Tonsillopharyngitis is one of the most common infections encountered in children. Most bacterial infections are caused by Streptococcus pyogenes (1). In addition, resurgence of severe forms of disease caused by S. pyogenes has been detected in various parts of the world (2, 3). Although all S. pyogenes strains remain exquisitely sensitive to penicillin, erythromycin has been the drug of choice for individuals who cannot take penicillin. However, resistance to macrolide antibiotics is an important problem in some regions of the world. For these reasons, we designed a study to determine the antibiotic susceptibility of S. pyogenes strains isolated from children with tonsillopharyngitis. Two hundred and sixty three S. pyogenes strains were examined for penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, erythromycin, clarithromycin and azithromycin, ofloxacin, and vancomycin susceptibility. Tolerance against penicillin was also investigated. All S. pyogenes strains were determined to be susceptible to penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, ofloxacin, and vancomycin. Resistance to erythromycin, clarithromycin, azithromycin, and clindamycin were detected as 3.8%, 4.2%, 4.2%, and 3.0%, respectively. Penicillin tolerance wasn't determined. These data indicate that antibiotic resistance of S. pyogenes strains is not a clinically significant problem in Turkey.

**Summary**

Streptococcus pyogenes is the most important causative agent of tonsillopharyngitis. Although penicillin is drug of choice, and macrolide antibiotics are recommended drugs in patients who have penicillin allergy, various antibiotics other than penicillin and macrolide antibiotics are also used in the treatment of streptococcal tonsillopharyngitis. In addition, resistance to macrolide antibiotics is an important problem in some regions of the world. For these reasons, we designed a study to determine the antibiotic susceptibility of S. pyogenes strains isolated from children with tonsillopharyngitis. Two hundred and sixty three S. pyogenes strains were examined for penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, erythromycin, clarithromycin, azithromycin, ofloxacin, and vancomycin susceptibility. Tolerance against penicillin was also investigated. All S. pyogenes strains were determined to be susceptible to penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, ofloxacin, and vancomycin. Resistance to erythromycin, clarithromycin, azithromycin, and clindamycin were detected as 3.8%, 4.2%, 4.2%, and 3.0%, respectively. Penicillin tolerance wasn't determined. These data indicate that antibiotic resistance of S. pyogenes strains is not a clinically significant problem in Turkey.

**Key Words:** Streptococcus Pyogenes, Tonsillopharyngitis, Antibiotic Susceptibility.
there is a concern that a significant incidence of erythromycin resistance of *S. pyogenes* has been reported from the various regions of the world (4-10). Because the nonsuppurative sequels of *S. pyogenes* infections are still an important problem in Turkey and invasive infections due to *S. pyogenes* have increased recently, the treatment of infections due to *S. pyogenes* is very important in our country (11). Because of these observations, it is important to determine the current status of antibiotic susceptibility of *S. pyogenes* strains.

**Methods**

Children with tonsillopharyngitis in Ankara University Faculty of Medicine, Department of Pediatrics between December 2000 and March 2001 were enrolled in the study. All children were examined by a pediatrician. Tonsillopharyngitis diagnosis was established based on symptoms such as fever, sore throat, headache and abdominal pain, and signs such as pharyngeal and tonsillar hyperemia, exudate and painful cervical lymphadenopathy.

Throat swabs were obtained from the children, and immediately cultured in Mueller-Hinton blood agar. After 24 hour incubation at 35ºC, colonies surrounded by beta hemolysis were selected for grouping and antimicrobial susceptibility procedures. Strains were grouped by Streptococcal Grouping Kit (Oxoid, Diagnostic Reagents, Hampshire, UK). Group A beta hemolytic streptococci were analysed with respect to ampicillin, cefazolin, cefuroxime, ceftriaxone, erythromycin, clarithromycin, azithromycin, clindamycin, ofloxacin, and vancomycin susceptibilities using the agar dilution method. Penicillin G susceptibility was determined by broth dilution method. The minimal inhibitory concentration (MIC) limits for selected were determined according to the values determined by National Committee for Clinical Laboratory Standards (12). For cefazolin and cefuroxime for which there are no established NCCLS break points for *Streptococcus pyogenes*, NCCLS break points established for *Streptococcus pneumoniae* were used (12). Resistance limits determined as: penicillin G ≥ 4.0 µg/ml, ampicillin ≥ 8.0 µg/ml, cefazolin ≥ 2.0 µg/ml, cefuroxime ≥ 2.0 µg/ml, ceftriaxone ≥ 2.0 µg/ml, erythromycin MIC≥1.0 µg/ml, clarithromycin MIC≥1.0 µg/ml, azithromycin MIC≥2.0 µg/ml, clindamycin ≥1.0 µg/ml, ofloxacin ≥8.0 µg/ml, and vancomycin ≥2.0 µg/ml. Minimal bactericidal concentrations (MBC) for penicillin G were also determined (13). Penicillin tolerance was defined as an MBC-MIC ratio of greater than or equal to 32 (13).

