Impact of diversity of antibiotic use on the development of antimicrobial resistance

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Received 4 November 2005; returned 25 January 2006; revised 21 February 2006; accepted 1 March 2006

Objectives: To evaluate the impact of different antibiotic strategies on acquisition of resistant microorganisms.

Methods: A prospective study was conducted over a 44 month period in a single ICU. Four empirical antibiotic strategies for ventilator-associated pneumonia (VAP) were sequentially implemented. Over the initial 10 months, patient-specific antibiotic therapy was prescribed; then, 4 month periods of prioritization or restriction rotation cycles of various antimicrobial agents were implemented for a total of 24 months; and, finally, during the last 10 months (mixing period) the first-line antibiotic for VAP was changed following a pre-established schedule to ensure maximum heterogeneity. Antibiotic consumption was closely monitored every month, and antimicrobial resistance patterns were regularly assessed. Antimicrobial heterogeneity was estimated using a modified Peterson index (AHI) measuring the ratios for the five most used antibiotics. Colonization by targeted microorganisms and susceptibility patterns were compared with the patient-specific period.

Results: Higher diversity of antibiotic prescription was obtained during patient-specific therapy (AHI = 0.93) or mixing periods (AHI = 0.95) than during prioritization (AHI = 0.70) or restriction periods (AHI = 0.68). High homogeneity was associated with increases in carbapenem-resistant Acinetobacter baumannii (CR-Ab) [relative risk (RR) 15.5; 95%CI 5.5–42.8], extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (RR 4.2; 95%CI 1.9–9.3) and Enterococcus faecalis (RR 1.7; 95%CI 1.1–2.9). During the restriction period, incidence of ESBL-producing Enterobacteriaceae and E. faecalis returned to patient-specific rates but CR-Ab remained higher.

Conclusions: Antibiotic prescription patterns balancing the use of different antimicrobials should be promoted to reduce the selection pressure that aids the development of resistance.

Keywords: antibiotic heterogeneity, ventilator-associated pneumonia, antibiotic rotation, cycling antibiotics, antimicrobial mixing

Introduction

Multiresistant pathogens have settled in our institutions, increasing mortality, morbidity and patient length-of-stay.1 Antimicrobial use has been related to the development of antimicrobial resistance.2 This suggests that reducing antimicrobial use would bring down resistance, but unfortunately reducing the total antibiotic use in hospitals is difficult and not always efficient.3 In recent years efforts have focused on rationalizing the management of the available antimicrobial armoury rather than on reducing its total use.4,5 Mathematical models have shown that heterogeneous antibiotic use, defined as a balanced use of the different antimicrobials available, is the most likely...
way of reducing the selection pressure that leads to antibiotic resistance.\textsuperscript{6,7} To date, little clinical information is available for the comparison of homogeneous and heterogeneous antibiotic policies. Our study hypothesis was that the best protection against the development of resistant pathogens in the ICU is provided by heterogeneous antibiotic use. To quantify the degree of heterogeneity of our antimicrobial prescription pattern, we hypothesized an ideal heterogeneous situation in which all the major antimicrobials were prescribed in equal proportions. For each study period, antimicrobial use was compared with this hypothetical situation using an antibiotic index. The aim was to compare the impact of heterogeneous and homogeneous antibiotic regimens on the incidence rate of resistant microorganisms and their susceptibility patterns in a medical-surgical ICU.

**Patients and methods**

**Study design**

During a 44 month period (March 2000–Oct 2003) a prospective cohort trial was conducted to compare the clinical impact of four different antibiotic strategies on microbiological ecology. The study was approved by the local ethics committee and the requirement for informed consent was waived.

**Study patients and setting**

This study was conducted in a 14 bed medical-surgical ICU, the only ICU in a 400 bed teaching hospital, where each patient was housed in a separate room. The nurse-to-patient ratio was 1:3 and the occupancy rate varied from 70 to 80% in the 2 years previous to the study. The ICU was staffed by seven full-time attending board-certified critical care physicians and three supervised residents. All patients admitted to the ICU for more than 48 h over the study period were eligible for the study. Exclusion criteria included patients aged below 18 years or patients who were severely immunocompromised (conditions such as AIDS, chemotherapy and haematological tumour that required specific empirical antibiotic regimens covering opportunistic pathogens). All patients who entered the study were followed prospectively until ICU discharge or death.

