Relationship between the number of different antibiotics used and the total use of antibiotics in European hospitals

Fiona M. MacKenzie1*, Dominique L. Monnet2 and Ian M. Gould1 on behalf of the ARPAC Steering Group†

1Medical Microbiology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK; 2National Center for Antimicrobials and Infection Control, Statens Serum Institut, Copenhagen, Denmark

Received 17 March 2006; returned 3 April 2006; revised 19 June 2006; accepted 23 June 2006

Objectives: The aim of this study was to establish whether there was a relationship between the number of antibacterial agents used and total antibiotic use in European hospitals.

Methods: A total of 139 hospitals from 30 countries supplied data on antibiotic use (ATC group J01) for 2001, expressed as the number of defined daily doses per 100 occupied bed-days (DDD/100 BD) and also numbers of different antibiotics used.

Results: Participating hospitals used a median of 46 antibiotics in 2001 (range 16–82). The most frequently used antibiotic per hospital accounted for a median of 16.5% (range 7.2–60.9%) of total use and the 10 most frequently used agents accounted for a median of 73.7% (range 53.0–98.5%) of total use. Numbers of antibiotics used varied significantly by European geographical region (Kruskal–Wallis test, \( P = 0.001 \)). The median total antibiotic use was 49.6 DDD/100 BD. A statistically significant relationship was found between the number of antibiotics used and total antibiotic use (Spearman’s rank, \( r = 0.40 \) and \( P < 0.01 \)) for all hospitals. Individual correlations were significant in Western (\( r = 0.57, P < 0.01 \)) and Southern Europe (\( r = 0.67, P < 0.01 \)) only.

Conclusions: The quantitative use of antibiotics in European hospitals was highly variable as was the number of different antibiotics used. In the two areas exhibiting highest total use, the greater the number of antibiotics used, the higher the total use of these drugs. Intervention studies are now needed to ascertain whether or not successful antibiotic restriction policies can reduce total antibiotic use and subsequently reduce antibiotic resistance.

Keywords: ARPAC, European Commission, antibiotic formulary

Introduction

Recently, Monnet et al.1 and Marra et al.2 independently reported on a relationship between antibiotic consumption and drug availability in the context of the outpatient setting. Monnet et al.1 found that community consumption of antibacterials in European countries was related to the number of trade names for oral antibacterial agents registered in these countries. Marra et al.2 looked at trends in antibiotic consumption associated with the listing of new agents on the drug formulary in British Columbia, Canada, over a 5 year period. They found that listing of a new antibiotic on the formulary was followed by a temporary increase in use of the agent.

The Antibiotic Resistance, Prevention And Control (ARPAC) study collected data on antibiotic use in European hospitals in 2001. The aim of the present investigation was to establish whether there was any relationship between the numbers of different antibiotics used in ARPAC participating hospitals and total, quantitative antibiotic use in these hospitals.

Materials and methods

This was an observational, cross-sectional study whereby hospital antibiotic use data for 2001 were collected as part of a Concerted Action project (ARPAC) funded by the European Commission (project number QLK2-CT-2001-00915). This part of the project was carried out under the auspices of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group on Antibiotic Policies (ESGAP).

*Corresponding author. Tel: +44-1224-554957; Fax: +44-1224-550632; E-mail: f.m.mackenzie@abdn.ac.uk
†Members are listed in the Acknowledgements section.

© The Author 2006. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
MacKenzie et al.

Table 1. Geographical classification of European countries detailing numbers of hospitals that contributed antibiotic use data

<table>
<thead>
<tr>
<th>Northern Europe</th>
<th>Western Europe</th>
<th>Centre/East + Baltic States</th>
<th>South-Eastern Europe</th>
<th>Southern Europe + Israel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 19</td>
<td>n = 52</td>
<td>n = 33</td>
<td>n = 8</td>
<td>n = 27</td>
</tr>
<tr>
<td>Denmark (n = 6)</td>
<td>Austria (n = 6)</td>
<td>Bulgaria (n = 6)</td>
<td>Albania (n = 0)</td>
<td>Greece (n = 7)</td>
</tr>
<tr>
<td>Finland (n = 0)</td>
<td>Belgium (n = 20)</td>
<td>Czech Republic (n = 3)</td>
<td>Bosnia (n = 0)</td>
<td>Israel (n = 2)</td>
</tr>
<tr>
<td>Netherlands (n = 5)</td>
<td>France (4)</td>
<td>Estonia (n = 2)</td>
<td>Croatia (n = 5)</td>
<td>Italy (n = 6)</td>
</tr>
<tr>
<td>Norway (n = 4)</td>
<td>Germany (10)</td>
<td>Hungary (n = 3)</td>
<td>Macedonia (n = 0)</td>
<td>Malta (n = 1)</td>
</tr>
<tr>
<td>Sweden (n = 4)</td>
<td>Luxembourg (n = 0)</td>
<td>Lithuania (n = 3)</td>
<td>Yugoslavia (n = 3)</td>
<td>Portugal (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Switzerland (n = 3)</td>
<td>Poland (n = 6)</td>
<td></td>
<td>Spain (n = 4)</td>
</tr>
<tr>
<td></td>
<td>UK (9)</td>
<td>Romania (n = 1)</td>
<td></td>
<td>Turkey (n = 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Russia (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovak (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovenia (n = 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All full members of ESCMID (~2500) were invited to participate in the ARPAC study during 2002 and to provide data relating to 2001. A total of 293 hospitals expressed an interest in participating, 30 of which were excluded because they were not from a European country. A total of 139 hospitals from 30 European countries provided antibiotic use data for 2001. Data are presented by five European geographical regions, defined using a modified version of a standard reference system, with UK hospitals placed in Western rather than Northern Europe. The participating hospitals were distributed into regions as detailed in Table 1.

