Antibiotic consumption and link to resistance

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Abstract

Antibiotic use in the treatment of respiratory tract infections is common in primary care. The European Surveillance of Antimicrobial Consumption (ESAC programme), collecting data from 35 countries, showed that antibiotic use was highest in southern European countries. Increased antibiotic consumption has been shown by numerous ecological studies to contribute to the emergence of antibiotic resistance in streptococci. A study comparing outpatient antibiotic consumption in the USA showed it to be similar to that in southern European countries, but macrolides, particularly azithromycin, are among the first-line agents prescribed in the USA for respiratory infections. In Europe, patients are more likely to receive a β-lactam; and when a macrolide is indicated, clarithromycin is more likely to be prescribed than azithromycin. Streptococci resistance to macrolides can be acquired via two mechanisms: by the \textit{mef} gene, which encodes for the efflux pump mechanism, producing low to moderate resistance, or the \textit{erm} gene (post-transcriptional modification of the bacterial ribosomal unit), resulting in high resistance. Macrolide resistance is mediated by \textit{erm}(B) and \textit{mef}(A) alone or in combination. A surveillance study showed that \textit{mef} was responsible for most of the macrolide resistance seen in the USA; a decrease in the number of isolates carrying \textit{mef}(A) was associated with a doubling of the number of isolates carrying both \textit{mef}(A) and \textit{erm}(B). Higher consumption of clarithromycin in Europe correlated with a predominance of \textit{erm}(B)-carrying \textit{Streptococcus pneumoniae}. The \textit{erm}(B) gene caused resistance in 84% of the isolates in Europe.

Keywords: Antibiotic use, antibiotic resistance, antimicrobial pressure, ecological study, \textit{S. pneumoniae}

Introduction

Antibiotic usage in primary healthcare settings is high, and respiratory tract infections are the most common indications for use [1]. Macrolides are often prescribed for respiratory infections caused by Gram-positive organisms such as \textit{Streptococcus} species [2]. Numerous ecological studies have confirmed that increased antibiotic consumption has led to the emergence of antibiotic resistance worldwide [3,4]. In addition to antibiotic use, other factors contributing to the emergence of resistance include dose and duration of antibiotic therapy and cross-selection, e.g. cross-selection of resistance and cross-selection between β-lactam–tetracycline–macrolide resistance.

\textit{Streptococci} acquire resistance to macrolides via two mechanisms. The first is the efflux pump mechanism encoded by the \textit{mef} (macrolide efflux) gene. Low to moderate resistance to macrolides develops with a minimum inhibitory concentration (MIC) of erythromycin ranging from 0.5 to 32 mg/L. The second mechanism of resistance is post-transcriptional modification of the bacterial ribosomal subunit by methylase encoded by the \textit{erm} gene. This results in high resistance, with an MIC of erythromycin ranging from 32 to >512 mg/L [2,4].

The worldwide problem of antibiotic resistance requires combined international efforts, as geographical differences exist in the rates of resistance to various classes of antibiotics. Differential selection pressure is thought to be responsible for this geographical difference. Hence, monitoring of antibiotic usage should accompany surveillance programmes for antibiotic resistance [2,3].

Antibiotic Use in Europe and the USA

The European Surveillance of Antimicrobial Consumption (ESAC) is an international network of national surveillance systems that collects comparable and reliable data on antibiotic use. This project was funded by grants from DG/SANCO of the European Commission. For the first time, it provided a comprehensive database of internationally comparable data on antibacterial consumption in Europe by outpatients and inpatients [1,3,5].
Thirty-five countries participate in the ESAC project. The participants comprise 27 European Union member states, Croatia and Turkey as applicants, and six other countries (Former Yugoslav Republic of Macedonia, Iceland, Israel, Norway, Russia and Switzerland) that have recently joined the project [5,6].

A study compared outpatient antibiotic consumption in the USA with data from the ESAC. The results showed that antibiotic use, defined by daily doses/1000 inhabitants/day, was high in southern European countries. The highest consumption was observed in Greece, France and Italy. Northern European countries reported comparably lower antibiotic use, with The Netherlands reporting the least consumption. Outpatient systemic antibiotic use in the USA was similar to that in southern European countries [3].