**Interventions**

Four consecutive time periods were established on the basis of the different antimicrobial strategies used for the empirical treatment of ventilator-associated pneumonia (VAP). During the first 10 months, patients with suspected VAP received empirical antibiotic treatment according to a patient-specific strategy. Multiple antibiotic choices were allowed and the regimen was chosen on the basis of length of hospitalization and recent antibiotic exposure.

During the next 24 months, three antimicrobial groups (anti-pseudomonal carbapenems, anti-pseudomonal cephalosporins and piperacillin/tazobactam) were alternated for the empirical treatment of VAP in pre-determined 4 month cycles. In the first 12 months, 4 month prioritization cycles were implemented in the following order: anti-pseudomonal carbapenems, anti-pseudomonal cephalosporins and piperacillin/tazobactam. During the subsequent 12 months the same antibiotics were restricted in 4 month cycles but in the reverse order: first piperacillin/tazobactam, then anti-pseudomonal cephalosporins and then anti-pseudomonal carbapenems. Aminoglycosides or ciprofloxacin were added to the antibiotic regimen if the presence of *Pseudomonas aeruginosa* was anticipated (for instance, in late-onset pneumonia).

During the last 10 months (the mixing period) the first-line antibiotic for VAP was changed in consecutive patients following a pre-established schedule (anti-pseudomonal carbapenems → ciprofloxacin → clindamycin + anti-pseudomonal cephalosporins → piperacillin/tazobactam → ... anti-pseudomonal carbapenems) to ensure that antibiotic use was distributed equally among patients.

The clinical approach to patients with suspected VAP in our ICU has been summarized previously.\textsuperscript{5–10} Empirical antibiotic therapy was started only after diagnostic procedures were performed, in accordance with the antimicrobial regimen defined for each period and narrowing the spectrum as culture results identified the causative organism and its susceptibility.

Antimicrobial prioritization and restriction rotation cycles were scheduled to last 4 months each in order to maximize the potential beneficial effects of rapid cycling periods postulated by mathematical models.\textsuperscript{1} The antimicrobial rotation sequence was designed to circumvent the resistance mechanisms that pathogens were likely to have developed after the previous antibiotic exposure. Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant Enterococcus (VRE) antibiotics were not prescribed empirically due to the low prevalence (<5%) in our ICU. Protocol deviations were allowed if a known allergy to the scheduled antibiotic, exposure to it within the previous 15 days or isolation of a pathogen non-susceptible to it was reported. Infection control practices were implemented following CDC guidelines.\textsuperscript{11} In 2002, during the course of the study an educational programme was implemented, including an update in the protocol for the management of central venous catheters.\textsuperscript{12}

**Study definitions**

The definition of VAP and information regarding diagnostic procedures have been reported elsewhere.\textsuperscript{8,13} CDC criteria were used to define other nosocomial infectious events.\textsuperscript{14} Infections were considered to be nosocomial in origin if they were not present or suspected on admission. Infectious episodes in the same patient were analysed as independent events if they were separated by an interval of 72 h. Antibiotic use was expressed in prescribed daily doses (PDDs), defined as the ratio of total grams of an antibiotic administered divided by the usual daily dose prescribed in the ICU setting for a patient with normal renal function.

*P. aeruginosa*, *Acinetobacter baumannii* and the Enterobacteriaceae family (including *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter spp.*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Morganella morgani*, *Proteus spp.* and *Serratia marcescens*) were defined as resistant Gram-negative organisms. MRSA and *Enterococcus faecalis* were defined as resistant Gram-positive organisms.

Bacterial susceptibility to antibiotics was recorded only in the first sample tested positive for the targeted microorganisms. Susceptibility to the antimicrobials used for VAP empirical treatment (anti-pseudomonal carbapenems, anti-pseudomonal cephalosporins, piperacillin/tazobactam and quinolones) was tested for Gram-negative microorganisms, and susceptibility to methicillin and vancomycin was tested for *S. aureus* and *Enterococcus sp.*

Susceptibility tests were performed using a semi-automated Wider I system (Fco Soria Melguizo, Madrid, Spain) using 6W and 5W panels. For extended-spectrum β-lactamase (ESBL) detection, double diffusion discs were used with cefazidime/cefazidime-clavulanate and cefotaxime/cefotaxime-clavulanate Etests. For the purposes of analysis, isolates with intermediate susceptibility were considered resistant.

