Departmental consumption of antibiotic drugs and subsequent resistance: a quantitative link

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Objective: To look for a quantitative model linking departmental consumption of antibiotic drugs to the subsequent isolation of resistant hospital-acquired coliform pathogens.

Materials and methods: Included in the study were all patients with hospital-acquired bloodstream infections caused by a coliform pathogen, detected in six departments of internal medicine of one university hospital during the period 1991–1996, who had not been hospitalized in the month before the infection (n = 394). Departmental consumption of antibiotics in the year before the infection [expressed as defined daily dosages (DDD)/100 patient days], antibiotic treatment given to the individual patient before the infection, the day of hospital stay on which the infection occurred, and the department and the calendar year were all included in a logistic model to predict the isolation of a resistant pathogen. We looked at five drugs: gentamicin, amikacin, cefuroxime, ceftazidime and ciprofloxacin.

Results: Five logistic models were fitted for the resistance to each of the antibiotic drugs. The multivariable-adjusted odds ratios for a pathogen resistant to the specific antibiotic were 1.03 [95\% confidence interval (CI) 0.70–1.50] for gentamicin, 1.80 (95\% CI 1.00–3.24) for amikacin, 1.12 (95\% CI 1.02–1.23) for cefuroxime, 1.45 (95\% CI 1.19–1.76) for ceftazidime and 1.06 (95\% CI 0.57–1.97) for ciprofloxacin, per 1 DDD/100 patient days.

Conclusions: The departmental consumption of cephalosporin drugs and amikacin in six autonomous departments of medicine in the same hospital was associated with a measurable and statistically significant increase in the probability of infection caused by a resistant pathogen.

Introduction

The prescription of antibiotics or the formulation of an antibiotic policy entails balancing the benefits and risks associated with antibiotics. For severe bacterial infections, appropriate treatment enhances the odds for survival and uneventful recovery.\textsuperscript{1–4} The benefit afforded by the appropriate antibiotic treatment of severe infections is of such an order of magnitude that the cost of the drug and its administration and monitoring, and that of any adverse effects, are of secondary importance.\textsuperscript{5} The major detriment associated with antibiotic treatment may be that of future resistance. A link between the consumption of antibiotics and subsequent resistance is widely believed. However, in most clinical situations this link is perceived by prescribers as weak and nebulous. The benefits to the present patient are perceived as outweighing the possible, and unmeasured, future changes in resistance.

Cost-effectiveness analyses of antibiotic treatment have not included the cost of resistance, partly on theoretical grounds, but mainly because of the lack of data and suitable models.\textsuperscript{6} Thus, we lack quantitative data to link consumption of antibiotic drugs to resistance, and the model to link resistance to its cost.\textsuperscript{7} Our inability to include resistance in a quantitative balance of antibiotic treatment is of particular concern given the rise in resistance rates and the appearance of pathogens resistant to almost all drugs.\textsuperscript{8–10}

In the present analysis, we have sought a quantitative...
link between consumption of antibiotic drugs and induction of resistance in a defined clinical setting, that is, departments of internal medicine. In patients with Gram-negative bloodstream infection, we have looked at the probability of the pathogen being resistant associated with departmental consumption of antibiotic drugs, when other predictors of resistance were taken into account. Our aim was to provide a quantitative link between consumption and resistance, in such a way that our understanding of a true balance of benefit and risk for antibiotic treatment, including resistance, would be possible.

Materials and methods

Setting

Beilinson Campus is a 900-bed university hospital that serves as a first-line facility an urban, elderly, mainly Jewish population of about 300 000. It is also a referral centre for several hospitals in the vicinity. The medical wing is comprised of six departments of internal medicine, with a total of 234 beds, and an average occupancy rate of about 100%. More than 80% of the admissions to the medical wing are through the emergency ward, and are assigned in turn to one of the departments of medicine. Each department has its own staff and separate geographical location. Transfers from one department of internal medicine to another are very rare. The mean duration of stay during the study years (1991–1996) for the six departments was <6 days.

The six departments are autonomous. The departments have no common policies or guidelines, except for institutional guidelines for treating febrile neutropenic patients. Prescription of some of the broad-spectrum antibiotic drugs necessitated the approval of a specialist in infectious diseases.