Antibiotic use data were collated using a pre-formatted Microsoft Excel spreadsheet (ABC Calc, available at http://www.escmid.org/esgap). Antibacterial agents were categorized using the Anatomical Therapeutic Chemical (ATC) classification index with 2005 WHO defined daily doses (DDDs) (available at http://www.whocc.no/atcddd/indexdatabase). Antibiotic use was measured using the WHO recommended unit of DDD per 100 occupied bed-days (DDD/100 BD). Data were collected for agents in ATC group J01: that is antibacterial agents for systemic use.

The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance.

Statistical analysis

Data were entered into a Microsoft Access database and analysis was conducted using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kruskal–Wallis test was used to compare variables across geographical regions. Spearman rank correlations were computed to investigate the relationship between total antibiotic use and number of different agents used.

Results

The median number of different antibacterial agents used per hospital was 46 (interquartile range (IQR) = 39–55, min = 16, max = 82) and varied significantly by geographical region (Figure 1) (Kruskal–Wallis test, P = 0.001).

The most frequently used antibiotic in each hospital accounted for a median of 16.5% (IQR = 12.8–24.2, min = 7.2, max = 60.9) of total use, whereas the 5 most frequently used antibiotics accounted for 53.3% (IQR = 44.8–57.5, min = 32.3, max = 84.1) and the 10 most frequently used antibiotics for 73.7% (IQR = 64.8–79.0, min = 53.0, max = 98.5) of total use. Overall, the most frequently used antibiotic was the oral formulation of the combination amoxicillin/clavulanic acid, followed by the parenteral formulation of this combination, followed by oral ciprofloxacin, parenteral cefuroxime and oral amoxicillin.

For the 139 hospitals, median total antibiotic use (ATC group J01) in 2001 was 49.6 DDD/100 BD (IQR = 37.1–65.4, min = 5.0, max = 121.0). For the five European geographical regions, the median total antibiotic use in DDD/100 BD was: Northern Europe, 48.3 (IQR = 44.1–55.4, min = 37.1, max = 66.9); Western Europe, 53.6 (IQR = 47.5–69.9, min = 23.3, max = 116.3); Central/Eastern Europe (including the Baltic States), 31.2 (IQR = 23.8–45.8, min = 5.0 max = 84.4); South-Eastern Europe, 42.3 (IQR = 30.1–53.6, min = 25.3, max = 76.4); and Southern Europe, 72.2 (IQR = 46.8–89.7, min = 6.6, max = 121.0). The difference in total antibiotic consumption across European regions was statistically significant (Kruskal–Wallis test, P < 0.001).

We found a statistically significant relationship between the number of different antibacterial agents used in each hospital and total use of these drugs (Spearman’s rank, r = 0.40, P < 0.01) (Figure 2). When correlations were investigated in each of the five geographical regions, however, significant correlations were found only in Western and Southern Europe (Table 2).

Discussion

To our knowledge, this is the first Europe-wide survey of hospital-level antibiotic use, although the European Surveillance of Antibiotic Consumption (ESAC) project has collated aggregate hospital data for individual countries. Comparison with data from ESAC is however not possible as ESAC has used a non-standard unit of measuring antibiotic use (DDDs/1000 inhabitants/day), whereas the current study used the WHO recommended unit (DDD/100 occupied bed-days), which is well standardized and considered to be optimum when investigating antibiotic resistance selection pressure.
The ARPAC project collated and analysed several different datasets including antibiotic resistance prevalence for a range of organisms, antibiotic susceptibility testing methods used, typing methods used, antibiotic policies and practices as well as infection control policies and practices. The lowest response amongst participating hospitals was to the request for antibiotic use data. Many of the hospitals had never collated their antibiotic use data before and this proved prohibitively problematic for some. Despite this, numbers of hospitals that provided antibiotic use data were greater than those that have taken part in similar studies in the USA.\textsuperscript{5–7} Thus, the strengths of this pan-European study do include the large sample of recruited hospitals as well as rigorous, piloted data collection methods and high quality data obtained from participating hospitals. We acknowledge that hospitals were self-selecting, increasing the risk of response bias, and coverage was sparse in some countries. Country-level hospital data were obtained from EUROSTAT\textsuperscript{8} and crude estimated coverage of European acute care beds was estimated to be 10% or less per country. This however is likely to be an underestimate as the EUROSTAT denominator value often included psychiatric, long-stay and community beds. Despite this disappointing coverage, other datasets, including the antibiotic resistance prevalence data gathered, were comparable with other European Commission surveillance projects.\textsuperscript{9}

