Empirical Antibiotic Use in Acute Bacterial Meningitis for the Elderly in Turkey

Türkiye’deki Yaşlılarda Akut Bakteriyel Menenjitte Ampirik Antibiyotik Kullanımı

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ABSTRACT

This article aims to outline the therapeutic rationale in acute bacterial meningitis in the elderly for Turkish population. The interpretations of national data reveal some suggestions. The combination of a third generation cephalosporin (ceftriaxone or cefotaxime) plus ampicillin appears to be the primary option. Adding an anti-gram positive agent like vancomycin or linezolid as an initial choice seems unnecessary. The alternative antimicrobials to third generation cephalosporins appear to be the new generation quinolones. In addition, meropenem is another option for the elderly in Turkey.

Key Words: Meningitis, elderly, Turkey.

ÖZET

Bu derleme, Türkiye’de yaşlı popülasyonda akut bakteriyel menenjit tedavisini irdelemeyi amaçlamaktadır. Ulusal verilerin yorumu bazı öneriler ortaya koymaktadır. Üçüncü kuşak sefalosporin (sefotaksin, seftriakson) ve ampicillin kombinasyonu ilk seçenek gibi görünmektedir. Ampirik başlangıç tedavisine vankomisin ya da linezolid gibi anti-gram pozitif ajanlar eklenmesinin gerekçiz olduğu söylenebilir. Üçüncü kuşak sefalosporinlere alternatif antimikrobiyaller yeni kuşak kinolonlar gibi görünmektedir. Ayrıca, meropenem ileri yaş menenjitlerinde diğer bir seçenek olarak karşımıza çıkmaktadır.

Anahtar Kelimeler: Menenjit, yaşlı, Türkiye.

INTRODUCTION

Community-acquired acute bacterial meningitis (CA-ABM) is a disease that necessitates immediate medical response (1). The mortality rates are increasingly high in the elderly in particular (2). Turkey is a large country with a population of 75 million at the southeast border of Europe and the clinicians in the country make use of therapeutic guidelines produced by the developed nations in the management of CA-ABM. This paper aims to delineate the therapeutic approaches based on the regional studies for this infection for those over the age 50.
STUDY DESIGN

The main causative agents of CA-ABM in a 28-center study for this group of age in Turkey are follows: Streptococcus pneumoniae 69.2%, Listeria monocytogenes in 8.8%, Staphylococcus epidermidis 4.4%, Streptococcus species 3.1%, Neisseria meningitidis 2.5%, Staphylococcus aureus 2.5%, Escherichia coli 2.5%, Haemophilus influenzae 1.3% and other various microorganisms with very limited shares (3). The publications related with the main CA-ABM agents were searched and considered for this review in both Turkish (Ulakbim and Pleksus) and international (Medline) databases along with the presentations either in national microbiology or infectious diseases congress' books. Moreover, only the antimicrobials suitable for central nervous system infections were taken into consideration.

Streptococcus pneumoniae

Pneumococci have the major share in CA-ABM. These microorganisms were detected in 28-32% of adult CA-ABM in Turkey (4,5). But the share is higher in the elder population (70%) (3). Apparently, the share of pneumococcus is increasing with age in Turkey and this issue reveals concerns on the therapeutic and preventive issues, for which pneumococci imposes to clinicians. Antibiotic resistance in invasive pneumococci has been steadily increasing in Turkey over the years (6). Today, 35% of the pneumococcal isolates in Turkey is penicillin resistant and one fifth of the resistant isolates confer high level resistance (7). Minimum inhibitor concentration 90 (MIC90) value is 1 µg/mL on the whole throughout the country (6,8-10). When these data are interpreted according to the Clinical and Laboratory Standards Institute guideline, which modified the minimum inhibitory concentrations thresholds as an update in 2008, this 35% resistance in Turkey seems directly to be correlated with therapeutic failures in CA-ABM (11). Accordingly, the mortality was obviously high in a Turkish clinical trial in which penicillin was compared to ceftriaxone in 1989-94 period. At that time the cumulative penicillin resistance was 27% and the high level resistance was 2.3% in Turkey (5,6). Thus, penicillin is not a reliable empirical treatment option in pneumococcal meningitis. However, the resistance rates for third generation cephalosporins are around 2% (7,10). That is, these drugs seem trustworthy in the management of pneumococcal meningitis although caution should be indicated for therapeutic failures. In addition, 23-valent pneumococcal vaccine that covers 79% of the invasive isolates in Turkey can be used when indicated to combat the invasive pneumococcal disease burden (12).

The cumulative pneumococcal antibiotic susceptibility rates verified from local Turkish studies are as follows: Trimethoprim-sulfamethoxazole 43%, cloramphenicol 3%, rifampicin 2%, ciprofloxacin 1%, levofloxacin 3%, moxifloxacin 0%, vancomycin 0% and linezolid 0% (10,13-21). The carbapenem resistance is around 2% (10). Thus, new quinolones (levofloxacin, moxifloxacin), cloramphenicol, linezolid and meropenem can be considered as single regimens in pneumococcal meningitis while rifampicin and vancomycin as the parts of combinations according to valid management strategies (1).

