus aureus* are resistant to β-lactams and about 30–40% of strains, mainly from critical care areas, are MRSA. Majority of MRSA strains are also resistant to most of other antibiotics. The antibiotics

inducing production of β-lactamases are: penicillin, ampicillin, 1st generation cefalosporins and cefamycin. They are hydrolysed as a result of enzyme action (5, 8, 9, 12).

It should be stressed that emergence and spread of resistance among microorganisms is associated with overuse of the same antibiotics, use of inadequate dosage and interrupting the therapy. The emergency of resistant bacteria strains, in turn, prevents or reduces effective action and the use of antibiotics (8).

In the upper respiratory tract infections the use of extended spectrum antimicrobials contributes to both emergence of resistant organisms and disturbance of the natural biocenosis of organism, by killing pathogens and also bacteria of physiological flora. The most dangerous symptom of that, mainly in young children, is vitamin deficiency – a consequence of symbiotic *Escherichia coli* killing. When natural microflora is infringed, the candidas are developing, mainly *Candida albicans*, responsible for organs candidiosis.

The fact that upper respiratory tract infections are predominantly caused by viruses, is also a limitation for antibiotics prescription. The respiratory syncytial virus (RSV) occurred during most winters, with attack rates approaching 90% in infants. Children, over 2 years of age are commonly infected by adenovirus. The other leading causes of viral respiratory illness are parainfluenzae virus and enteroviruses (7).

Despite these facts, approximately 60% of patients receive antibiotic treatment. So the question is why so many young patients with upper respiratory infections receive them. There are some answers to this question, but commonly it is parental influence on physicians, expecting and asking for antibiotics. According to parents, only with antibiotic the treatment is effective. Many of them do not have accurate knowledge of antibiotics and do not understand the indications for antibiotics and they frequently cannot distinguish an antibiotic from nonantibiotic medicine (5, 7, 15).

The aim of the present work was to estimate paediatrician's preferences in antibiotics prescription and therapy effectiveness in cases of ambulatory bacterial upper respiratory tract infections in children.

MATERIAL AND METHODS

Paediatricians, working mainly at basic medical care centers in the Lublin area, were asked for filling in an inquiry that estimated their preferences to the prescription of antibiotics for children, aged 4–11 years, with upper respiratory tract infections. The medicines were mentioned from the most frequently to the most rarely used in day practice of each physician.

Additionally, we performed microbiological examination for the purpose of determination of treatment effectivity. To this effect, testing was performed two times – at the beginning of the disease and after successful treatment. The materials for our study were

pharyngeal swabs that were incubated onto traditional in microbiology practice agars. The drug susceptibility was tested by disc–diffusion method on Mueller-Hinton agar. The antibiotics were: amoxicillin/clavulanate, ampicillin, erythromycin, penicillin, lincomycin, kotrimoxazol, cefaclor, cefalotin, and cefuroxime.

RESULTS AND DISCUSSION

The inquiry was performed in June and July 1998 in Lublin. From among 159 paediatricians working at that time in the Lublin area, it was filled by 47 persons, working at basic medical care centres.

Cefuroxime, in Poland available as Zinnat and Zinacef, was the most frequently prescribed antibiotic. Cefuroxime is the 2nd generation cephalosporin and it is clinically effective against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and G (+) cocci. It is also effective against producing β-lactamase *Haemophilus influenzae* and *Moraxella catarrhalis*. *Guide to Antimicrobial Therapy* recommends cefuroxime in the cases of bacterial upper respiratory tract infections with epiglottitis, where etiologic agents are *Haemohilus influenzae, Streptococcus pneumoniae, Streptococus pyogenes or Staphylococcus aureus* (6).

Other antibiotics were prescribed more rarely – amoxicillin (78.7%) and cefradoxil (72.3%). It should be stressed that amoxicillin is not effective clinically against *Staphyloccus aureus* and it is usually used in the cases of *Haemohilus influenzae* (4).