**Study variables**

The following data were prospectively collected for all patients: age, gender, severity-of-illness based on the Acute Physiology and...
Antibiotic heterogeneity reduces antimicrobial resistance

Chronic Health Evaluation (APACHE) II score, admission category (surgery, medicine or trauma), origin of patients (different hospital, community or another ward within the hospital), length of stay in ICU (LOS), survival.

Total antibiotic use was recorded on a monthly basis as PDD/100 ICU stays, which reflects the probability that a patient will receive a specific antibiotic during the ICU stay. An antibiotic homogeneity index (AHI) was used to quantify the degree of antibiotic homogeneity of a given period. A modified version of the Peterson homogeneity index was used:\textsuperscript{15}

$$\text{AHI} = 1 - \frac{n}{2 \times (n - 1)} \times \sum (a_i - b_i)$$

where $a_i$ is the proportion of the given antimicrobial in a hypothetical perfectly heterogeneous situation, $b_i$ is the proportion of the given antimicrobial in the given study period and $n$ is the number of antimicrobials considered in the equation.

Antimicrobials whose use represented more than 10% of the total antibiotic prescription during the study period were introduced in the equation.

Use of each of the antimicrobials chosen was then converted into a proportion of the selected antimicrobial group. AHI was then calculated comparing the antimicrobial use of each period with its hypothetical proportion in the case of ideally heterogeneous use. AHI assumes a value between 0 and 1, with 1 indicating complete heterogeneity. AHIs of each prioritization and restriction schedule were analysed separately and then pooled together to obtain the mean AHI for prioritization and restriction periods.

For all targeted microorganisms the incidence rate of colonization and/or infections was calculated by dividing the number of patients with a positive culture by the total number of patients admitted to the ICU from 30 days post-initiation of the intervention period until 30 days post-study finalization. Surveillance cultures to determine colonization on ICU admission were not routinely performed. Microbiological data collection was extended 1 month beyond the end of each period, on the assumption that the effects of antibiotic pressure on microbiological ecology may not occur immediately after its prescription.

Statistical analysis

Each period was compared with the patient-specific antibiotic therapy period used as the control group. Proportions were compared using the $\chi^2$ test with Yates correction or Fisher's exact test when necessary. Means were compared using the Student's $t$-test. The Bonferroni correction was used to adjust for multiple comparisons and $P$ values of <0.016 were considered significant. For each antibiotic a Poisson regression model with the dependent variable PDD and the exposure variable total days of stay was used to estimate the relative risk (RR) of antibiotic consumption in two different periods. The patient-specific period was used as the reference category, and 95% confidence intervals of the RRs were obtained. The analyses were performed using Stata software.\textsuperscript{16} The incidences of colonization/infection of each of the targeted microorganisms were compared using the RR with a 95% confidence interval.

Results

Demographic results

During the 44 months of the study, 2677 patients were prospectively evaluated (794 in the patient-specific period, 626 in the prioritization period, 568 in the restriction period and 689 in the mixing period). No significant differences were found in any of the epidemiological variables analysed between the different study periods (Table 1) except for a significant increase in the proportion of trauma patients during the mixing period ($P < 0.016$) due to the opening of a neurosurgical unit in our institution in 2002, which served as a referral centre for the area. This fact resulted in an increase in the number of patients admitted from other hospitals. Patients admitted during the mixing period were younger than those admitted during the patient-specific period ($P < 0.016$).

Antibiotic use

Table 2 details the antibiotic use during the different study periods. Total antibiotic use was similar in patient-specific and