In the context of well-publicized antibiotic resistance problems as well as relationships between antibiotic use and resistance, the results of the present study are not surprising, showing Southern Europe to have the highest levels of total antibiotic use. Similar findings have also been described for antibiotic use in primary care.\textsuperscript{10} The relative closeness of the median total antibiotic use in Western and Northern Europe in the current study is, perhaps, more surprising although the West exhibited a much wider range than the North. The fact that Central and Eastern Europe had the lowest antibiotic use might have been anticipated due to their less developed economies and previously centralized healthcare systems.\textsuperscript{11}

It is probably fair to assume that virtually every agent listed on a hospital formulary is used to a greater or lesser extent in any year. As the data supplied by the ARPAC participating hospitals listed consumption for 2001, down to the last tablet, capsule or
vial used, it may be assumed that the agents used in 2001 approximated to the agents on the hospital formulary that year. Although the ARPAC hospitals used up to 82 different antibiotics in 2001, a large proportion of total use was accounted for by a limited number of antibiotics. The most utilized antibiotic accounted for a median of 16.5% of total use, but this percentage was as low as 7.2% and as high as 60.9% depending on the individual hospital. This is comparable to what has been reported by Polk et al.\textsuperscript{12} in a subset of US hospitals. Mathematical modelling suggests that heterogeneous antibiotic use is more likely to result in low prevalence of resistance.\textsuperscript{13} Further analyses are needed to study the influence of different patterns of antibiotic use on resistance in ARPAC hospitals.

The findings of this hospital-based study were very similar to the community-based findings of Monnet et al.\textsuperscript{1} Across all participating hospitals, there was a significant relationship between the number of different antibiotics used in 2001 and total use of antibiotics, although this association only explained 16% of the variation in total use. When correlations were also explored on a regional basis, they were only significant in Western and Southern Europe, where 32% and 45% of the variation in total use, respectively, could be explained by the number of different antibiotics available. Notably, these two regions had the highest antibiotic use. It should be noted however that numbers in South-Eastern Europe were too small to explore correlations with any confidence, with only eight contributing hospitals.

In summary, total antibiotic use in European hospitals is highly variable, as is the number of different antibacterial agents used. In general, we found a significant relationship between the number of antibiotics used and the total use of these drugs and this was most robust in Western and Southern Europe. One way of controlling antibiotic use may be to narrow the choice of available agents, while maintaining heterogeneity of the different antibacterials used to reduce resistant selection pressures. Rigorous intervention studies with assessment of patient outcome are required however, before antibiotic restriction could be widely implemented.

Acknowledgements

The ARPAC study was funded by the European Commission (project QLK2-CT-2001-00915). F. M. M. was supported by the ESCMID Study Group on Antibiotic Policies to write this manuscript. In addition to the named authors, the ARPAC Steering Group comprised the following members: J. Bruce (UK), J. Mollison (UK), M. J. Struelsen (Belgium), H. Goossens (Belgium), K. J. Towner (UK), J. W. M. van der Meer (The Netherlands), V. Krčmery (Slovak Republic), B. Cookson (UK), P. van den Broek (The Netherlands), L. Dijkshoorn (The Netherlands), J. Vila (Spain), G. Cornaglia (Italy), F. Baquero (Spain), D. Wagner (Belgium), M. van Looveren (Belgium).

MacKenzie et al.

Transparency declarations

F. M. M. has recently received funds for speaking at a symposium organized by Merck Sharp and Dohme Ltd and has also received funds from Merck Sharp and Dohme Ltd to carry out research. F. M. M. recently received sponsorship to attend ICAAC 2005 from Wyeth Ltd and to attend ECCMID 2006 from AstraZeneca. D. L. M. has none to declare. I. M. G. is a member of advisory boards of Wyeth, Jansen-Cilag, Scherring-Plough and Novartis and has recently received consultancies or lecture fees from Merck Sharp and Dohme and Pfizer. I. M. G. is also in receipt of research grants from Pfizer, AstraZeneca and Merck Sharp and Dohme and has recently been supported to attend meetings by Gilead, Wyeth, Novartis and Pfizer.

References