Antibiotic Choices in an Outpatient Community with Acquired Respiratory Tract Infections in Turkey

Türkiye'de Ayaktan Tedavi Edilen Toplum Kökenli Solunum Yolu İnfeksiyonlarında Antibiyotik Seçenekleri

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ABSTRACT

The purpose of this article is to bring up the efficacy of antimicrobials and the therapeutic problems that the antibiotic resistance imposes on clinicians for acute bacterial sinusitis (ABS), acute otitis media (AOM), and outpatient community acquired pneumonia (CAP) in adults in Turkey. The publications associated with respiratory pathogens on which this paper focuses were searched for in both Turkish (Ulakbim and Pleksus) and International (Medline) databases along with the presentations in national congress books related with both microbiology and infectious diseases. Amoxicillin seems to be an incompatible choice in Turkey due to high beta lactamase production either in H. influenzae or M. catarrhalis isolates, although it is very efficient for pneumococci. Amoxycillin clavulanate, extended spectrum cephalosporins (cefuroxime, ceftriaxone, cefotaxime), and respiratory quinolones appear to be more reliable options for ABS, AOM and CAP in Turkey. Countrywide macrolide resistance incidence is around 15% and macrolides should be used with caution. When an atypical component is suspected, either the addition of a macrolide or doxycyclin to beta lactams or using macrolides with caution can be considered in outpatient CAP. Finally, trimethoprim-sulfamethoxazole, and tetracyclines are not suitable alternatives. (Tur Toraks Der 2009;10:86-90)

Key words: Respiratory, infection, community, Turkey

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ÖZET

Bu makalenin amacı antibiyotik direncinin Türkiye'de hekimlere yüklediği tedavi sorunlarını ve antimikrobiyallerin etkinliğini erişkinlerde akut bakteriyel sinüzit (ABS), akut otitis media (AOM) ve ayaktan tedavi edilen toplumda gelişen pnömonilerde (TGP) ortaya koymaktır. Bu yazının odaklandığı solunum patojenleri ile ilişkili yayınlar hem uluslararası (Medline) hem de bölgesel (Ulakbim ve Pleksus) veri tabanları yanında Mikrobiyoloji ve İnfeksiyon Hastalıkları ulusal kongre kitapları kullanılarak araştırılmıştır. Amoksisilin pnömokoklarda oldukça etkin olmakla birlikte, *H. influenzae* ve *M. catarrhalis* izolatlarındaki sık beta-laktamaz üretimine bağlı olarak uygun görülmemektedir. Amoksisilin klavulanat, geniş spektrumlu sefalosporinler (sefuroksim, seftriakson, sefotaksim) ve solunum kinolonları Türkiye'de ABS, AOM ve ayaktan tedavi edilen TGP vakalarında daha güvenilir görülmektedirler. Ülke çapında makrolid direnci % 15'ler civarında olduğundan makrolidler dikkatli kullanılmalıdır. Ayaktan tedavi edilen TGP vakalarında atipik komponentten şüpheleniliyorsa beta laktamlara makrolid veya doksisiklin eklenmesi ya da makrolidlerin tek başına dikkatle kullanılması önerilebilir. Son olarak, bu infeksiyonlarda trimetoprim sulfametoksazol ve tetrasiklinler uygun alternatifler değildir.

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Anahtar sözcükler: Solunumsal, infeksiyon, toplum, Türkiye

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INTRODUCTION

Community acquired acute bacterial respiratory infections in adults are among the most frequent reasons for daily patient visits to clinicians in Turkey [1], which is a large, heavily-populated country at the intersection [point] of Europe and Asia. Acute bacterial sinusitis (ABS) and acute otitis media (AOM), which are usually self-limited diseases, are among the commonest forms of respiratory pathologies. Unfortunately, neither the clinical features nor the diagnostic tools available are sensitive enough to allow the [practicing] physician to make a diagnosis of a bacterial infection with accuracy in these pathologies. This is the main reason for unnecessary antibiotic prescribing and its negative consequences of development of resistance, increased toxicity and increased costs. On the other hand, untreated patients with ABS and AOM have bothersome morbidity and are at risk of developing intracranial and orbital complications and [of] possibly developing chronic sequela [2,3]. Another respiratory infection, community acquired pneumonia (CAP), was historically accepted by Sir William Osler who, in the 1901 edition of his book The Principles and Practice of Medicine, described it as "the most widespread and fatal of all acute diseases" [4]. The majority of CAP patients are treated as outpatients. In fact, the causative agents in CAP are generally very similar to ABS and AOM, and emerging antibiotic resistance in respiratory tract pathogens has long been an important topic for the healthcare community. With the evolving challenges of

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antibiotic resistance, the treatment of respiratory tract infections is not as straightforward as it has been in the past.