Table 1. Epidemiological characteristics of patients included in the study

<table>
<thead>
<tr>
<th>Study periods</th>
<th>patient-specific</th>
<th>prioritization</th>
<th>restriction</th>
<th>mixing</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>777</td>
<td>614</td>
<td>556</td>
<td>674</td>
<td>2621</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>59.4 ± 17.6</td>
<td>59.5 ± 15.4</td>
<td>57.4 ± 17.1</td>
<td>57.2 ± 14.6*</td>
<td>58.3 ± 16.1</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>70.5</td>
<td>72.3</td>
<td>69.7</td>
<td>72.7</td>
<td>71.1</td>
</tr>
<tr>
<td>APACHEII ± SD</td>
<td>13.0 ± 2.6</td>
<td>12.8 ± 1.6</td>
<td>12.9 ± 2.0</td>
<td>13.3 ± 3.5</td>
<td>13.0 ± 2.4</td>
</tr>
<tr>
<td>MV %</td>
<td>50</td>
<td>50.2</td>
<td>51.9</td>
<td>49.2</td>
<td>50.2</td>
</tr>
<tr>
<td>Medical patients %</td>
<td>66.2</td>
<td>69</td>
<td>68.4</td>
<td>62.6</td>
<td>66.4</td>
</tr>
<tr>
<td>Surgical patients %</td>
<td>25.6</td>
<td>23.8</td>
<td>20.0</td>
<td>20.8</td>
<td>22.5</td>
</tr>
<tr>
<td>Trauma patients %</td>
<td>8.2</td>
<td>7.2</td>
<td>11.6</td>
<td>16.6*</td>
<td>10.9</td>
</tr>
<tr>
<td>Patients referred from the community %</td>
<td>55.4</td>
<td>58.9</td>
<td>49.0</td>
<td>57.8</td>
<td>55.2</td>
</tr>
<tr>
<td>Patients referred from another hospital %</td>
<td>6.4</td>
<td>9.5</td>
<td>18.7*</td>
<td>20.0*</td>
<td>13.6</td>
</tr>
<tr>
<td>Patients referred from other wards within the hospital %</td>
<td>38.2</td>
<td>31.6</td>
<td>32.3</td>
<td>22.2*</td>
<td>31.0</td>
</tr>
<tr>
<td>Mean ICU stay ± SD (days)</td>
<td>7.4 ± 3.1</td>
<td>7.7 ± 2.9</td>
<td>7.8 ± 3.4</td>
<td>7.0 ± 4.3</td>
<td>7.4 ± 3.4</td>
</tr>
<tr>
<td>ICU mortality %</td>
<td>16.6</td>
<td>16.0</td>
<td>18.9</td>
<td>20.1</td>
<td>17.9</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; MV %, percentage of mechanically ventilated ICU patients.

*P < 0.016 compared with the patient-based period after applying Bonferroni correction for multiple comparisons.
Of the total antimicrobial prescription 71% was for the treatment of VAP. Piperacillin/tazobactam, amoxicillin/clavulanate, cephalosporins, carbapenems and quinolones were the most prescribed antimicrobials (overall prescription >10%) during the entire study period, representing 69.4% of the total. Figure 1 details antibiotic consumption of the most prescribed agents during the different study periods. Amoxicillin/clavulanate was the most prescribed antibiotic during the patient-based period. AHI during this period was estimated to be 0.93 (Figure 2).

During the prioritization periods the most prescribed antimicrobial was the currently prioritized antibiotic, which was used significantly more than during the patient-specific period: antipseudomonal carbapenems RR 2.06 (95% CI: 1.76–2.39); antipseudomonal cephalosporins RR 4.9 (95% CI: 4.02–5.92) and piperacillin/tazobactam RR 1.59 (95% CI: 1.34–1.89). AHI of carbapenem (0.75), antipseudomonal cephalosporins (0.55) and piperacillin/tazobactam (0.79) schedules were more homogeneous than the index estimated for the patient-specific period. The pooled AHI of the prescription regimens implemented during prioritization schedules was 0.70 (Figure 2).

During the restriction period the restricted antibiotic was among the least prescribed during its corresponding schedule. Its use dropped significantly compared with the patient-specific period: RR 0.15 (95% CI: 0.09–0.22) for piperacillin/tazobactam, RR 0.26 (95% CI: 0.16–0.45) for antipseudomonal cephalosporin and RR 0.34 (95% CI: 0.25–0.46) for antipseudomonal carbapenems. Restriction of the pre-scheduled antimicrobials led to a peak in cephalosporin use during the

