Impact of ertapenem use on *Pseudomonas aeruginosa* and *Acinetobacter baumannii* imipenem susceptibility rates: collateral damage or positive effect on hospital ecology?

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Background: Conflicting evidence has been reported on the impact of ertapenem use on the susceptibility of *Pseudomonas* spp. to group 2 carbapenems. No extensive data for *Acinetobacter baumannii* are currently available.

Methods: A retrospective time-series segmented regression analysis was conducted in a tertiary centre from January 2001 to December 2011. Ertapenem was introduced in January 2005. Antimicrobial drug use was defined as the number of defined daily doses/100 patient-days (DDDs/100 PDs). Susceptibility (CLSI) was measured in terms of proportion and incidence density.

Results: Mean monthly use of imipenem was 2.9 ± 0.9 DDDs/100 PDs, as compared with 1.2 ± 0.7 DDDs/100 PDs for meropenem and 1.0 ± 0.7 DDDs/100 PDs for ertapenem (after its introduction). After ertapenem adoption, a downward trend was seen in the use of imipenem (P = 0.016) and ciprofloxacin (P = 0.004). A total of 6272 *Pseudomonas aeruginosa* and 1093 *A. baumannii* isolates were evaluated. Susceptibility of *P. aeruginosa* to imipenem improved after ertapenem introduction, both according to the proportion of susceptible isolates (P = 0.002) and to the incidence density of resistance (P ≤ 0.001). No significant change was seen in *A. baumannii* susceptibility to imipenem (P = 0.772). By multiple linear regression analysis, the incidence density of imipenem-resistant *P. aeruginosa* increased with the use of imipenem (P = 0.003) and ciprofloxacin (P = 0.008). Occurrence of outbreaks (P ≤ 0.001) and use of gentamicin (P = 0.007) were associated with *A. baumannii* resistance to imipenem.

Conclusions: Use of ertapenem was directly associated with a downward trend in the use of imipenem and ciprofloxacin, which may have contributed to improve the susceptibility of *P. aeruginosa* to imipenem. Ertapenem use had no impact on the susceptibility of *A. baumannii* to imipenem.

Keywords: carbapenems, antimicrobial resistance, time-series analysis

Introduction

Antimicrobial resistance driven by antimicrobial selective pressures is an increasing concern in hospitalized patients and surveillance of clinical isolates for the presence of resistance is mandatory following the introduction of a new antimicrobial agent.

Ertapenem is a group 1 carbapenem with little activity against *Pseudomonas* and *Acinetobacter* species. The lack of clinically relevant activity against these microorganisms has raised uncertainties about its selection for mutants with cross-resistance to group 2 carbapenems (imipenem, meropenem and doripenem). Published *in vitro* and *in vivo* research has yielded conflicting results.1,2 A few clinical studies have shown no association between ertapenem use and decreased *Pseudomonas aeruginosa* susceptibility to antipseudomonal carbapenems;1,4 however, short monitoring periods were usually assessed and doubts have been expressed about methodological issues.5 Whether ertapenem may influence the selection of *Acinetobacter* species with cross-resistance
to group 2 carbapenems is a concern that remains to be ascertained.

The aim of our study was to assess the impact of ertapenem use on the imipenem susceptibility of *P. aeruginosa* and Acinetobacter baumannii after ertapenem inclusion in the hospital formulary, also considering risk factors for resistance other than antimicrobial use.

**Methods**

**Setting, participants and study design**

**Setting**

Hospital A Coruña is a 1445 bed, tertiary-level public hospital in northwest Spain. The hospital has medical and surgical specialties and four intensive care units (ICUs). The paediatric and neonatal ICUs have 9 and 10 beds, respectively. The medical and surgical ICUs for adults have 64 beds between them. The hospital has very active bone marrow and solid organ transplantation programmes and also serves as a referral institution.

**Participants**

There were a total of 480562 patient admissions during the study period, representing 4652776 patient-days (PDs).

**Dates**

The study was carried out from January 2001 to December 2011. Ertapenem was introduced in January 2005.

