Effect of individual- and group-level antibiotic exposure on MRSA isolation: a multilevel analysis

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Objectives: To observe the relative role of individual and group-level antimicrobial selective pressure on subsequent methicillin-resistant Staphylococcus aureus (MRSA) isolation in a university hospital.

Methods: For this purpose, 18 596 patients were included in a retrospective statistical analysis, applying multilevel modelling with discrete time intervals at the lowest level. Individual-level and hospital group variables on antimicrobial exposure and MRSA colonization pressure were collected from computerized databases.

Results: The simultaneous hospital group- and individual-level analysis showed individual exposure to fluoroquinolones and collective exposure to penicillins to be associated with MRSA isolation after adjustment for colonization pressure and other potential confounders.

Conclusions: These results support efforts to reduce prescriptions of selected antimicrobial drug classes such as fluoroquinolones and show the added value of multilevel analysis for research on the adverse outcomes of antibiotic prescribing.

Keywords: methicillin-resistant Staphylococcus aureus, antimicrobial use, individual exposure, ecological bias

Introduction

Recent studies have highlighted the importance of antibiotic exposure as a significant risk factor for the acquisition and transmission of methicillin-resistant Staphylococcus aureus (MRSA).1 However, the effect of this individual-level antibiotic exposure can be decreased or amplified as a result of an interaction between the individual and the group effect.2 This group-level effect (also called ecological effect) may be particularly important for Gram-positive pathogens, such as MRSA. In a recent article, Monnet et al.3 have reported that, at a hospital level, use of antimicrobial drugs may be an important factor in perpetuating a hospital-wide MRSA outbreak. We have also demonstrated a relationship between antimicrobial use and MRSA spread at the hospital unit (HU) level.4 Notwithstanding their many pitfalls, ecological studies provide a potentially useful function in studies of infectious agents, because they allow measurement of the global effect of an exposure. This is important, because the global effects of antibiotics encompass not just the direct effects on the individual who receives the antibiotic but also the indirect effects mediated by effects on transmissibility or on the likelihood of transmission of susceptible organisms.5 The present study was specifically designed to determine the relative part of individual- and group-level (HU) antimicrobial pressure on subsequent MRSA isolation. For this purpose, we used advanced statistical multilevel modelling, which takes account of factors at the individual and group level simultaneously.

Materials and methods

Setting, study period and patients

The Besançon Hospital is a French university-affiliated hospital. Data for year 2001 were collected for the following departments: medicine, surgery and adult intensive care. Psychiatric, paediatric and gynaecology-obstetric units were excluded. All patients admitted for...
MRSA and antibiotic use

Results

In 2001, 41 790 patients (excluding re-admissions) were admitted, of whom 18 596 were included in our study. We identified 59 MRSA-positive patients according to our selection criteria. Characteristics of the patients are shown in Table 1. In univariate analysis, group-level MRSA colonization pressure ($P = 0.002$), group-level penicillin use ($P = 0.001$) and individual fluoroquinolone exposure ($P < 0.001$) were associated with MRSA isolation. In Figure 1, MRSA isolation is plotted by individual antibiotic exposure and level of antibiotic use in the HU. Figure 1(a) suggests a unique increase with the individual fluoroquinolone exposure regardless of the level of fluoroquinolone use in the HU. Conversely, Figure 1(b) suggests a unique increase with high level of penicillin use in the HU regardless of the individual penicillin exposure.

The simultaneous hospital group- and individual-level analysis showed individual exposure to fluoroquinolones and collective exposure to penicillins to be associated with MRSA isolation after adjustment for colonization pressure and other potential confounders (Table 2). For fluoroquinolones, the effect of individual exposure was not modified when adjusted on collective exposure. Conversely, for penicillins, the observed collective effect was not influenced by individual exposure.