Macrolids were prescribed rarely. Among them spiromycin and roxitromycin was recommended in 14.9% of cases, and erythromycin was used only in 6.4% of cases. It is probably the result of commonly existing resistance to that group of drugs among staphylococci (4). Of the currently available macrolides and β-lactams, only daily intramuscular ceftriaxone and amoxicillin/clavulanate are active against more than 90% of respiratory pathogens (9).

The aim of the present study was also to analyse the pathogenic flora in children with upper respiratory tract infections and to determine the treatment effectivity.

Table 1 shows the results of testing 34 ill children and compares them with the results of testing after successful treatment.

As the data show, during infection state, the predominant strain isolated from pharynx was *Staphylococcus aureus* (70.5%). According to authors describing the bacterial flora in sore throat and tonsillitis, the percentage of *S. aureus* strains isolation was 37% and they were frequently present at these sites. In Chylak report, they were in 69% of cases (3). *Staphylococcus aureus* strains may share the responsibility for inflammation state, and with other bacteria producing β–lactamases, contribute to protecting *Streptococcus pyogenes* against penicillin activity (13).

In our work, the second commonly isolated species was *Streptococcus pyogenes,* presented in 14.7% of the examined children. Those findings overlap with Radosz-

Table 1. Results of testing pharyngeal swabs from children with infection and after treatment

Isolated species	Infection (34 children) percentage of isolated strains	Control (31 children) percentage of isolated strains
Staphylococcus aureus	70.5%	55.8%
Moraxella catarrhalis	5.8%	0%
Streptococcus pyogenes	14.7%	2.9%
Haemophilus influenzae	8.8%	9.6%
Haemophilus parainfluenzae	11.7%	20.5%
Enterobacteriaceae	2.9%	0%
Candida albicans	5.8%	44.1%

Control – results after treatment

Komniewska report. In her study *Streptococcus pyogenes* strains were present in 12.5% of cases (13). According to other authors, the percentage of *Streptococcus pyogenes* in respiratory tract infections were about 20% (3, 10).

From the examined material, the haemophilus bacilli (*Haemophilus influenzae* and *Haemophilus parainfluenzae)* were also isolated in 20.5% of cases. The isolation frequency of these bacillifrom patients is various, but as a rule it is high. Difficulty in the assessment of the pathogenic role of that bacterium is the commonly appearing carrier-state mainly in children – 80%, but also in adults – 50% (13). According to some authors, that percentage is 30%–60% (3, 13).

From the clinical specimens, *Moraxella catarrhalis* and *Candida albicans* were isolated at low percentage – 5.8% each. G (+) rods from the *Enterobacteriaceae* family were isolated at the lowest percentage – 2.9%.

After antimicrobial treatment, all children were regarded as healthy. Data obtained after treatment suggest a significant increase in *Candida albicans* isolation (44.1%). Most of people are carriers of *Candida*, but as a result of post antimicrobial therapy and vitamin deficiency, the secondary infection may occur.

Haemophilus influenzae was the second frequently isolated species, beside *Candida albicans*. According to our findings, those bacteria were present in 20.5% of patients. Chylak after treatment showed a minimal fall in isolation of both *H. parainfluenzae* (from 11.5% to 7.6%) and *Haemophilus influenzae* (from 21.5% to 17.3%) (3).

However, in our study in control group (after treatment), we a observed significant fall in isolation of *S. pyogenes* (from 14.7% to 2.9%) and *S. aureus* (from 70.5% to 55.5%). G (+) rods from the *Enterobacteriaceae* family and *M. catarrhalis* were com-

pletely eliminated. The above data suggest the possibility of simultaneous isolation of several microorganisms from the same child and also the existence of carriers.