**Design**

A retrospective time-series segmented regression analysis was conducted, with a pre-ertapenem period of 48 months (from January 2001 to December 2004) and an ertapenem period of 84 months (from January 2005 to December 2011).

**Infection control**

The Department of Preventive Medicine follows the CDC Guideline for Isolation Precautions in hospitals. Contact isolation is practised for patients with multidrug-resistant (MDR) organisms.

The staff of the infection control team did not significantly change during the study period. An antimicrobial stewardship programme has been in place during the past decade. No restrictions on antimicrobial prescription have been imposed. The new agents active against Gram-negative microorganisms added to the formulary during the study period were tigecycline in 2007 and doripenem in 2010, which was marginally used. In May 2010, a campaign to promote frequent hand washing to prevent the spread of the H1N1 flu virus was implemented and wall dispensers of alcohol hand rubs were progressively placed in each patient’s room. No other major changes were made in infection control practices.

There were two significant outbreaks of imipenem-resistant *A. baumannii* at our institution during the study period: from October 2001 to August 2002 and from September to December 2011. The characteristics of the first outbreak have been published previously. During the second hospital outbreak, 24 patients became infected or colonized, mainly in the post-operative ICU, by a single epidemic strain. *A. baumannii* was also associated with several ICU sporadic outbreaks, occurring in January and May 2008 and January and September 2009, caused by various MDR strains. Extensive cleaning of common sources and the general environment, active surveillance and contact isolation for colonized and infected patients were the main measures taken during outbreaks.

**Data source and variables**

Data were collected at monthly intervals from the Pharmacy Department, the Clinical Microbiology Laboratory and the hospital information warehouse.

**Measurement of antimicrobial use**

The use of antimicrobials was measured as the number of defined daily doses (DDDs)/100 PDs, as recommended by the Anatomical Therapeutic Chemical Classification System and the DDD index. Ertapenem was used as treatment, rather than as surgical prophylaxis, mainly for community-acquired, complicated intra-abdominal infections and for coverage of β-lactamase-producing microorganisms. In addition to ertapenem, data were collected on imipenem, meropenem, selected fluoroquinolones (levofloxacin and ciprofloxacin), aminoglycosides (amikacin, gentamicin and tobramycin), all penicillins, all cephalosporins, metronidazole, colistin and tigecycline.

**Measurement of microorganism susceptibility**

Susceptibility rates of *P. aeruginosa* and *A. baumannii* to imipenem were measured as the proportion of isolates susceptible to the drug and the incidence density of resistant and susceptible isolates on a monthly basis. The incidence density was calculated as the number of isolates/1000 PDs. The MICs of carbapenems and other antimicrobials were measured using a MicroScan instrument (Siemens) in accordance with CLSI guidelines. The specific MIC values of imipenem were as follows: MIC ≤4 mg/L, susceptible; MIC 8 mg/L, intermediate; and MIC ≥16 mg/L, resistant. Resistance to imipenem was considered as defined by CLSI breakpoints for resistance; isolates with intermediate susceptibility to imipenem were not included in the analysis. To avoid duplicates, one isolate with the same susceptibility pattern per patient, per month, was included in the analysis, irrespective of the body site from which it was obtained. Microbiological isolates from community samples, outpatient clinics or the emergency room were excluded.

**Administrative data and potential confounders**

Number of PDs, number of admissions, bed occupancy, mean length of stay in ICUs, hospital comorbidity and mortality indices, alcohol hand rub use (as an indirect measure of hand hygiene compliance) and outbreaks were recorded. Alcohol-based hand rub use was measured in mL/100 PDs.

**Statistical analysis**

Associations between the use of antimicrobial agents and the incidence of imipenem resistance and between the use of ertapenem and other antimicrobials were evaluated using Pearson’s or Spearman’s correlation coefficients as appropriate, after checking for normality with the Kolmogorov–Smirnov test. Joinpoint log-linear regression was used to calculate the trend in imipenem use for the period.