### Table 2. Consumption of antibiotics during the study periods

<table>
<thead>
<tr>
<th>Antibiotic use PDD/100 ICU stays</th>
<th>patient-specific</th>
<th>CBP</th>
<th>CEP</th>
<th>P/T</th>
<th>NO P/T</th>
<th>NO CEP</th>
<th>NO CBP</th>
<th>mixing</th>
<th>Overall antibiotic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>7.8</td>
<td>12.1</td>
<td>14.3</td>
<td>8.2</td>
<td>23.4</td>
<td>9.5</td>
<td>7.7</td>
<td>9.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>10.1</td>
<td>20.8</td>
<td>6.7</td>
<td>5.7</td>
<td>13.7</td>
<td>15.8</td>
<td>3.5</td>
<td>12.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>11.6</td>
<td>8.0</td>
<td>9.6</td>
<td>7.0</td>
<td>3.6</td>
<td>12.0</td>
<td>17.5</td>
<td>12.7</td>
<td>10.6</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>10.5</td>
<td>9.1</td>
<td>7.3</td>
<td>16.8</td>
<td>1.6</td>
<td>6.9</td>
<td>7.6</td>
<td>11.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Quinolones</td>
<td>7.6</td>
<td>7.6</td>
<td>3.7</td>
<td>7.8</td>
<td>8.1</td>
<td>3.5</td>
<td>13.2</td>
<td>13.4</td>
<td>8.4</td>
</tr>
<tr>
<td>Antipseudomonal cephalosporins</td>
<td>4.2</td>
<td>4.0</td>
<td>20.5</td>
<td>1.9</td>
<td>8.9</td>
<td>1.2</td>
<td>4.7</td>
<td>5.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Metronidazole/ornidazole</td>
<td>3.7</td>
<td>7.3</td>
<td>10.4</td>
<td>2.5</td>
<td>10.5</td>
<td>5.3</td>
<td>3.9</td>
<td>5.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5.8</td>
<td>9.7</td>
<td>6.1</td>
<td>5.0</td>
<td>4.2</td>
<td>1.5</td>
<td>2.7</td>
<td>3.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>6.8</td>
<td>3.7</td>
<td>3.9</td>
<td>3.8</td>
<td>1.7</td>
<td>2.8</td>
<td>3.4</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>2.5</td>
<td>4.4</td>
<td>4.8</td>
<td>3.0</td>
<td>3.7</td>
<td>3.0</td>
<td>4.8</td>
<td>5.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>6.2</td>
<td>3.9</td>
<td>1.6</td>
<td>0.3</td>
<td>2.9</td>
<td>0.8</td>
<td>2.3</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.5</td>
<td>4.7</td>
<td>3.2</td>
<td>0.0</td>
<td>2.3</td>
<td>1.6</td>
<td>0.0</td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>9.6</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Total</td>
<td>78.3</td>
<td>95.3</td>
<td>92.1</td>
<td>62.1</td>
<td>84.6</td>
<td>64.0</td>
<td>81.0</td>
<td>92.6</td>
<td>82.1</td>
</tr>
</tbody>
</table>

CBP, carbapenem prioritization schedule; CEP, antipseudomonal cephalosporin prioritization schedule; P/T, piperacillin/tazobactam prioritization schedule; NO P/T, piperacillin/tazobactam restriction schedule; NO CEP, antipseudomonal cephalosporins restriction schedule; NO CBP, carbapenem restriction schedule; Mixing, mixing period.
During the mixing period the AHI was estimated to be 0.95 (Figure 2); cephalosporins were the most frequently prescribed group of antibiotics.

**Incidence rate of targeted microorganisms**

Figure 3 shows the incidence rate of the different targeted microorganisms.

The *A. baumannii* incidence rate increased significantly during the prioritization period (RR 4.2; 95%CI: 2.4–7.2), with a 15.5-fold increase (95%CI: 5.5–42.8) in the carbapenem-resistant strains (from 0.48% in the patient-specific period to 7.6% in the prioritization period). An index case in the patient-specific therapy period developed three secondary cases, whereas the index case during the carbapenem prioritization period generated 43 secondary cases. Selective restriction of antibiotics partially controlled the rate of *A. baumannii* strains (4.1%) and carbapenem-resistant *A. baumannii* strains (3.6%) although their incidence remained significantly higher than during the patient-specific period (RR 2.2; 95%CI: 1.2–4.0 and RR 8.4; 95%CI: 2.9–24.3, respectively). During the mixing period, total isolates of *A. baumannii* returned to levels similar to those seen during the patient-specific period but the percentage of carbapenem-resistant strains remained significantly higher (3.8%) (RR 3.8; 95%CI: 1.2–12.1).