**Results**

During the study period, 3127 children were diagnosed as tonsillopharyngitis. *S. pyogenes* were isolated from 345 throat swabs (11.0%). Because of contamination or missing of isolated strains, 263 *S. pyogenes* strains were found eligible.

**Penicillin G susceptibility.** All *S. pyogenes* strains were found to be susceptible to penicillin G. MIC values of *S. pyogenes* strains for penicillin G were determined as 0.0004-0.03 µg/ml (Table 1). Tolerance to the penicillin G was not determined in any of the isolates (Table 2, and Figure 1).

**Macrolide resistance in *S. pyogenes* strains.**

Out of 263 *S. pyogenes* strains, 10 (3.8%) were resistant to erythromycin, 11 (4.2%) were resistant to both clarithromycin and azithromycin (Table I).

**Susceptibility to other antibiotics.** All *S. pyogenes* strains were found to be susceptible to ampicillin, cefazolin, cefuroxime, ceftriaxone, ofloxacin and vancomycin. Eight of the 263 *S. pyogenes* strains (3%) were resistant to clindamycin (Table 1).

**Discussion**

Antimicrobial resistance is an important problem in the management of patients with infectious diseases. Interestingly, *Streptococcus pyogenes* remains susceptible to penicillin during the past 70 or 80 years. The reason for this unique lack of development of resistance to penicillin is unknown (14). On the other hand, numerous reports have demonstrated a significant prevalence of erythromycin resistant *S. pyogenes*
around the world during the past three decades (4-10). This resistance has been temporally related to increased or excessive use of macrolide antibiotics. Because of this relation, it is important to determine the geographic prevalence of resistant S. pyogenes to facilitate clinical care and to address public health concerns.

Our study shows that penicillin is active for S. pyogenes in low MIC values. This finding is

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistant strains (n%)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
<th>MIC ranges (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>0/0</td>
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<td>0.0004-0.03</td>
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<td>Ampicillin</td>
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<td>≤ 0.125-0.25</td>
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<tr>
<td>Cefazolin</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-1.00</td>
</tr>
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<td>Cefuroxime</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-0.50</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0/0</td>
<td>≤ 0.125</td>
<td>≤ 0.125-0.25</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0/0</td>
<td>1.0</td>
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</tr>
<tr>
<td>Vancomycin</td>
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<td>≤ 0.25</td>
<td>≤ 0.25-0.50</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>8/3.0</td>
<td>0.25</td>
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<td>≤ 0.125-2.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>11/4.2</td>
<td>0.25</td>
<td>≤ 0.125-&gt;2.0</td>
</tr>
</tbody>
</table>

**Table 1:** Resistance to eleven antibiotics, MIC<sub>90</sub> values, and MIC ranges of 263 S. pyogenes strains.

<table>
<thead>
<tr>
<th>MBC/MIC</th>
<th>Number of strains</th>
</tr>
</thead>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>263</td>
</tr>
</tbody>
</table>

**Table 2:** Penicillin G MBC/MIC ratios of S. pyogenes strains.

**Figure 1:** Penicillin G MIC and MBC values of S. pyogenes strains.
concordant with other studies from around the world (15-17). We also could not determine any S. pyogenes strain tolerant to penicillin G. Penicillin G MIC and MBC values of S. pyogenes were similar in our study. Penicillin failure in streptococcal tonsillopharyngitis reported as 10-25% (18, 19). Some authors blamed penicillin tolerance in patients with penicillin failure (20, 21). Although we could not determine clinical response of our patients, our results do not support penicillin tolerance theory for penicillin failure.

Like various parts of the world, invasive infections due to S. pyogenes have increased recently in Turkey (unpublished data). Causative agents sometimes cannot be determined, and various antibiotics are chosen in these patients. Thus, it is important to know the current status of antibiotic susceptibility in S. pyogenes strains. Our study shows that many antibiotics are active for S. pyogenes strains. Although these antibiotics are not first choice, they can be used in invasive streptococcal infections.

Resistance to erythromycin, clarithromycin, azithromycin, and clindamycin were detected as 3.8%, 4.2%, 4.2%, and 3.0%, respectively in this study. During the past three decades, numerous reports have demonstrated a significant prevalence of erythromycin resistant S. pyogenes around the world (4-10). Furthermore, several reports have demonstrated that the increase in the incidence of erythromycin resistant S. pyogenes strains is related to increased macrolide consumption in the community (22-26). Macrolide antibiotics, especially new ones such as clarithromycin and azithromycin, are widely selected for the treatment of upper respiratory tract infections such as sore throat in our country. In a recent study from Ankara, erythromycin resistant S. pyogenes strains were increased from 3.29% to 15.74% in a 7-year-period. The authors emphasized that a substantial increase in erythromycin resistance was associated with the increase in the consumption of macrolide antibiotics.

Our results demonstrate that antibiotic resistance of S. pyogenes strains is not a clinically significant problem in Turkey. However, the susceptibility pattern of S. pyogenes strains must be monitored.
REFERENCES