A time-series segmented regression analysis was performed to determine significant changes in the trend in antibiotic use and susceptibility patterns after ertapenem introduction. In this model, the linear trend from month to month for drug usage or susceptibility patterns before ertapenem introduction and the change in the linear trend after introducing ertapenem are each expressed by a coefficient (β).
A multiple linear regression analysis was performed with a backward stepwise approach to identify factors associated with resistance rates. Values of $P<0.05$ were considered statistically significant.

Justification of sample size

Data corresponding to 132 months were analysed to assess the impact of ertapenem on antimicrobial susceptibilities with an accuracy of $\pm 8.6\%$ and 95% certainty. The analysis was made using SPSS v20.0 (SPSS Inc., Chicago, IL, USA) statistical software.

Ethics

The study was approved by the institutional Review and Ethics Committee.

Results

The mean monthly number of patient admissions during the whole period was 3640.62 $\pm 270.35$ and the mean number of PDs was 35248.30 $\pm 1924.68$. A total of 6272 P. aeruginosa and 1093 A. baumannii clinical isolates were evaluated: 13.05 and 2.27 cases/1000 admissions, respectively. The mean bed occupancy was 75% $\pm 11\%$ and 78% $\pm 6\%$ ($P=0.118$) in the pre-ertapenem (2001–04) and post-ertapenem (2005–11) periods, respectively. The hospital comorbidity index changed from 1.72 $\pm 0.06$ to 1.88 $\pm 0.12$ ($P \leq 0.001$) between the two periods. The mean length of stay in the paediatric and adult medical ICUs did not significantly change, but the mean length of stay in the post-operative ICU changed from 3.04 $\pm 0.97$ to 4.22 $\pm 1.43$ days ($P \leq 0.001$) between the two periods. There was a significant increase in alcohol hand rub use from 96 to 464 mL/100 PDs ($P \leq 0.001$) before and after ertapenem introduction, respectively.

Use of antimicrobials

The mean use of quinolones, aminoglycosides and third-generation cephalosporins was 12.21 $\pm 3.19$, 6.33 $\pm 1.02$ and 3.47 $\pm 1.39$ DDDs/100 PDs in the whole period, respectively. The mean use of amoxicillin/clavulanate and piperacillin/tazobactam was 18.36 $\pm 2.98$ and 3.14 $\pm 1.31$ DDDs/100 PDs, respectively. The mean use of carbapenems was 4.74 $\pm 1.97$ DDDs/100 PDs: 2.94 $\pm 0.92$ DDDs/100 PDs for imipenem, 1.15 $\pm 0.73$ DDDs/100 PDs for meropenem and 1.02 $\pm 0.67$ DDDs/100 PDs for ertapenem (after its introduction).

The use of ertapenem increased progressively following its inclusion in the hospital formulary, with a mean of 0.09 $\pm 0.08$ DDDs/100 PDs in 2005 and a mean of 2.02 $\pm 0.41$ DDDs/100 PDs in 2011 ($r=0.935$; $P \leq 0.001$). There was also a positive correlation in the use of imipenem ($r=0.563$; $P \leq 0.001$), meropenem ($r=0.841$; $P \leq 0.001$) and piperacillin/tazobactam ($r=0.892$; $P \leq 0.001$) during the study period. There were significant decreases in use of clindamycin ($r=-0.306$; $P \leq 0.001$), gentamicin ($r=-0.733$; $P \leq 0.001$) and metronidazole ($r=-0.547$; $P \leq 0.001$). Although the use of group 2 carbapenems increased from 2001 to 2008, their use has decreased since then. Trend analysis revealed a significant change for imipenem use, which increased until January 2008 (month 85), with an average percentage change (APC)/month of 0.99 (95% CI: 0.74, 1.25), and decreased from that date, with an APC of $-0.78$ (95% CI: $-1.38$, $-0.18$) (Figure 1). A negative correlation was found between ertapenem and imipenem use ($r=-0.364$; $P=0.011$) and between the use of ertapenem and group 2 carbapenems ($r=-0.293$; $P=0.043$) during the last 4 years of the study.