Enterobacteriaceae incidence increased progressively during the prioritization (15.7%), restriction (18.8%) and mixing (19.0%) periods with respect to the patient-specific period (10.1%) (RR 1.5, 95%CI: 1.4–2.0; RR 1.8, 95%CI: 1.3–2.3 and RR 1.8, 95%CI: 1.4–2.4, respectively). Similarly, ESBL-producing strains increased from 0.9% during the patient-specific period to 3.8% during the prioritization period (RR 4.2, 95%CI 1.9–9.3). Selective restriction of antimicrobials was associated with the control of ESBL-producing Enterobacteriaceae (2.1%), which remained within similar limits during the mixing period (2.2%).

*P. aeruginosa* isolates increased significantly from 6.4% during the patient-specific period to 9.5% in the restriction period (RR 1.4; 95%CI: 1.02–2.19) and 10.0% during the mixing period (RR 1.5; 95%CI: 1.0–2.2), but strains resistant to one or more antibiotics did not suffer significant variations between periods.

Among Gram-positive cocci, an increase in *E. faecalis* isolates (5.6%) was observed during the prioritization period (RR 1.7; 95%CI: 1.2–2.3) and there was no significant variation in the restriction and mixing periods. An increase in *S. aureus* (from 0.48% to 0.77%) was observed during the prioritization period, but there was no significant variation in the restriction and mixing periods. MRSA isolates did not show significant variations throughout the study period.

Figure 3. Incidence of patients with clinical isolates of resistant microorganisms. *P < 0.05 compared with the patient-specific period. **<5% of *Enterococcus faecalis* resistant to vancomycin. PS, patient-specific period; PP, prioritization period; RP, restriction period; MP, mixing period.
The study periods.

variations in period.
in Gram-positive microorganisms its effect was limited to an

<table>
<thead>
<tr>
<th>Patients with clinical samples</th>
<th>Pseudomonas aeruginosa</th>
<th>Acinetobacter baumannii</th>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS (%)</td>
<td>PP (%)</td>
<td>RP (%)</td>
</tr>
<tr>
<td>n = 54</td>
<td>93.3</td>
<td>84.7</td>
<td>98.2</td>
</tr>
<tr>
<td>n = 46</td>
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<td>n = 56</td>
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<tr>
<td>n = 55</td>
<td>88.3</td>
<td>69.6</td>
<td>70.9</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>72.2</td>
<td>82.6</td>
<td>85.7</td>
</tr>
<tr>
<td>Imipenem</td>
<td>64.8</td>
<td>80.4</td>
<td>71.4</td>
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<tr>
<td>Ciprofloxacin</td>
<td>68.5</td>
<td>84.7</td>
<td>69.6</td>
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</tbody>
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PS, patient-specific period; PP, prioritization period; RP, restriction period; MIX, mixing period. *P < 0.016 compared with the patient-specific period (PS) after applying Bonferroni correction for multiple comparisons.

95% CI: 1.1–2.9). Incidence rates of E. faecalis returned to those of the patient-based period (3.1%) during the restriction (4.2%) and mixing periods (2.5%). Fewer than 5% of the E. faecalis strains were resistant to vancomycin through all the study periods. There were no significant differences in the incidence rate of MRSA during the different study periods.

Susceptibilities to antibiotics of Gram-negative bacilli

Susceptibility of the targeted microorganisms to the major selected antimicrobials is detailed in Table 3. A. baumannii susceptibility to carbapenems was significantly lower during the prioritization (13.7%) and restriction (11.1%) periods than in the patient-specific period (76.4%) (P < 0.016). Susceptibility to piperacillin/tazobactam paralleled susceptibility to carbapenems (10.0%, 14.8% and 23.1% during the prioritization, restriction and mixing periods, respectively) with respect to the patient-specific period (87.8%) (P < 0.016). Enterobacteriaceae susceptibility to ceftazidime fell significantly during the prioritization period (74.4%) (P < 0.016) and returned to values similar to those observed during the patient-specific period (90.5%) in the restriction (88.1%) and mixing periods (86.5%). Susceptibility of Enterobacteriaceae to ciprofloxacin decreased significantly during the restriction period (70.7%) in comparison with the patient-specific period (91.7%) (P < 0.016). No significant variations in P. aeruginosa susceptibility were noted in any of the study periods.