The difference in outpatient macrolide, lincosamide and streptogramin (MLS) use between the USA and Europe may be due to variations in the types of infection treated in these countries. In the USA, macrolides are among the first-line agents prescribed for respiratory infections, and treatment guidelines approve macrolides for infections due to atypical pathogens. In Europe, atypical infections, e.g. those caused by *Mycoplasma* and *Chlamydia*, are considered less clinically relevant, and since the emergence of macrolide resistance poses a considerable clinical threat, patients with these infections would probably receive a β-lactam [7]. A comparison of outpatient MLS use according to corresponding antibiotic subclass and defined daily dose in Europe and the USA is presented in Table 1 [3].

### Ecological Evidence for the Link between Antibiotic Use and Resistance in *Streptococcus pneumoniae*

Numerous studies have shown an association, but not a causal link, between antibiotic consumption and resistance. A study was conducted to analyse the ecological association between antibiotic use and antibiotic resistance rates [1]. Antibiotic susceptibility data were collected from the European Antimicrobial Resistance Surveillance System project, the telithromycin surveillance (PROTEKT) project, and the pan-European project. A correlation between antibiotic use and resistance was calculated. A positive correlation was demonstrated between resistance and antibiotic consumption. Differences in selection pressure accounted for geographical variations in resistance; higher rates of resistance were observed in European countries where antibiotic consumption is moderate to high [1]. A comparison of outpatient MLS use in Europe and the USA according to drug and defined daily dose is presented in Table 2 [3].

### Selective Pressure of Macrolides

Viridans group streptococci (VGS) are increasingly recognized as being macrolide-resistant. A study was conducted with 154 healthy Belgian adults to determine oropharyngeal carriage of VGS resistant to macrolides and other common antibiotics [2]. Seventy-one percent of adults in the study presented with oropharyngeal carriage of macrolide-resistant VGS, and 32% had more than one unique macrolide-resistant isolate. *Streptococcus mitis* was the most common and most resistant isolate, and was recovered from 51% of adults; constitutive macrolide–lincosamide–streptogramin (cMLS) was the predominant phenotype among the unique isolates [2].

A significant correlation was found between phenotypic and genotypic profiles. The majority of cMLS isolates carried erm(B), either alone or together with mef(A). *S. mitis* showed the highest percentage prevalence of mef(A) and of erm(B) + mef(A). Among tet genes, tet(M) was the most prevalent, indicating a higher prevalence of tetracycline resistance among macrolide-resistant isolates. The presence of the same resistance determinants in both commensals and pathogens suggested the possibility of interspecies gene transfer [2].

### Table 1. Outpatient macrolide, lincosamide and streptogramin use in Europe and the USA [3]

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Corresponding antibiotic (sub)class</th>
<th>US DID (%)</th>
<th>European DID (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01F</td>
<td>Macrolides, lincosamides and streptogramins</td>
<td>3.52 (14.14)</td>
<td>2.98 (15.66)</td>
</tr>
<tr>
<td>Intermediate-acting macrolides</td>
<td>0.43 (1.73)</td>
<td>0.48 (2.54)</td>
<td></td>
</tr>
<tr>
<td>Long-acting macrolides</td>
<td>1.16 (4.66)</td>
<td>1.71 (8.96)</td>
<td></td>
</tr>
<tr>
<td>J01FF</td>
<td>Lincosamides</td>
<td>0.25 (1.02)</td>
<td>0.16 (0.85)</td>
</tr>
<tr>
<td>J01FG</td>
<td>Streptogramins</td>
<td>&lt;0.01 (0.00)</td>
<td>0.10 (0.55)</td>
</tr>
</tbody>
</table>

**ATC**, anatomical therapeutic chemical; **DID**, defined daily doses per 1000 inhabitants per day.

### Table 2. Outpatient macrolide, lincosamide and streptogramin use in Europe and the USA according to drug and defined daily dose per 1000 inhabitants per day (DID) [3]