Patients

Included in the present analysis were all patients with hospital-acquired, bloodstream infections with a single coliform pathogen, detected in the six departments of internal medicine during 1991–1996. We excluded patients who were hospitalized elsewhere in the month before the bloodstream infection, to minimize the influence of patients acquiring hospital-type microflora in the previous hospitalization. Only the first episode for each patient in the database was included. A bloodstream infection was defined as ‘hospital acquired’ if it occurred 48 h or more after admission to the hospital.

From 1988, all episodes of bloodstream infection were recorded in the Beilinson Bacteraemia Database.2,4 Demographic data on the patient, as well as the source and presentation of infection, underlying disorders, prior medication (including details of antibiotic treatment in the month before the bloodstream infection), any pathogen and their in vitro susceptibility to antibiotics, treatment and outcome were gathered and recorded contemporaneously. Susceptibility to antibiotics was tested by the disc diffusion method on Mueller–Hinton agar according to the procedures established by the NCCLS.11 For the purpose of the present analysis, isolates with intermediate susceptibility were defined as resistant.

Departmental consumption of antibiotic drugs

Consumption of an antibiotic drug for a department of internal medicine was expressed as the number of defined daily dosages (DDD) per 100 patient days per calendar year.

Analysis

The present analysis pertains to five antibiotic drugs: gentamicin, amikacin, cefuroxime, ceftazidime and ciprofloxacin. Thus, five regression models were fitted. The counting unit was the isolate (patient-unique), and the dependent variable was the in vitro susceptibility to one of the antibiotic drugs (as a dichotomous variable).

The independent variables introduced in each model were: departmental consumption of the respective antibiotic in the previous year, expressed as DDD/100 patient days (as a continuous variable); whether the patient was treated with the same antibiotic in the month before the infection; whether the patient was treated with any other antibiotic for ≥24 h in the month before the infection (both of them as dichotomous variables); department (in six categories); year of infection (in six categories); and the duration of hospital stay before the first positive culture (as a continuous variable).12–14 For example, the model for gentamicin included resistance to gentamicin as the dependent variable; and departmental consumption of gentamicin in the year before the infection, whether the patient has been treated with gentamicin before the infection, whether the patient has been treated with any antibiotic drug before the infection, the department, the year of infection and the duration of hospital stay until the infection, all as independent variables.

To perform a logistic regression analysis, the CATMOD procedure of SAS (Cary, NC, USA) was used, and the parameters of the model were estimated using the maximum-likelihood method. For univariate comparisons of continuous variables, Wilcoxon rank sum test was used.

Results

The study population included 394 patients. The pathogens were as follows: Escherichia coli in 88 patients (22%), Klebsiella pneumoniae in 87 patients (22%); Pseudomonas aeruginosa in 87 patients (22%); Acinetobacter sp. in 46 patients (12%); Enterobacter sp. in 32 patients (8%) and others in 54 patients (14%). The median hospital stay until the first
positive blood culture was 9 days, range 3–177. Half of the patients were treated with antibiotics in the month before the bacteraemia. The susceptibilities of all isolates during the years of the study are given in Figure 1. One hundred and ten (28%) of the isolates were resistant to ciprofloxacin; 122 (28%) to ceftazidime; 154 (39%) to gentamicin; 81 (21%) to amikacin; and 259 (66%) to cefuroxime. Eight per cent of the isolates were resistant to all five drugs, 14% to four drugs and 14% to three drugs.

The consumption of antibiotic drugs per department and per year is detailed in Figure 2. The departmental consumption of each antibiotic drug was higher in the year before the infection for patients with a strain resistant to the same antibiotic drug than for patients with a susceptible strain (Table 1). All regression models were significantly related to the dependent variable (from \( P = 0.01 \) for the gentamicin model to \( P = 0.03 \), while it was negative and not significant for ceftazidime \( r = -0.02 \) and cefuroxime \( r = -0.09 \)).

To address the question of whether the rise in resistance was associated with selection of specific bacteria rather than with selection of resistance vectors in all Gram-negative bacteria, we performed the analyses again, this time only in patients with an infection caused by \( E. coli \), \( K. pneumoniae \), \( P. aeruginosa \) or \( Acinetobacter \) sp. A term for ‘pathogen’ (four categories) was included in the model and, as expected, emerged as highly predictive of resistance. However, the coefficients for antibiotic consumption did not change by much (data not shown).

