Consumption of Imipenem Correlates with β-Lactam Resistance in *Pseudomonas aeruginosa*

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It is generally assumed that the antibiotic prescription policy of a hospital has a significant impact on bacterial resistance rates; however, few studies are available to support this concept with valid statistical data. During a 3-year period from 1997 to 2000, we monitored the consumption of β-lactam and other antibiotics with known activity against *Pseudomonas aeruginosa* in a 600-bed community hospital. Monthly isolations of *P. aeruginosa* were assessed, and resistance rates were recorded. Partial correlation coefficients between consumption and resistance rates were determined, taking into account possible associations with other variables such as seasonal effects and transfers from other hospitals. A total of 30 ± 7 novel *P. aeruginosa* strains per month were isolated without epidemic clustering. Prescriptions of imipenem varied significantly during the study period, while prescriptions of other antipseudomonal agents were stable, with the exception of an increase in piperacillin-tazobactam prescriptions. Rates of resistance of *P. aeruginosa* to the antimicrobial agents used showed a time course similar to figures for imipenem consumption. Monthly rates of resistance to imipenem (partial correlation coefficient [cc], 0.63), piperacillin-tazobactam (cc, 0.57), and ceftazidime (cc, 0.56) were significantly associated with imipenem prescription rates in the same or the preceding month, while consumption of ceftazidime or piperacillin-tazobactam had no apparent association with resistance. Among the variables investigated, imipenem consumption was identified as the major factor associated with both carbapenem and β-lactam resistance in endemic *P. aeruginosa*. Periods of extensive imipenem use were associated with significant increases in resistance. Our data support the concept that a written antibiotic policy which balances the use of various antibiotic classes may help to avoid disturbances of a hospital’s microbial sensitivity patterns.

**Materials and Methods**

**Bacteriology.** *P. aeruginosa* was identified biochemically from routinely obtained specimens by means of the Vitek ATB Expression System, version 2.7.8 (BioMérieux Deutschland GmbH, Nürtingen, Germany), which uses 32 biochemical reactions. Antibiotic susceptibility testing was performed by the same system, using a microbroth dilution technique with an inoculum of 5 × 10⁴ organisms per ml and a test volume of 135 μl in 18-well microtiter trays. MICs of the drugs were read automatically after aerobic incubation at 35°C for 18 to 24 h. The susceptibility breakpoints (susceptible and resistant, respectively, in milligrams per liter) for *P. aeruginosa* were those of the German National Standard: ≤2 and ≥8 for imipenem, ≤4 and ≥32 for ceftazidime, and ≤4 and ≥64 for piperacillin (in the presence of 4 mg of tazobactam/liter) (5). For comparison, breakpoints of the National Committee for Clinical Laboratory Standards (NCCLS) are as follows: ≤4 and ≥16 for imipenem, ≤8 and ≥32 for ceftazidime, and ≤64 and ≥128 for piperacillin in the presence of 4 mg of tazobactam/liter (19). Susceptibility data were recorded monthly using a computer-based laboratory documentation system (Medat Software, Munich, Germany). The system is adjusted to count only primary isolates from individual patients, but to include follow-up isolates if the primary isolates show a different pattern of antibiotic resistance.

**Antibiotic consumption.** Antibiotic deliveries to the hospital were recorded in the clinical pharmacy on a monthly basis using a computer-based pharmacy documentation system. Deliveries could be assumed to reflect usage because the supply of pharmacy items to the wards was maintained continuously by the “Pharmacy Stock Control (top-up)” system. This system is based on an inventory or stock list placed on the ward, describing the contents and optimum stock levels of all trays and baskets, including correct locations. The labels on each tray and basket indicate the contents by bar code and in writing. A member of the pharmacy staff visits the wards three times a week (for wards with known high drug turnover) or twice a week (wards with low drug turnover) and checks the entire cupboard for the presence of bar codes, pharmacy requirements, expiration dates of drugs, and recent changes in prescribing. Thus, in the same way as all other drugs, antibiotics that had been ordered but not used were returned to

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the pharmacy within the same week, and supplies were delivered within 24 h after the visit of the pharmacist.