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>US DID (%)</th>
<th>European DID (%)</th>
<th>Highest European DID (country)</th>
<th>Lowest European DID (country)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>1.68 (6.7)</td>
<td>0.52 (2.7)</td>
<td>1.34 (Croatia)</td>
<td>0.04 (Sweden)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1.10 (4.4)</td>
<td>1.23 (6.5)</td>
<td>7.16 (Greece)</td>
<td>0.06 (Sweden)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.43 (1.7)</td>
<td>0.34 (1.8)</td>
<td>1.72 (UK)</td>
<td>0.01 (Bulgaria)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.25 (1.0)</td>
<td>0.14 (0.8)</td>
<td>0.70 (Hungary)</td>
<td>&lt;0.01 (Italy)</td>
</tr>
</tbody>
</table>
A clinical trial with 224 healthy volunteers investigated the direct effects of azithromycin and clarithromycin in promoting carriage of macrolide-resistant oral streptococci and temporal persistence of the selected resistant commensals [4]. At study inception, prior to drug dosing, 30.1% of clarithromycin subjects, 25.9% of azithromycin subjects and 27.5% of placebo subjects were carriers of macrolide-resistant streptococci. Following dosing, an increase in resistant pneumococci was observed in both the azithromycin group and the clarithromycin group; the increase persisted at levels significantly above that in the placebo group for 6 months. Multivariate analysis showed that macrolide exposure was the strongest variable that was independently associated with the proportion of macrolide-resistant streptococci. Gene analysis showed that the use of clarithromycin was associated with a significant decrease in $\text{erm} \,(A)$ carriage and a parallel increase in $\text{erm} \,(B)$ and $\text{tet} \,(M)$ carriage. A two-fold increase was observed in the MIC of erythromycin for macrolide-resistant streptococci that carried $\text{erm} \,(B)$ after azithromycin exposure. The MIC$_{90}$ increased from 8 mg/L at day 0 to 16 mg/L at day 42 [4].

**Emergence of Macrolide Resistance**

An understanding of trends in antibiotic resistance may help to explain the differences observed between the USA and Europe. The PneumoWorld study (31 centres in eight European countries) demonstrated that 28% (618/2279) of isolates from Europe were macrolide-resistant. The $\text{erm} \,(B)$ gene caused resistance development in 84% of the isolates [8].

The results of the 3-year Prospective Resistant Organism Tracking and Epidemiology for Ketolide Telithromycin US surveillance (PROTEKT) study showed that $\text{erm} \,(B)$ was responsible for most of the macrolide resistance in the USA, as well as for changing trends in the mechanism of resistance in the USA. A decrease in the number of isolates carrying $\text{erm} \,(A)$ was associated with a doubling of the number of isolates carrying both $\text{erm} \,(A)$ and $\text{erm} \,(B)$ [9].

Coenen et al. described the changing trends in MLS use in Europe. Total MLS use varied greatly among countries, with the highest recorded use in Greece and the lowest in Sweden. Marked variations across countries were observed in the use of short-acting, intermediate-acting and long-acting macrolides. Extreme seasonal variations in macrolide consumption were observed among the European countries, and suggested inappropriate use for familiar conditions such as the common cold (viral upper respiratory tract infection), influenza and bronchitis [10].

Dias and Canica demonstrated that the emergence of erythromycin-resistant strains correlated well with the use of azithromycin in Portugal, suggesting that antibiotic use is linked with resistance [11].

**Conclusions**

Many surveillance systems have documented a positive correlation between antibiotic consumption and resistance development. Geographical variations in antibiotic use in Europe substantiate the correlation. Countries with high antibiotic consumption, e.g. those in southern and eastern Europe, have higher rates of antibiotic resistance than countries with lower rates of antibiotic consumption, e.g. those in northern Europe. Outpatient MLS use in Europe varies greatly according to country and according to specific antibiotic. Macrolide resistance is mediated by $\text{erm} \,(B)$ and $\text{mef} \,(A)$ alone or in combination. Selective pressure on resistance expression by $\text{erm} \,(B)$ and $\text{mef} \,(A)$ has been demonstrated for macrolides.

Ecological evidence exists linking antibiotic use and resistance. Data collected from many European countries show a positive correlation between use of penicillin or erythromycin and the development of penicillin-resistant *S. pneumoniae*.

Macrolide use was the single most important driver for the emergence of macrolide resistance. High levels of consumption of azithromycin in the USA and Canada correlated with the predominance of $\text{mef}$-carrying *S. pneumoniae*. The community-wide shifts in certain European countries, Canada and the USA toward $\text{mef}$ strains expressing higher macrolide resistance might result from azithromycin consumption.

Clarithromycin qualitatively selected the higher resistance-conferring $\text{erm} \,(B)$ gene. The higher consumption of clarithromycin in Europe correlated with a predominance of $\text{erm} \,(B)$-carrying *S. pneumoniae*. This may have implications that include resistance to MLS and tetracyclines (co-carriage with $\text{tet} \,(M)$ on one genetic element).

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**Transparency Declaration**

H. Goossens declares no conflicts of interest.
References