Segmented regression analysis showed a significant change in the use of imipenem, amoxicillin/clavulanate, ciprofloxacin, amikacin and aminoglycosides after ertapenem introduction from a previously increasing to a subsequently decreasing trend (Table 1).

Susceptibility of P. aeruginosa

An average of 71.46% $\pm 7.59\%$ of P. aeruginosa isolates were susceptible to imipenem during the whole period. The mean incidence density of imipenem-susceptible P. aeruginosa was 0.96 $\pm 0.23$ and the mean incidence density of imipenem-resistant P. aeruginosa was 0.33 $\pm 0.12$. A total of 2150 and 4122 Pseudomonas isolates were analysed before (2001–04) and after (2005–11) ertapenem introduction, respectively. The proportion of imipenem-susceptible P. aeruginosa isolates changed from 77% in 2001 to 64% in 2005 and to 69% in 2011 (Table 2).

Segmented regression analysis showed an improved susceptibility of P. aeruginosa to imipenem after the introduction of ertapenem, regardless of whether the main outcome considered was the proportion of susceptible isolates (trend before: $-0.148$; $P=0.030$ and trend after: $0.233$; $P=0.002$) or the incidence density of resistance (trend before: 0.004; $P \leq 0.001$ and trend after: $-0.005$; $P \leq 0.001$) (Figure 2). These results did not significantly change when other variables, such as the hospital index of comorbidity and mortality, mean stay in ICUs, alcohol hand rub use and bed occupancy index, were taken into account.

After analysing the use of antimicrobials, alcohol hand rub use, mean stay in ICUs and bed occupancy and comorbidity indices, imipenem use [coefficient ($B$)=$0.033$; standard error (SE)=$0.011$; $P=0.003$] and ciprofloxacin use ($B=0.042$; SE=$0.016$; $P=0.008$) were found to be associated with an increase in the incidence density of imipenem-resistant P. aeruginosa, according to multivariate linear regression analysis. Imipenem use paralleled the P. aeruginosa incidence of imipenem resistance, as shown in Figure 3.

Susceptibility of A. baumannii

We tested 450 and 643 isolates before and after ertapenem introduction, respectively. The mean proportion of susceptible isolates/month was 83.94% $\pm 21.42\%$. The mean incidence densities of imipenem-susceptible and imipenem-resistant A. baumannii were 0.19 $\pm 0.13$ and 0.03 $\pm 0.07$, respectively (Table 3).

After ertapenem introduction, no significant trend was seen in the proportions of susceptible isolates (trend before: $-0.201$; $P=0.326$ and trend after: $-0.067$; $P=0.772$) or in the incidence of resistance (trend before: 0.000; $P=0.504$ and trend after: 0.000; $P=0.630$) whilst controlling for the existence of outbreaks (Figure 4).

After analysing the use of carbapenems and other antimicrobial classes, alcohol hand rub use, outbreaks, mean stay in ICUs
and comorbidity index, the existence of outbreaks \((B=0.155; SE=0.021; P\leq0.001)\) and use of gentamicin \((B=0.036; SE=0.013; P=0.007)\) were significantly related to an increased incidence of imipenem resistance in multiple regression analysis. The use of ertapenem was not related to a reduction in \textit{A. baumannii} susceptibility to imipenem.

Table 1. Segmented regression analysis of antimicrobial use

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Trend before ertapenem introduction</th>
<th>Trend after ertapenem introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>(B=0.023) (SE=0.008) (P=0.003)</td>
<td>(-0.020) (0.008) (0.016)</td>
</tr>
<tr>
<td>Group 2 carbapenems</td>
<td>(0.029) (0.008) (0.001)</td>
<td>(-0.005) (0.009) (0.560)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>(-0.009) (0.013) (0.514)</td>
<td>(0.025) (0.014) (0.082)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>(0.156) (0.025) (&lt;0.001)</td>
<td>(-0.170) (0.027) (&lt;0.001)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>(0.033) (0.006) (0.001)</td>
<td>(-0.004) (0.007) (0.539)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>(0.023) (0.006) (&lt;0.001)</td>
<td>(-0.018) (0.006) (0.004)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>(0.060) (0.015) (&lt;0.001)</td>
<td>(0.010) (0.016) (0.533)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>(0.009) (0.004) (0.032)</td>
<td>(-0.013) (0.004) (0.004)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>(0.033) (0.010) (0.002)</td>
<td>(-0.038) (0.011) (0.001)</td>
</tr>
</tbody>
</table>