Gram amounts of antibiotics were converted to "defined daily doses" (DDDs) by using the daily doses mostly frequently prescribed in this hospital, which were as follows: imipenem, 3 g; piperacillin, 12 g, and tazobactam, 1.5 g; ceftazidime, 6 g; gentamicin and tobramycin, 0.24 g; amikacin, 1 g; ceftriaxone, 2 g; cefotaxime, 6 g; intravenous ciprofloxacin, 0.4 g; oral ciprofloxacin, 1.0 g.

Statistics. The time series of resistance to imipenem, ceftazidime, and piperacillin-tazobactam were cross-correlated with the corresponding time series for use of the drugs in the same period. Associations were quantified using nonparametric and partial correlation coefficients according to Pearson and Spearman, assuming a lag of 1 month between use and resistance, and assuming no delay in between. In this context, a partial correlation between the use of and resistance to a β-lactam means that seasonal effects, patient transfers from other hospitals, and the use of other antibiotics with activity against P. aeruginosa were eliminated from the association. For example, in estimating the association between ceftazidime resistance and imipenem use 1 month earlier, adjustments were made for the use of ciprofloxacin, gentamicin, tobramycin, piperacillin-tazobactam, and ceftazidime 1 month earlier. P values refer to testing to rule out the possibility that the indicated coefficients were equal to zero.

In a further analysis, we modeled the dynamic relationship between antimicrobial use and resistance by using the time series method of Box and Jenkins as described by Lopez-Lozano et al. (15). Here, each of the antibiotic use series was modeled by an autoregressive low-order time series. Then transfer functions were modeled by Lopez-Lozano et al. (15). Here, each of the antibiotic use series was described by Lopez-Lozano et al. (15).

RESULTS

Hospital setting. The 600-bed acute-care community hospital serves a city of 40,993 inhabitants with a surrounding community of more than 200,000 inhabitants. All major medical and surgical disciplines are represented. During the study period, 19,000 to 20,000 patients were admitted every year, and fewer than 3% were transfers from other hospitals. On average, 30 novel P. aeruginosa strains were isolated every month without epidemic clustering (Table 1).

<table>
<thead>
<tr>
<th>Yr</th>
<th>Monthly no. of admissions ± 1 SD</th>
<th>Monthly no. of transfers ± 1 SD (%)</th>
<th>Monthly no. of P. aeruginosa isolates ± 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 (July–Dec.)</td>
<td>NA*</td>
<td>NA</td>
<td>27 ± 10</td>
</tr>
<tr>
<td>1998</td>
<td>1,602 ± 60</td>
<td>39 ± 9 (2.4)</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>1999</td>
<td>1,650 ± 76</td>
<td>45 ± 11 (2.7)</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>2000 (Jan.–July)</td>
<td>1,699 ± 114</td>
<td>41 ± 8 (2.4)</td>
<td>31 ± 9</td>
</tr>
</tbody>
</table>

* NA, data not available.

Vol. 46, 2002 IMIPENEM AND RESISTANCE OF P. AERUGINOSA 2921

this hospital. Striking variations were noted for the use of imipenem, which was the only carbapenem used during the study period. In fact, even when expanded-spectrum cephalosporins other than ceftazidime were taken into account, imipenem use was the major factor determining overall parenteral antibiotic consumption (Fig. 1). Increasing consumption of imipenem during the first half of 1998 coincided with a marketing campaign by the manufacturer, who presented data showing that primary therapy of nosocomial pneumonia, secondary peritonitis, and other infections with imipenem led to significant cost savings (20, 21). Reprints and summaries of these studies were distributed to hospital physicians by a representative of the manufacturer.

Resistance of P. aeruginosa to imipenem. Shortly after the intensified use of imipenem, we noted a dramatic increase in the resistance of P. aeruginosa isolates to this drug (Fig. 2A).

In the early summer of 1998, the infection control and antimicrobial committees of the hospital expressed concern regarding increasing resistance of P. aeruginosa to imipenem and increasing use of this drug. Analysis of hospital microbiology data revealed no objective need for an intensified use of imipenem, because there was no increase in the number of P. aeruginosa isolates or organisms belonging to other species that would have been sensitive to carbapenems only. Therefore, it was decided that imipenem should not be delivered by the pharmacy unless written prescription forms were filled out stating the reason why other drugs could not be used (e.g., because of microbiologically documented resistance). Furthermore, prescriptions had to be countersigned by the chief or vice-chief of the respective clinical department. Following this decision, imipenem use decreased rapidly, as did resistance rates (Fig. 2A).