Discussion

This study is unique in comparing the impact of multiple guideline-driven strategies with a patient-specific regimen of empirical antibiotic prescription on the selection of resistant pathogens and susceptibility patterns over a long period. The diversity of the antimicrobial prescription was estimated using the Peterson homogeneity index (AHI). We found that high antibiotic homogeneity protocols (prioritization and restriction periods) led to more homogeneous prescription patterns. In contrast, patient-specific and mixing regimens led to a heterogeneous prescription pattern. In Gram-negative microorganisms, homogeneous antibiotic prescription was associated with a significant increase in ESBL-producing Enterobacteriaceae and a 15-fold increase in isolates of carbapenem-resistant A. baumannii (CR-Ab), whereas in Gram-positive microorganisms its effect was limited to an increase in E. faecalis isolates (<5% VRE) in the prioritization period.

Though many studies of antimicrobial cycling and scheduling have been performed,17–21 the evaluation of the strategy is hampered by ambiguities in the definition of the notion of cycling and by methodological problems.22,23 In the present study, prioritization and restriction periods were considered as different strategies. Although the regimens alternated the use of the empirical antimicrobials over equal periods of time, the antimicrobials selected were first prioritized and then restricted. Prioritization and restriction regimens attained a significantly more homogeneous prescription index than the patient-specific and mixing periods. During the prioritization period, as expected, the selection pressure in each schedule was exerted by the prioritized antimicrobial; in contrast, its restriction produced unexpected increases in cephalosporins, carbapenems and β-lactam-β-lactamase inhibitors.

In the clinical setting, alternating different antibiotic classes during pre-defined time periods has been proposed as a structured way of introducing antibiotic heterogeneity into prescribing practices.24 Although global antibiotic use measured at the end of the cycle may be balanced, there may be substantial divergences in antibiotic prescription during the different prioritization/restriction schedules that compose each cycle. These periods, of variable duration, in which homogeneous selective antibiotic pressure is imposed, may favour the emergence of resistance, as predicted by mathematical models.25,26 Recently, van Loon et al.27 reported that in clinical practice, quarterly homogeneous antibiotic exposure alternating quinolones and β-lactams increased Gram-negative microorganism resistance to the antibiotic in use. In our study, a significant increase in A. baumannii was noted, including an outbreak of carbapenem-resistant strains after increasing the carbapenem use. Similarly, increased third-generation cephalosporin use was associated with a significant increase in Enterobacteriaceae isolates including ESBL-producing strains.

Several studies have reported the impact of implementing antibiotic restriction policies on the incidence of resistant Gram-negative microorganisms.28,29 A decrease in ESBL-producing Enterobacteriaceae was observed after restricting the cephalosporin use in this study. However, antibiotic restriction did not bring down CR-Ab strains to levels similar to those seen during the patient-specific period. Failure to control CR-Ab incidence may be associated with increases of 37% and 58% during the patient-specific period. Failure to control CR-Ab incidence may be associated with increases of 37% and 58% during the patient-specific period. Similar findings have been described by Meyer et al.24 who found that the implementation of a cephalosporin class restriction programme to
control a cephalosporin-resistant Klebsiella outbreak was associated with an unintended increase in the use of imipenem and concomitant increase in imipenem-resistant A. baumannii. This phenomenon, described by Burke as ‘squeezing the balloon’ (constraining one end causes the other end to bulge), could be responsible for the failure to control CR-Ab incidence during the restriction period.30

The impact of antimicrobial strategies on resistant microorganisms may vary depending on the bacterial species and the type of resistance mechanism involved. For instance, we know that resistance genes to several antibiotic classes may be contained in gene cassettes. So, reduction of one antibiotic class may not necessarily have any direct influence on the existence of these gene cassettes, and the resistance levels may remain unchanged.31

This mechanism has been suggested as the cause of the lack of reduction in E. coli resistant to sulphonamides after a reduction in its use in the UK.32

Antibiotic administration following a pre-established order in consecutive patients (mixing) was suggested by Bergstrom et al.33 as a strategy to control and prevent resistance by imposing, under broad conditions, greater heterogeneity than does cycling. Our findings confirmed that mixing achieved a more heterogeneous use of antimicrobials than prioritization and restriction periods. Unfortunately, the mixing period failed to reduce colonization/infection by carbapenem-resistant A. baumannii, P. aeruginosa and Enterobacteriaceae spp. to patient-specific regimen rates. The increase of 18% in total antibiotic consumption during this period with respect to the patient-specific regimen may have been responsible for this finding.