Coefficient ‘\(B\)’ represents the linear trend of drug usage from month to month without ertapenem in the formulary (i.e. trend before ertapenem introduction) and the change in the linear trend for drug usage after introducing ertapenem (i.e. trend after ertapenem introduction). ‘\(SE\)’ is the standard error of \(B\).

**Discussion**

The main findings of this study show that the widespread use of ertapenem during the 7 years following its introduction into the hospital formulary was directly associated with a downward trend in the use of group 2 carbapenems (e.g. imipenem) and ciprofloxacin, among other antimicrobials, which may have contributed to the improved susceptibility of \textit{P. aeruginosa} to imipenem. Ertapenem use had no impact on the susceptibility of \textit{A. baumannii} to imipenem.

Since ertapenem was approved in the USA in 2001, some \textit{in vitro} mutant studies have demonstrated that selection of \textit{P. aeruginosa} resistant to other carbapenems may occur. Kohler \textit{et al.}\(^{11}\) found that ertapenem selected for both OprD\(^{-}\) and efflux mutants, and for a phenotype resistant to ertapenem and meropenem. Livermore \textit{et al.}\(^{1}\) examined the selection of imipenem- and meropenem-resistant \textit{P. aeruginosa} in laboratory experiments with MIC multiples and at the concentrations likely to apply in patients. These authors noted that ertapenem selected for \textit{P. aeruginosa} mutants lacking the ‘carbapenem-specific’ porin OprD, as for various carbapenem-resistance types, and queried whether it would do so in a clinical setting.\(^{1}\)

Several single-centre studies and two multicentre studies examined this issue under clinical conditions.\(^{2–6,12–16}\) A review on this subject has recently been published.\(^{17}\) Those studies differed in whether ertapenem use was mandatory (owing to institutional policies autosubstituting ertapenem for ampicillin/sulbactam or group 2 carbapenems) or unrestricted, in the measurement of antimicrobial use and susceptibility, and in the rigor with which the data were analysed. The length of the study periods varied from 2 to 9 years and the number of isolates

![Figure 1. Joinpoint log-linear regression of imipenem use for the period. Use of imipenem was measured as the number of DDDs/100 PDs. The APC in imipenem use/month is shown in the panel. There was a significant increase until January 2008 (month 85) with an APC 1 of 0.99 and a significant decline from that date with an APC 2 of −0.78.](image-url)
Ertapenem and imipenem resistance in *P. aeruginosa* and *A. baumannii*

### Table 2. Susceptibility of *P. aeruginosa* and *A. baumannii* to imipenem

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of isolates/month</th>
<th>Proportion susceptible</th>
<th>Incidence density of <em>S</em></th>
<th>Incidence density of <em>R</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>40.1+11</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2002</td>
<td>38.8</td>
<td>71.5%</td>
<td>0.3 ± 0.09</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2003</td>
<td>42.8</td>
<td>72.7%</td>
<td>0.3 ± 0.09</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2004</td>
<td>48.8</td>
<td>64.7%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2005</td>
<td>50.1+1</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2006</td>
<td>54.7</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2007</td>
<td>51.5</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2008</td>
<td>52.7</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2009</td>
<td>51.5</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2010</td>
<td>57.2</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
<tr>
<td>2011</td>
<td>48.8</td>
<td>72.1%</td>
<td>0.2 ± 0.08</td>
<td>0.1 ± 0.07</td>
</tr>
</tbody>
</table>

The number of *P. aeruginosa* isolates/month, the proportion of isolates susceptible to imipenem (*Percentage susceptible*), the incidence density of imipenem-susceptible *P. aeruginosa* (*Incidence density of *S**) and the incidence density of imipenem-resistant *P. aeruginosa* (*Incidence density of *R**) are presented per year. The values per year are the mean monthly values ± SD. The incidence density was calculated as the number of isolates/1000 PDs.