ABS, AOM and CAP are the major pathologies that will be considered in this paper on a regional basis. The purpose of this article is not to produce algorithms for this part of the world, but rather to bring up the efficacy of antimicrobials and the therapeutic problems that the antibiotic resistance imposes on clinicians for these frequent infections.

STUDY DESIGN

This article evaluates the frequent community acquired bacterial infections that are treated outside the health care settings in Turkey. The patients in need of hospitalization and their probable causative agents are beyond the scope of this review. The publications associated with respiratory pathogens that this paper focuses on were searched through both Turkish (Ulakbim and Pleksus) and international (Medline) databases along with the presentations in national congress books related with both microbiology and infectious diseases. For the evaluation of the susceptibility trends of invasive Streptococcus pneumoniae (pneumococci) for which Turkey has extensive data, the resistance profiles are obtained by adding the number of isolates detected in the regional studies and cumulative results are achieved. Recent meta-analyses, including pneumococcal studies using the aforementioned methodology, are also taken into consideration [5-8]. But for other respiratory pathogens that have sparse data in Turkey, either the median antibiotic susceptibility profiles or the resistance rates of sister antibiotics (like erythromycin, azithromycin, clarithromycin) are considered to have a thorough understanding.

If an antibiotic is seen to have a resistance trend of less than 10% for all of the probable causative agents in a given infectious pathology, then this drug is accepted as a rational empirical choice. On the other hand if the antibiotic has a resistance up to 20% for any of the etiological agents, then it is concluded to be used in caution. Up to 30% of non- susceptibility was regarded as low priority antibiotic choice and for those exceeding this value is accepted as non-applicable for the empirical basis. When the laboratory data is lacking to offer antibiotic efficacy for the respiratory pathogens, then the clinical trails are considered. Polymicrobial pathologies like aspiration pneumonia or lung abscess is excluded from this review.

MICROBIAL ETIOLOGY

Three species of bacteria account for most of the bacterial isolates in ABS and AOM: Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis [9-11]. All three pathogens now exhibit resistance to commonly prescribed antimicrobials, although resistance prevalences vary considerably throughout the world [12]. Accordingly, pneumoccocci, H. influenzae, Mycoplasma pneumoniae and Chlamydophila pneumoniae are the main causative agents in CAP that does not require hospitalization [13,14].

Pneumococci

Forty percent of the invasive isolates in Turkey is penicillin resistant today and one fifths of the isolates confer high level resistance. Minimum inhibitor concentration 90 (MIC 90) value is 1 mg/L on the whole [5,8,15]. In light of this data, is penicillin no longer the drug of choice for CAP in Turkey? Actually no... A retrospective analysis revealed an intriguing association of late mortality (deaths after 4 days of therapy) in patients infected with pneumococci highly resistant to penicillin (MIC > 4 mg/L). The odds ratio for mortality was 7.1 with a 95% confidence interval of 1.7-30. In the study, there was no association between penicillin MICs < 2 mg/L and mortality [16]. As a general understanding today, penicillin is accepted as an efficient therapeutic modality in suitable doses for the management of nonmeningeal infections when the MIC of the infecting strain is below 4 mg/L [13,17]. One gram of amoxycillin three times daily provides a blood concentration for the 40% of the dosing interval over 2-4 mg/L [18]. This amoxicillin dose efficacy is also confirmed by the clinical studies [19]. The cumulative resistance for cefuroxime in local Turkish studies is around 15% and MIC 90 value for the country on the whole is 2 mg/L[5,8]. If 750 mg of cefuroxim is given for three times daily, the antibiotic offers a blood concentration of 2 mg/L or more for the 50% of the dosing interval [8]. The resistance profiles for third generation cephalosporins are lower than 3% in Turkey [5,6,8]. Similar to penicillin, this is not a real resistance for third generation cephalosporins for nonmeningeal infections [6,13,20].