**Table 1.** Departmental consumption of antibiotics as DDD/100 patient days (median and the 25th and 75th percentiles) in the year before the bloodstream infection: comparisons of resistant and susceptible isolates

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>resistant (DDD/100 patient days)</th>
<th>susceptible (DDD/100 patient days)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>3.1 (2.3–4.2)</td>
<td>2.0 (1.8–3.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0.8 (0.7–1.2)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>14.4 (9.7–17.6)</td>
<td>14.3 (10.0–19.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2.0 (0.8–3.5)</td>
<td>1.5 (0.7–3.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4.7 (3.4–5.0)</td>
<td>3.8 (2.9–5.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Discussion**

We have been able to show that a high departmental consumption of cephalosporin drugs and amikacin in six autonomous departments of medicine in the same hospital was associated with a measurable and statistically significant rise in the odds for a bloodstream infection caused by a resistant coliform pathogen. The extent of the association...
is such that the addition of 100 DDD/100 patient days per year for third-generation cephalosporin or amikacin (i.e. one more patient out of the 30–38 patients in the department, every day for 1 year) caused a significant rise in resistance in the following year. This association was evident even when corrected for the consumption of antibiotic drugs of the particular patient.

The notable exception was the regression model for ciprofloxacin, which was not significantly related to resistance to ciprofloxacin. This is probably explained by the frequent use of the drug in the community, whereas the other drugs were used mostly in hospitals.

Consumption of ceftazidime and amikacin had the highest risk of being associated with resistance in the following year. We could not demonstrate a significant relationship between consumption of gentamicin and development of resistance during the years of the study.

The main question as to the validity of our results is whether a confounding variable, not included in the analysis, caused a spurious association between the annual consumption in the departments and resistance. The inclusion of the department and year as variables in the regression models guards against this to a considerable extent. The fact that the only model that was not predictive of resistance was with ciprofloxacin points toward a biological plausibility for the models.

The multivariate analysis may reflect only the peculiarities of our database, with little correspondence to biological phenomena. This concern could be addressed if our model (which assumes a correlation between consumption of an antibiotic in a defined clinical unit and the risk of a patient acquiring a serious, hospital-acquired infection, caused by a pathogen resistant to the same drug) is tested in other medical settings.

We used a simple model in which resistance is related to the consumption of an antibiotic in the previous year. There are few and confusing indications as to what timeframe should be used for this purpose. Although it is clear that the consumption of antibiotics should be related to some measure of activity of the department, we have no good evidence to show that the denominator chosen by us (total number of patient days) is the most appropriate.

The relationships described here may be particular to our setting but be of a different magnitude for other hospitals. For example, some studies showed a lesser impact of amikacin consumption than of gentamicin consumption on resistance. The opposite was shown in our data. A similar analysis applied at other hospitals should show how robust our results are.

To complete our analysis, it should be extended to other antibiotics and pathogens, and include the influence of consumption of antibiotics on resistance to other antibiotics.
Antibiotic consumption and resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Departmental consumption$^b$</th>
<th>Prior specific antibiotic$^c$</th>
<th>Prior treatment with any other antibiotic$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>1.03 (0.70–1.50)</td>
<td>2.12 (1.29–3.48)</td>
<td>1.81 (1.40–2.33)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1.80 (1.00–3.24)</td>
<td>2.40 (1.31–4.40)</td>
<td>1.31 (1.49–2.20)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1.12 (1.01–1.23)</td>
<td>3.24 (1.97–5.34)</td>
<td>2.77 (1.99–3.87)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1.45 (1.19–1.76)</td>
<td>3.88 (1.89–7.97)</td>
<td>1.55 (1.18–2.04)</td>
</tr>
<tr>
<td>Ciprofloxacin$^d$</td>
<td>1.06 (0.57–1.97)</td>
<td>4.05 (2.00–8.21)</td>
<td>1.27 (0.62–2.70)</td>
</tr>
</tbody>
</table>

$^a$The results are from five different logistic regression models. The odds ratio and 95% CI in each row of the table pertain to resistance to the specific antibiotic of this row.  
$^b$In the calendar year before the bloodstream infection (continuous variable, increment of 1 DDD/100 patient days). 
$^c$Given to the specific patient in the month before the bloodstream infection for at least 24 h (dichotomous variable). 
$^d$The logistic regression model for resistance to ciprofloxacin was not significantly explanatory.

In summary, the present results are a first step toward an important contribution to the cost-effectiveness analysis of antibiotics, including induction of resistance. Treatment with an antibiotic is associated with a higher chance of infection caused by resistant pathogens in the following month, as shown by Pedersen et al. and in the present results. Consumption of antibiotic drugs is related to a measurable increase in the risk for all patients in the specific medical setting to harbour resistant pathogens.

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