At the end of the observation period, after the restrictions had been loosened, the use of imipenem increased again. Over the whole study period, imipenem consumption correlated significantly with imipenem resistance, with a (nonpartial) correlation coefficient of 0.63 (P < 0.05) (Fig. 2B). This correlation was seen not only when monthly prescription rates were compared with resistance data from the same month, but also with those of the following month. By contrast, correlation coefficients dropped to insignificant levels when other time lags between use and resistance were used for calculation (Fig. 2C).

Resistance of P. aeruginosa to β-lactams. Piperacillin-tazobactam was used more frequently for empirical therapy after July 1998, with monthly prescriptions rising from 28.2 DDDs in July 1997 to 153.8 DDDs in February 1999. Mean monthly prescriptions during the first period of high imipenem use (September 1997 to May 1998) were 68.9 ± 11.8 DDDs per month, compared with 106.0 ± 39.5 DDDs per month during the period of low imipenem use (June 1998 to December 1999). Despite increasing use, no correlation was seen between consumption of this drug and resistance (Table 2). By contrast, both resistance to ceftazidime and resistance to piperacillin-tazobactam showed time courses similar to that of imipenem consumption, with peak ceftazidime resistance rates of 42% and peak piperacillin-tazobactam resistance rates of 25% during the period of maximum imipenem consumption in 1998 (data not shown). Partial correlation coefficients for imipenem consumption and resistance revealed significant statistical associations between imipenem use and resistance to ceftazidime or piperacillin-tazobactam (Table 2).
Time series analysis. Results similar to those indicated by the Pearson coefficients were obtained by calculating Spearman's rank coefficients (data not shown) and by using time series modeling according to the work of Box and Jenkins. When modeling imipenem resistance, we found positive regression coefficients quantifying an association with imipenem use in the same month \((P < 0.1)\) as well as with use during the preceding month \((P < 0.05)\). The same was true when we checked the dependence of ceftazidime resistance \((P < 0.06)\) and piperacillin-tazobactam resistance \((P < 0.01)\) on imipenem use during the same month. Neither the use of ceftazidime nor that of piperacillin-tazobactam could be identified as a factor associated with resistance to one of the three antibiotics when intervals of up to 6 months between use and resistance were considered.

Hospital epidemiology and hygiene practices. The hospital had two infection control nurses and a consultant hospital epidemiologist. Microbiology data and printouts detailing the distribution of isolates on individual wards were analyzed monthly by the epidemiologist and summarized in written reports every 2 to 3 months. During the period under study, no epidemic clustering of \(P.\ aeruginosa\) isolates was documented. Cases were randomly distributed over as many as 23 wards, and no apparent breakdown in common hygiene practices was noted. Furthermore, infection control practices and disinfectants were not changed during this period, and the infection control team had been the same for a number of years. Records of microbiological sampling activity were kept during the whole period and showed that between 0.76 and 0.8 cultures were performed monthly per admitted patient, with variations of less than 3% between years and a maximum difference of 10% between corresponding months of successive years (1997 to 2000). Admission rates from other hospitals were no longer available for 1997, but in the beginning of 1998 (up to May 1998) the mean monthly percentage of patients admitted from other hospitals was 1.0%, compared with a mean of 2.6% for the rest of 1998. Mean total patient numbers admitted each month during the periods of low and high imipenem consumption varied by less than 10% (e.g., 1,608 ± 82 [range, 1,533 to 1,792] patients per month from January to May 1998, compared to 1,540 ± 70 [range, 1,428 to 1,613] patients per month for the rest of 1998).

Resistance in primary versus secondary isolates. The frequency of primary versus secondary \(P.\ aeruginosa\) isolates and their patterns of resistance could be evaluated only for the second peak of imipenem consumption in 2000, because earlier data were no more available. From January to May 2000, when consumption figures peaked again to values of >300
A total of 183 isolates from various wards were isolated, 39 (21.3%) of which were secondary isolates. Thirteen of 144 (9.0%) primary isolates were resistant to imipenem, compared with 21 of 39 (53.8%) secondary isolates (P < 0.01 by the chi-square test). This shows that resistance was not due to an epidemic of primary imipenem-resistant isolates during this period.