The cumulative pneumococcal non-beta lactam antibiotic nonsusceptibility rates verified from local Turkish studies are as follows: Trimethoprim-sulfamethoxazole 39%, tetracycline 19%, erythromycin 18%, azithromycin 18%, clarithromycin 10%, ofloxacin 13%, clindamycin 9%, chloramphenicol 5%, rifampicin 1.6%, ciprofloxacin 1%, levofloxacin 2%, moxifloxacin 0%, gemifloxacin 0%, telithromycin 0%, vancomycin 0% [21-37].

H. influenzae and M. catarrhalis

H. influenzae and M. catarrhalis have similar nonsusceptibility profiles in Turkey. The former has a beta lactamase production up to 36% while almost all of the latter produce these enzymes. Beta-lactamase–producing H. influenzae provide resistance to the penicillins as a class, as well as resistance to some of the earlier cephalosporins such as cephalexin and cefaclor. Still, H influenzae remains highly susceptible to many other parenteral and oral cephalosporins, such as cefuroxime and the third-generation cephalosporins, ceftriaxone and cefotaxime, as well as the expanded-spectrum oral cephalosporins, cefixime and cefpodoxime. If M. catarrhalis isolate is the infecting agent, the likelihood that it will be resistant to the penicillins and early cephalosporins is quite high [38]. Accordingly, the efficacy of aminopenicillins is beyond satisfaction for these two pathogens in Turkey due to regional data. On the other hand, ampicillin-sulbactam, amoxicillin clavulanate, quinolones, macrolides, extended spectrum cephalosporins and tetracyclines seem effective for both of the microorganisms (Table 1) [39-55].

Table 1. The antibiotic resistance profiles in M. catarrhalis and H. influenzae in Turkey (The median rate is presented in parentheses)

References	AMP	A-CL	Amp-S	SXT	CFXM	CEC	CFXN	LEVO	CLAR	AZT	TET	Bl-a
M. catarrhalis	6-82	0	0-7	9-87	0	14	0-0	0-0	0	0	9	44-100
(34, 39, 49, 50, 54, 55, 58)	(70)		(4)	(17)			(0)	(0)				(76)
H. influenzae	8-34	0-11	0-13	5-35		1-5	1	0-0	2-50	5	3-7	0-36
(34, 39-52, 59)	(24)	(2)	(2)	(22)		(2)		(0)	(5)		(5)	(6)

Refs: References, AMP: Ampisilin, A-Cl: Amoxicillin-clavulanate, Amp-S: Ampicillin-sulbactam, SXT: Trimethoprim-sulfametaxazole CFXM: Cefuroxim, CEC: Cefaclor, CFXN: Ceftriaxone, LEVO: Levofloxacin, CLAR: Clarithromycin, AZT: Azithromycin TET: Tetracycline, Bl-a: Beta lactamase activity

Atypical Pathogens

M. pneumoniae, C. pneumoniae and L. pneumoniae have 10-40% share in CAP in Turkey [14]. The former two are the main causative agents of atypical pneumonia treated outside the hospitals in particular [13,14]. In this group of bacteria antibiotic susceptibility, testing is not standardized and regional clinical data is insufficient in Turkey. In a comparative trial for Legionella strains, an atypical pathogen that is rarely in outpatients, the efficacy of antibiotics according to MIC values were as follows: Rifampicin > ciprofloxacin > azithromycin = clarithromycin = levofloxacin [56]. Consequently, the antibiotic choices for these atypical pathogens are based on clinical trials and macrolides, tetracyclines, quinolones are the well-known therapeutic options [13, 57].