Data about improvement in *Pseudomonas* susceptibility to group 2 carbapenems directly related to ertapenem use are more conflicting. The adequate use of ertapenem appears to improve the overall hospital ecology in some cases. Goldstein et al. concluded that the addition of ertapenem to the hospital formulary increased the susceptibility to imipenem amongst *Pseudomonas* spp., presumably because of a decreased use of group 2 carbapenems. The ertapenem use reported in the present study is similar to that found in other studies. A significant, but not immediate, reduction in imipenem use was seen after ertapenem was introduced, as well as a downward trend in the use of other antimicrobials, such as ciprofloxacin and aminoglycosides. While no mandatory restrictions were introduced during the study period, recommendations for the use of ertapenem instead of group 2 carbapenems, when clinically appropriate, were part of the antimicrobial stewardship institutional policies. The decline in the use of ciprofloxacin (as well as amoxicillin/clavulanate and others) may be explained by increased resistance of Gram-negative bacilli and a growing need for coverage of β-lactamase-producing microorganisms. This need is in accordance with local susceptibility patterns and in line with data from global surveillance studies on antimicrobial resistance, as reflected by the Study for Monitoring Antimicrobial Resistance Trends.

Based on the consistency of results, it may be assumed that the decrease in *Pseudomonas* resistance was at least partially related to the decreased use of imipenem and ciprofloxacin, as both antimicrobial agents were significantly associated with increased imipenem resistance density in the multiple linear regression analysis. These findings also agree with previous publications. The rate of carbapenem-resistant *P. aeruginosa* infections may be decreased by reducing the use of carbapenems, ciprofloxacin, third-generation cephalosporins, piperacillin/tazobactam and aminoglycosides. Combinations of agents may also prevent or promote resistance, even if the single use of each one of them might not, but this possibility cannot be assessed with the current study design.

Although the focus has been placed on *Pseudomonas*, some improvements have also been reported in the susceptibility of other Gram-negative microorganisms, such as the Enterobacteriaceae, after ertapenem introduction. This is the first interrupted time-series study to investigate this issue in *A. baumannii*. The use of ertapenem did not alter the susceptibility of *A. baumannii* to imipenem. Lima et al. reported the proportions of imipenem-susceptible *A. baumannii* isolates 2 years before and 2 years after the implementation of a carbapenem stewardship programme. Ertapenem use was mandated for appropriate infections, while group 2 carbapenems were restricted. The number of isolates collected before and after the ertapenem-use policy was 64 and 36, respectively, and the proportion susceptible to imipenem changed from 64% to 33%. However, the authors considered that this change was not due to ertapenem use, because a similar trend was seen in
Figure 2. Percentages of imipenem-susceptible *P. aeruginosa* isolates. The coefficients by segmented regression analysis for the trends during the pre- and post-ertapenem periods are represented in the panel.

Figure 3. Imipenem use and incidence density of imipenem-resistant *P. aeruginosa* per year. Use of imipenem was measured as the number of DDDs/100 PDs and the incidence density of imipenem-resistant isolates was measured as the number of imipenem-resistant isolates/1000 PDs.
Ertapenem and imipenem resistance in *P. aeruginosa* and *A. baumannii*