The antimicrobial therapy caused changes in bacterial flora of pharynx. After treatment the strain responsible for infection, was commonly isolated. Sometimes another species appeared, and sometimes no microorganisms responsible for infection were isolated. Those findings overlap with Chylak report (3). In his study, he confirmed the existence of carriers. The carriers were children that, within five times performed testing, four times possess the same species. The carrier-state concerns mainly *S. aureus.*

The antibiotics were prescribed for children without earlier determination of susceptibility to antimicrobial agents. Bacteria, responsible for infection, were often resistant to prescribed antibiotic (data not shown). Such treatment had an influence on the appearance of postantimicrobial candidiosis, establishment of carrier-state and increasing *S. aureus* MRSA strain (1 case). The resistance among microorganisms, acquired before or during treatment, is the most frequent cause of unsuccessful therapy (8).

Antibiotic prescription thus, should be more rational and always preceded by bacteriological testing of materials from the site of infection. It is impossible to perform antibiogram at the time of physician visiting. The physician starts the therapy empirically, taking into consideration data about most likely pathogens at the site of infection and resistance to antibiotics. But only microbiological analysis is able to establish the actual pathogen and its susceptibility to antimicrobial agents. Those facts are the basis of the proper treatment, ideally by narrowest spectrum antimicrobials (8, 11).

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SUMMARY

Respiratory tract infections still represent a serious medical problem, mainly in people with different dysfunctions of the immune system. That kind of infections frequently occurs in the children and in the elderly. The aim of the present work was to estimate paediatrician's preferences in antibiotics prescription and therapy effectiveness in cases of ambulatory bacterial upper respiratory tract infections in children. Paediatricians working in the Lublin area were asked to fill in an inquiry that estimated their preferences to the prescription of antibiotics in children. Additionaly, the microbiological examinations were performed determining the treatment effectivity. The inquiry was filled by 47 persons. The most frequently prescribed antibiotic was cefuroxime (93.6%), and the macrolids were prescribed rarely. During infection state, the predominant strain isolated was *S. aureus* (70.5%) and *S. pyogenes* (14.7%). After treatment, there was a significant increase in *C. albicans* isolation (44.1%) and *H. influenzae* (20.5%). There was a significant fall in isolation of *S. pyogenes* and *S. aureus*. Antibiotic prescription without earlier determination of susceptibility to antimicrobial agents had an influence on the appearance of postantimicrobial candidiosis, establishment of carrier state and increasing resistance among bacteria.

Antybiotykoterapia w zakażeniach dróg oddechowych u dzieci

Infekcje dróg oddechowych wciąż stanowią poważny problem medyczny, szczególnie u osób z różnego typu dysfunkcjami układu odpornościowego. Na tego typu infekcje w dużej mierze podatne są dzieci i osoby starsze. Niniejsza praca miała na celu poznanie preferencji lekarzy pediatrów w stosowaniu antybiotyków i skuteczności terapii w ambulatoryjnych zakażeniach bakteryjnych dróg oddechowych u dzieci. Lekarze pediatrzy z obszaru Lublina poproszeni zostali o wypełnienie ankiety oceniającej ich preferencje w stosowaniu antybiotyków u dzieci. Wykonano również badania mikrobiologiczne określające skuteczność leczenia. Ankietę wypełniło 47 lekarzy. Antybiotykiem najczęściej przepisywanym przez nich był cefuroksym (93,6%), natomiast makrolidy przepisywane były najrzadziej. W okresie choroby najczęściej izolowanym gatunkiem był *S. aureus* (70,5%) i *S. pyogenes* (14,7%). Po antybiotykoterapii zaznaczył się znaczny wzrost częstotliwości izolowania *C. albicans* (44,1%) i *H. parainfluenzae* (20,5%). Wyraźnie spadła natomiast liczba *S. pyogenes* oraz *S. aureus*. Przepisywanie leków bez wcześniejszego wykonania antybiogramu miało wpływ na pojawienie się drożdżycy poantybiotykowej, ustalenie się nosicielstwa i narastanie oporności wśród bakterii.