**DISCUSSION**

Although it is often said that the pattern of antibiotic resistance in a given hospital is nothing but the negative imprint of the antibiotic prescription behavior in that hospital, few valid statistical data are available to substantiate this assumption. For some organisms, such as quinolone-resistant *Escherichia coli*, vancomycin-resistant enterococci, or quinolone-resistant coagulase-negative staphylococci, relationships have been established between consumption rates of the respective drugs and the increasing isolation rates of resistant organisms in individual hospitals (7, 12, 16). However, the association is less convincing for the use of broad-spectrum β-lactam agents in relation to the epidemiology of resistance of common gram-negative bacteria. In a recent prospective study involving eight U.S. hospitals, it was not possible to find an association of consumption with resistance for individual antimicrobial-agent–organism pairs (18). It was speculated that other factors, such as interhospital transfer of resistance due to patient transfers, a community contribution to resistance, or a complex relationship between resistance and the use of a variety of antimicrobial agents, might have acted as confounding variables (18). Thus, the question of whether the control of antibiotic prescriptions by infectious-disease specialists (26; R. P. Wenzel, Editorial, Clin. Infect. Dis. 24:456, 1997) or the scheduled cycling of antibiotics in high-risk areas such as intensive-care units is appropriate for reducing resistance rates is still a matter of controversy (8, 17, 27).

In the hospital described here, several of the confounders just mentioned were virtually absent. Although some specialized outpatient services were offered, these did not include patient groups likely to carry drug-resistant *P. aeruginosa*. As shown in Table 1, transfers from other hospitals accounted for less than 3% of total admissions, which excludes a significant impact of antibiotic-resistant strains from other institutions on this hospital’s ecology. The epidemiology of *P. aeruginosa* was

**TABLE 2. Correlations between antibiotic consumption and resistance of *P. aeruginosa***

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Partial coefficient of correlationa between antibiotic consumption and resistance to:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imipenem</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Same mo</td>
<td>Next mo</td>
<td>Same mo</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.58</td>
<td>0.63</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>−0.24</td>
<td>−0.07</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>−0.27</td>
<td>−0.10</td>
</tr>
</tbody>
</table>

* Coefficients for the month of antibiotic consumption and the month following consumption are given. Boldface indicates significance (P ≤ 0.005).
characterized by regular isolations of this organism at a low but rather constant rate, reflecting a situation of endemicity. It has been shown previously that about one-half of endemically occurring nosocomial *P. aeruginosa* infections or colonizations are due to horizontal transmissions of the organism between patients, e.g., via fomites, fingernails of the personnel, or water from contaminated sinks (6, 24). In the setting described here, horizontal transmissions may have acted as an ampliﬁer of individual molecular events leading to resistance.

Nevertheless, a signiﬁcant association between antibiotic exposures and resistance at a level affecting the whole hospital would not have been detected had there not been enormous variations in the consumption of imipenem during the 3-year period examined. These variations were difﬁcult to explain, because there were no apparent changes in the spectrum of patients treated or the monthly number of admissions. The primary use of carbapenems for empirical therapy of nosocomial infections was supported by various opinion leaders in Germany since the mid-1990s, and studies apparently proving a superior clinical cure rate achievable with imipenem compared to broad-spectrum cephalosporins or penicillins appeared in 1997 and 1998. According to these publications, the less frequent need to switch to other antibiotic regimens and the shorter overall hospital stay of carbapenem-treated patients led to signiﬁcant cost savings (20, 21). Issues of drug resistance were not addressed in these reports (20, 21). Because drug orders in our hospital were served by the pharmacy without requests for authorization, we hypothesize that these publications promoted the intensiﬁed use of imipenem for empirical therapy. Although we cannot prove this hypothesis, the immediate decline in imipenem prescriptions by more than 80% after the introduction of written, countersigned prescriptions supported the assumption that ordering behavior during the preceding period had not been dictated by actual medical needs.