DISCUSSION

The physician in daily medical practice is motivated to give the best treatment, often without regard to the spectrum of activity of the chosen agent. Some physicians believe that if a small amount of drug is effective, greater and more prolonged administration may be better. Another approach is using multiple antimicrobial agents or broad-spectrum combinations to cover uncommon organisms. Pressure from the patients to be treated with antimicrobial agents is another obstacle in rational antibiotic use. Inadequacy of the physician's knowledge in the management of patients with infectious diseases is becoming more important in an era of increasingly complex infectious disease issues, such as evolving and changing antibiotic resistance patterns. Besides, over diagnosis of bacterial respiratory infections leads to the excessive prescription of antibiotics, thus contributing to the emergence and spread of bacterial resistance [60]. Today the medical community is in the midst of an emerging crisis of antibiotic resistance for microbial pathogens throughout the world. For this reason, optimizing therapeutic outcomes in infectious diseases should be based on local and updated strategies combined with the classical pharmacological principles in anti-infective therapy.

In the management of ABS, the current evidence from 32 trials supports the treatment with penicillin or amoxicillin [61] including penicillin non-susceptible isolates when administered in off-label high dosages (1.5 g twice daily in adults). However, amoxicillin is ineffective against beta lactamase producing pathogens [62,63] and seems to be an incompatible choice in Turkey due to high beta lactamase production either in H. influenzae or M. catarrhalis isolates. Rather amoxycillin clavulanate, extended spectrum cephalosporins (cefuroxime, ceftriaxone, cefotaxime) and respiratory quinolones like levofloxacin, gemifloxacin and moxifloxacin appear to be reliable options. Similarly, although there are ongoing disputes over antibiotic use in either childhood or adult AOM [64], the same therapeutic options with ABS seem to be applicable in Turkey due to current data.

Macrolides seem very effective in M. catarrhalis and H. influenzae infections in Turkey with susceptibility profiles around 5%. But, the pneumococcal macrolide resistance is around 15% and in a multicentric trial MIC 90 value for macrolides is less than 1 mg/L [33]. In another report, 11% of the isolates had MIC values exceeding 16 mg/L [31]. As there have been bacteriologically documented failures in patients infected with pneumococci when the MIC is over 8 mg/L [65], in regions with a high rate (> 25 %) of infection with high-level (MIC ≥ 16 mg/L) macrolide-resistant pneumococci, using of alternative agents like respiratory fluoroquinolones (moxifloxacin, gemifloxacin, levofloxacin) or a beta-lactam plus a macrolide is recommended in outpatient CAP [13]. Although Turkish pneumococcal resistance profile is below this threshold, macrolides should be used with caution. But, telithromycin, which is derived from the macrolide family, looks very efficient for respiratory pathogens. However, there have been recent postmarketing reports of life-threatening hepatotoxicity [66]. At present, supplementary assessment of the safety of this antibiotic is ongoing.

When an atypical component is suspected either using macrolides or the addition of a macrolide or doxycyclin to a beta lactam is considered for the outpatient CAP [13]. Since macrolides seem effective to beta lactamase producers (H. influenzae, M. catarrhalis) in Turkey, amoxicillin can be the baseline beta lactam for this combination. On the other hand, new quinolones like levofloxacin and moxifloxacin seem to be brilliant choices including atypical pneumonias [67,68]. However, infrequent antibiotic resistance may well be correlated with therapeutic failures [69]. On the other hand, quinolones are commonly used either

in gastrointestinal, urinary and respiratory infections or as the second line drugs in the management of tuberculosis. Thus sparing of quinolones as much as possible and the preference of macrolides initially for the outpatient CAP appears to be more appropriate.

While trimethoprim-sulfamethoxazole is rarely used for the management respiratory tract infections in developed countries, it remains the drug of choice in developing world [70]. There are no data on the clinical relevance of trimethoprim-sulphamethoxazole resistance for the management of pneumonia, although reports of the bacteriological failures with this agent have been known [71]. This drug is the most nonsusceptible antibiotic for pneumococci, Haemophilus influenzae, and Moraxella catarrhalis in Turkey and thus should be out of empirical choice in community acquired respiratory infections. Similarly, tetracyclines are low priority antibiotics and should be used cautiously in ABS, AOM and CAP in Turkey.

Microbes do not need our help in developing antibiotic resistance. What human beings did was to affect the spread of bacterial resistance by applying selective pressure via exposure to the thousands of metric tons of antibiotics used in patients and livestock over the past half century [72]. Today, what we are supposed to do is to use these medications on a rational basis to preserve our weapons as much as possible.

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