Table 3. Susceptibility of *A. baumannii* to imipenem

<table>
<thead>
<tr>
<th>Year</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of isolates/month</td>
<td>9</td>
<td>41</td>
<td>4</td>
<td>57</td>
<td>38</td>
<td>71</td>
<td>36</td>
<td>42</td>
<td>18</td>
<td>7</td>
<td>51</td>
</tr>
<tr>
<td>Percentage susceptible</td>
<td>91</td>
<td>14</td>
<td>66</td>
<td>13</td>
<td>81</td>
<td>16</td>
<td>99</td>
<td>29</td>
<td>2</td>
<td>99</td>
<td>12</td>
</tr>
<tr>
<td>Incidence density of S</td>
<td>0.23</td>
<td>0.09</td>
<td>0.16</td>
<td>0.10</td>
<td>0.28</td>
<td>0.19</td>
<td>0.33</td>
<td>0.37</td>
<td>0.18</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Incidence density of R</td>
<td>0.03</td>
<td>0.04</td>
<td>0.10</td>
<td>0.04</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The number of *A. baumannii* isolates/month, the proportion of isolates susceptible to imipenem (‘Percentage susceptible’), the incidence density of imipenem-susceptible *A. baumannii* (‘Incidence density of S’), and the incidence density of imipenem-resistant *A. baumannii* (‘Incidence density of R’) are presented per year. The values per year are the mean monthly values ± SD. The incidence density was calculated as the number of isolates/1000 PDs.

Cross-transmission and ICU stay are well-known factors having an impact on *A. baumannii* resistance other than antimicrobial use alone. Outbreaks in ICUs were independently correlated with resistance in the current study and it may be hypothesized that a significant increase in the hospital comorbidity index, as an indicator of severity, might have contributed to an increased antimicrobial resistance. In contrast, the marked rise in the use of alcohol hand rub may have impacted the emergence of resistance by decreasing the nosocomial transmission of MDR organisms; although this relationship was not observed in the multivariable analysis in the present study, as was found by a recent study in a Brazilian hospital. The non-significant association could be due to the modest use of the alcohol-based antiseptic solution at our institution, where bedside dispensers were not systematically installed until 2010. Although no systematic epidemiological research has been conducted, it is plausible that, in contrast with mostly polyclonal imipenem-resistant *P. aeruginosa*, primarily related to OprD loss, carbapenemases are much more common in *Acinetobacter* spp., which makes infection control practices more important than antibiotic interventions for carbapenem resistance.

Few studies with adequate methods have been conducted to assess the impact of antibiotics on hospital ecology. The ORION statement provides recommendations for the conduct of such quasi-experimental studies. The importance of reporting incidence rather than only proportions has been emphasized. In the present study, proportions and incidence densities were considered as primary outcomes in order to represent data from the clinical perspective (probability) and the absolute change in resistance. Moreover, for microorganisms such as *A. baumannii*, with a low number of isolates/month, variations in data obtained only as percentages may be significantly misleading. Antimicrobials were assessed as individual agents or groups from the same class, although no significant differential effects on resistance were detected.

Resistance to imipenem was categorized in accordance with CLSI guidelines during the study period. No changes occurred in the breakpoints from 2001 to 2011 for *Pseudomonas* or *Acinetobacter* spp., which meant there were no related implications for the study results. The retrospective use of the currently applied CLSI 2012 breakpoints for *P. aeruginosa* would have increased the number of imipenem-resistant isolates during the entire study period and, consequently, the resistance rates that are reported. Despite this, the trends in the susceptibility patterns, before and after ertapenem introduction, probably would not have altered significantly and the conclusions of the study would remain unchanged.

Our study had some limitations, including those inherent to group-level and single-centre studies. Population studies lack the necessary detail to examine the development of resistance promoted by combinations of agents. Time-series analysis may identify trends, but does not establish causation, which can only be examined using patient data. However, this study included a large number of *P. aeruginosa* and *A. baumannii* strains during the longest period evaluated to date: 4 years before and 7 years after ertapenem introduction. In addition, the study included a segmented regression analysis, the best
methodological approach to estimate the effect of interventions on susceptibility rates and antibiotic usage patterns.

In conclusion, the increased use of ertapenem in the 7 years following its introduction into the pharmacotherapeutic guide may have had a positive impact on the hospital ecology by decreasing the selective pressure caused by antipseudomonal agents, without compromising the susceptibility of \textit{A. baumannii} to imipenem. The development of drug resistance at the individual patient level warrants further research. Continuous surveillance is needed to guide clinical practice and stewardship programmes, in order to optimize patient care whilst minimizing collateral ecological damage.

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**References**


Ertapenem and imipenem resistance in *P. aeruginosa* and *A. baumannii*