In addition to the correlation between imipenem use and resistance of *P. aeruginosa* to the drug itself, our data also revealed an association between imipenem consumption and resistance to ceftazidime and piperacillin-tazobactam (Table 2). In contrast, rates of consumption of ceftazidime and piperacillin-tazobactam showed no association with resistance to these two drugs. These observations are in accordance with data from Carmeli et al., who analyzed antibiotic treatment courses in individual patients suffering from *P. aeruginosa* infections (2). In their study, imipenem therapy was not only associated with emergence of resistance to imipenem (hazard ratio [HR], 44.0 compared to other antipseudomonal drugs; *P* < 0.001); it also had the strongest association with emergence of resistance to any of the antipseudomonal drugs under study, which included piperacillin-tazobactam and ceftazidime (HR, 2.9; *P* < 0.008). By contrast, patients treated with piperacillin-tazobactam or ceftazidime had no signiﬁcantly increased risk of resistance (2). Similarly, in a case control study, Troillet et al. analyzed 40 patients whose ﬁrst *P. aeruginosa* isolate was fully or intermediately resistant to imipenem and compared them to 387 control patients harboring fully susceptible strains. Pretreatment with imipenem was identiﬁed as the major risk factor for harboring a resistant strain (HR, 16.9; *P* < 0.0001), while pretreatment with cephalosporins or any intravenous β-lactam was not a risk factor (25). Imipenem-resistant strains had a 3.6-fold-higher rate of concomitant ceftazidime-resistance, and a 2.3-fold-higher rate of piperacillin-tazobactam resistance, than imipenem-sensitive strains (25). It should be noted, however, that in a recent case control study that included several different control groups, pretreatment with piperacillin-tazobactam also carried a 2.4-fold-increased risk for isolation of an imipenem-resistant *P. aeruginosa* strain (10).

The rapid emergence of resistance in clinical *P. aeruginosa* isolates during imipenem therapy has been well described (11, 23). Commonly, imipenem resistance in this species is due to an interplay between β-lactamase activity and reduced permeability of the bacterial outer membrane, which results from the loss of a speciﬁc membrane protein, the OprD2 porin (14). Treatment with other β-lactam drugs could predispose to imipenem resistance by selecting strains with stably derepressed β-lactamase production, which would then be more likely to lose their porin OprD2 during subsequent imipenem therapy (25). We did not analyze the mechanisms leading to imipenem and β-lactam resistance in our strains. However, given the possibility that a proportion of the isolates were harbored by the patients during their prehospital phase, the possibility that these strains had been exposed to β-lactam agents in the community cannot be excluded. This hypothesis would explain both the rapid emergence of resistance to imipenem and the concomitant β-lactam resistance seen in our study.

Several limitations of our study have to be addressed. Firstly, a more detailed analysis of resistance in primary and secondary isolates would have been desirable, in particular during the ﬁrst peak of imipenem consumption. During the second peak, the analysis showed that horizontal transfers of resistant strains apparently played a minor part, because only 9% of primary isolates were imipenem-resistant, in contrast to 53.8% of follow-up isolates. Secondly, molecular typing was not done. Demonstration of molecular strain diversity would have excluded a common-source clonal expansion of a single strain during the periods of increased imipenem resistance. Lacking molecular data, our argument against the assumption of a clonal outbreak is that every physician in our hospital is trained to change an initial empirical antibiotic regimen as soon as microbiological tests showing resistance to the empirically used drug(s) are available. Because test results were available within 48 h, an outbreak of primarily imipenem-resistant strains would have led to a decrease rather than an increase in imipenem consumption. Further arguments against an outbreak are the time course between use and resistance (Fig. 2A and C), regular visits of an experienced infection control team to all wards, and the absence of clustering of *P. aeruginosa* isolates on individual wards. Finally, had there been an outbreak due to an unidentified lapse in hygiene precautions, restriction of imipenem prescriptions as the only measure taken would not have resulted in an almost immediate reversion of resistance to normal levels. A third limitation of our study is that overall consumption of antibiotics varied signiﬁcantly, although this was due mainly to variations in imipenem usage (Fig. 1). It is possible that any other agent in the place of imipenem might have been associated with similar phenomena of resistance. Therefore, we believe that our study provides an argument for a regulated, preferably written antibiotic policy which balances the use of individual antibiotics. Most likely, such a policy will prevent the occurrence of major disturbances of a hospital’s...
microbial-sensitivity patterns by unrestricted use of particular agents.

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P. M. Lepper and E. Grusa contributed equally to this work.

REFERENCES