During the patient-specific period, selection of empirical antimicrobial therapy for suspected VAP was based on individual factors. This ‘a la carte’ treatment of patients requires higher levels of training than guidelines recommending prioritization or restriction. During the patient-specific period greater heterogeneity was achieved than during prioritization and restriction. Many studies evaluating different antibiotic policies were designed in response to an increasing rate of resistance.34,35 In contrast, the interventions carried out in this study were compared with the patient-specific period, which accounted for the lowest resistance rates of all periods analysed.

The present analysis is novel in that it quantifies the diversity of the antibiotic prescription using an objective index of heterogeneity. It has several other strengths which merit comment. Unlike prior studies of cycling which report only single interventions,18,20,21,27 the present analysis started with a high degree of heterogeneity and after various interventions also ended with a period of high heterogeneity. The use of guideline-specific protocols was analysed and contrasted with mixing or patient-specific regimens. In all the intervention periods the therapy was streamlined, based on the susceptibility patterns of the microorganisms considered responsible; this is probably one of the best ways of ensuring heterogeneous antibiotic prescription. Other unique characteristics of this report were the comparison of multiple antibiotic interventions and a very long-term follow up.

A major limitation is that this is a single centre study carried out over a long period, and we should be cautious about extrapolating the results to other settings. Antibiotic regimens were focused only on VAP treatment, but VAP is the most frequent nosocomial infection in the ICU, consuming the highest percentage of antibiotic prescriptions,36 and in our cohort almost two-thirds of antimicrobial prescriptions were for VAP. Second, the study design and prolonged study period cannot account for temporal confounders such as seasonal variations which may have affected the impact of the different antibiotic policies observed. Similarly, the sequential design of the study may have conflated the final analysis of resistance patterns. However, according to mathematical modelling the dynamics of resistance are driven by the replacement of resistant strains by new admissions.7 Because the mean duration of our ICU stay was 8 days it is likely that complete replacement of the patient population was possible within a matter of weeks/months. Taking this into account, the incidence of colonization and infection were measured in patients admitted to the ICU from 30 days post-initiation of the intervention period until 30 days post-study finalization. Third, case-mixes experienced some variations, with an increase in head injured patients during periods of restriction and mixing. This may have altered the microbial ecology responsible for VAP episodes because S. aureus has been reported to be the leading aetiological agent of VAP in patients in coma.37 Nevertheless, no changes in Gram-positive microorganisms were documented during the last two periods. Other groups have previously implemented infection control practices concurrent with a restriction programme.21,35 Similarly, though nurse-to-patient ratio, occupation rate and hands hygiene policy remained stable throughout the study period, during the restriction period an infection control programme for the management of central venous catheters was introduced which may have reduced the emergence of new resistant strains. Fifth, as with previous antibiotic heterogeneity studies, multiple interventions seem to be occurring. This is evident from the overall increases in antibiotic use during the prioritization and the mixing periods (6 and 18%, respectively). Finally, the prolonged study period involving nearly 3000 patients precluded both the performance of surveillance cultures to determine colonization on ICU admission and the precise characterization of the isolated strains using genotyping techniques. For the same reason, bacterial susceptibility was recorded only from the first sample.

In summary, guideline-driven strategies of empirical antibiotic prescription for pneumonia were not associated with any benefit in terms of contention of resistance in the ICU when compared with a patient-specific antibiotic regimen. Moreover, both prioritization and restriction determined high homogeneity, facilitating colonization by Enterobacteriaceae and non-fermentative Gram-negative bacilli, including outbreaks of CR-Ab in the period of imipenem prioritization and ESBL-producing Enterobacteriaceae in the period of cephalosporin prioritization. Our results provide clinical confirmation of the findings of mathematical models, suggesting that antibiotic prescription patterns favouring a balanced use of different antimicrobials should be preferred.

Acknowledgements

We are indebted to Michael Maudsley for editing the manuscript. This work was supported in part by grants from RED Respira-ISCIII-RITIC-03/11, SEMICYUC and CIRIT SGR 2005/920.

Transparency declarations

A. S.: Lilly and Sociedad Española de Medicina Intensiva, Critica y Unidades Coronarias (SEMICYUC) Grant, Sevilla 2002. All other authors: none to declare.
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