Discussion

The results reported here demonstrate a significant association between antibiotic exposure and subsequent isolation of MRSA in our hospital. This relationship persists when other identified risk factors such as age, sex, MRSA colonization pressure and the type of unit are taken into account. The advanced multilevel analysis fits the complex structure of the data and allows differentiation between individual and collective antibiotic exposure for each antimicrobial class.

Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>MRSA-negative patients</th>
<th>MRSA-positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18 537</td>
<td>59</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>58 years (20.91)</td>
<td>72 years (16.37)</td>
</tr>
<tr>
<td>Percentage of patients who were men</td>
<td>54.4%</td>
<td>57.6%</td>
</tr>
<tr>
<td>Mean (SD) hospitalization duration in the first unit</td>
<td>7.4 days (9.84)</td>
<td>35.3 days (23.89)</td>
</tr>
<tr>
<td>Mean (SD) delay between admission and MRSA isolation</td>
<td>16.2 days (4.73)</td>
<td></td>
</tr>
<tr>
<td>Percentage of patients who received at least one antimicrobial</td>
<td>23.6%</td>
<td>64.4%</td>
</tr>
<tr>
<td>Percentage of patients simultaneously hospitalized with at least one MRSA-positive patient in the same unit</td>
<td>48.2%</td>
<td>74.6%</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus.
Regarding the fluoroquinolone effect, our results are concordant with those of Weber et al., who demonstrated that this class has a specific individual effect on MRSA. Our multilevel model shows that this effect is observed regardless of the amount of fluoroquinolones used at the HU level. It suggests that the ecological effect of fluoroquinolones reported by previous studies may just reflect the sum of individual effects. Fluoroquinolones, which are frequently ineffective against nosocomial MRSA, have an excellent tissue diffusion, which could promote the acquisition of MRSA by eradicating susceptible microorganisms, such as methicillin-susceptible Staphylococcus aureus (MSSA). Moreover, Bisognano et al. have demonstrated that exposure to subinhibitory levels of ciprofloxacin results in increased expression of adherence factors promoting host colonization. It seems that the combination of the two mechanisms gives a plausible explanation for the specific effect of fluoroquinolones on MRSA: fluoroquinolone exposure would promote Staphylococcus aureus colonization while selectively eradicating MSSA strains.

We observed a group-level effect of penicillin use on MRSA isolation and this could not be explained by an ecological fallacy because both individual- and group-level antibiotic exposure was considered using adequate statistical modelling. Thus, an ecological effect purely explained by the aggregated effect of individual exposures can be excluded. The observed ecological effect could be due either to a confounding factor or to a real effect. Penicillins are the most frequently prescribed antibiotic class in our hospital, making it possible that an ecological effect would only manifest above a certain threshold of use.

Some limitations of our study have to be addressed. First, our findings are supported by data collected in a single hospital. It would be of interest to apply our multilevel model to other settings. Second, due to statistical complexity, we used a nested multilevel model which implies that one level is related to only one upper level. So, we only retained the first unit-stay for analysis and consequently did not consider the entire spectrum of MRSA colonization occurring in our hospital. Third, our microbiological data, i.e. isolation of MRSA from clinical sample, were laboratory-based. We did not collect clinical information to confirm MRSA infection. MRSA screening on admission was performed for 15% of the patients admitted. So, we have not evidenced a specific association of antibiotic exposure with MRSA acquisition or with progression from MRSA colonization towards infection but an association between antibiotic exposure and a mix of these two stages.

Finally, our results are consistent with several studies, supporting a relationship between antimicrobial use, particularly individual exposure to fluoroquinolones, and MRSA spread. Interestingly, hospitals in Nordic European countries, with very low MRSA incidence, use the least fluoroquinolones. Our findings support efforts to further study the effect of implementing programmes to control antibiotic use. To conclude, our multilevel analysis shows that exploring the problem of antimicrobial resistance at the individual level or at the collective level alone will miss either of these aspects of the problem.

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Transparency declarations

Conflicts of interests: none.

References