Listeria monocytogenes

L. monocytogenes is an infectious agent in newborns, pregnant women, immunosuppressed population and the elderly (22). In a meta-analysis reviewing Turkish literature, meningitis was the most-frequently recognized listerial infection in more than half of the cases (23). A study from The Netherlands disclosed that underlying disease was present in 50% of non-neonatal patients, most often haematological malignancies and the use of immunosuppressive therapies (24). Antibiotic resistance have been known to be infrequent a general understanding (25). One critical point on this issue is the inefficacy of cephalosporins in Listeriosis (26). The records in the literature in Turkey related to L. monocytogenes are limited to case reports. In a case series involving nine patients brought up that the infecting L. monocytogenes strains were susceptible to all antimicrobials tested excluding cephalosporins (22). There are individual case reports supporting the same antibiotic susceptibility trend (27). Given the fact that penicillin or ampicillin are not suitable choices in pneumococcal meningitis in Turkey, which makes up the major portion, combining one of these drugs to therapy would be the rational approach (28).

Neisseria meningitidis

N. meningitidis is 28-52% etiological agent in CA-ABM for adults in Turkey (4,5). However, its share is 2.5% in the elder population (3). Meningococcal meningitis has been treated successfully with penicillin in the past and the clinicians were not in need of cephalosporin use (5,29). However, epidemiological data are limited throughout the country and the susceptibility profi
les are lacking. On the other hand, case reports with decreased susceptibility to penicillin are reported (30). In a laboratory based study cefuroxime, ceftriaxone and ciprofloxacin resistance was not detected while the penicillin nonsusceptibility was 9% (31). Therefore, traditional penicillin therapy may pose potential problems and extended generation cephalosporins can be regarded as the initial therapeutic option in probable meningococcal meningitis for which the cultures are pending.

**Escherichia coli**

*E. coli* is an infrequent cause of CA-ABM in the elderly (3). The antibiotic susceptibility profiles of this microorganism derived from Turkish community-acquired isolates are presented in Table 1 (32-59). When this microorganism is suspected in the initial examination of central nervous system fluid as the presence of gram-negative bacilli by Gram stain, then the use of meropenem can be considered. Because all other choices have elevated profiles over 5%. However, if an antibiotic other than meropenem is used in the management of CA-ABM in the elderly without the initial clue of a gram-negative, than the clinical stabilization of the patient is the best way to decide on the efficacy of this particular drug when the culture results are pending.

**Haemophilus influenzae**

One of the most important epidemiologic changes in CA-ABM has been the reduction in the incidence of *H. influenzae* meningitis owing to childhood vaccination (60). Turkey experiences the same trend and *H. influenzae* CA-ABM meningitis in the elderly is rare in Turkey (3). In local Turkish studies presented in Table 2, *H. influenzae* isolates are relatively susceptible. But, the beta-lactamase production is up to 36% with the co-existing elevated penicillin and ampicillin resistance. Thus, second and third generation cephalosporins and quinolones seem reliable choices in Turkey for *H. influenzae* meningitis. Although carbapenems are not tested and since this pathogen is generally sensitive to extended spectrum beta cephalosporins, meropenem, a suitable carbapenem for ABM, is probably very efficient in *H. influenzae* meningitis.

**CONCLUSIONS**

Penicillin G, ampicillin, third-generation cephalosporins, cefepime, meropenem, fluoroquinolones, chloramphenicol, aztreonam and trimethoprim-sulfamethoxazole are the therapeutic choices in CA-ABM (1). Although microbiological diagnosis is the crucial modality in curtailing anti-infective therapy in CA-ABM, the interpretation of local antibiotic susceptibility patterns in Turkey discloses some suggestions for the elderly:

1. The combination of a third generation cephalosporin (ceftriaxone or cefotaxime) plus ampicillin or penicillin is the primary empirical option in Turkish population.

2. Adding an anti-gram positive agent like vancomycin or linezolid as an empirical choice seems unnecessary.

### Table 1. Studies evaluating the resistance rates of community-acquired *Escherichia coli* isolates in Turkey (32-59)

<table>
<thead>
<tr>
<th>AMP</th>
<th>AMX-CL</th>
<th>CFX</th>
<th>CEP</th>
<th>SXT</th>
<th>CIP</th>
<th>MER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>37-82.4</td>
<td>9.8-40</td>
<td>1.6-29.6</td>
<td>1.7-13</td>
<td>11.7-63.3</td>
<td>6.2-39</td>
<td>0-3</td>
</tr>
<tr>
<td>(55.2)</td>
<td>(26)</td>
<td>(7)</td>
<td>(9.7)</td>
<td>(40.2)</td>
<td>(18.5)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

Median ratio is presented as bold.
* Extrapolated from imipenem data.

### Table 2. The antibiotic resistance patterns of *Haemophilus influenzae* in Turkey (61-75)

<table>
<thead>
<tr>
<th>AMP</th>
<th>AMX-CL</th>
<th>AMP-SUL</th>
<th>CEC</th>
<th>CFX</th>
<th>LEVO</th>
<th>SXT</th>
<th>Bi-a</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-34</td>
<td>0-11</td>
<td>0-13</td>
<td>1-5</td>
<td>1</td>
<td>0-0</td>
<td>5-35</td>
<td>0-36</td>
</tr>
<tr>
<td>(24)</td>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
<td>(0)</td>
<td>(22)</td>
<td>(6)</td>
<td></td>
</tr>
</tbody>
</table>

Median ratio is presented as bold.
3. The alternative regimens to third generation cephalosporins appear to be the new generation quinolones.
4. Meropenem, which is also accepted as an alternative agent for *L. monocytogenes*, is another option (1).
5. Although chloramphenicol, an old and ignored drug due to fatal side effects, seems efficient, data is lacking for *L. monocytogenes*.
6. Penicillin G, ampicillin, and trimethoprim-sulfa-methoxazole alone are not suitable choices on the empirical basis.
7. Satisfactory data is lacking for aztreonam.

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