Are laboratory-based antibiograms reliable to guide the selection of empirical antimicrobial treatment in patients with hospital-acquired infections?

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Objectives: Antibiograms are often taken into account to define a rational selection of an empirical antimicrobial therapy for treating patients with hospital-acquired infections. In this study, we performed a paired comparison between the antibiogram constructed with laboratory-based data and that formed with data subjected to prior clinical validation.

Methods: Between 2003 and 2005, the laboratory of microbiology printed in duplicate every individual susceptibility report corresponding to hospitalized patients and the copy was sent to the department of infection control. Every individual report was assessed in real time at the bedside of the patient by a multidisciplinary team for clinical significance and appropriateness of the specimen, as well as for the type, source and origin of the infection. Cumulative resistance rates were estimated in parallel at the laboratory with the whole data, and at the infection control department with data subjected to prior clinical validation. These rates were designated as 'laboratory-based' and 'clinically based', respectively.

Results: A total of 2305 individual susceptibility reports were assessed. Only 1429 (62.0%) were considered as clinically significant by the multidisciplinary team. Escherichia coli, Enterobacter cloacae, Citrobacter freundii group, Klebsiella species and Proteus mirabilis resistant to broad-spectrum cephalosporins, as well as methicillin-resistant Staphylococcus aureus, were significantly more frequent in the clinically based rates (P < 0.03).

Conclusions: Laboratory-based data underestimate the frequency of several major resistant organisms in patients with hospital-acquired infection. Previous clinical validation of the individual susceptibility reports seems to be a suitable strategy to get more reliable data.

Keywords: antibiotics, antimicrobial resistance, susceptibility reports

Introduction

Increasing bacterial resistance is a current and worrisome problem, especially in the nosocomial setting. This is exemplified by methicillin-resistant staphylococci, vancomycin-resistant enterococci, Gram-negative organisms producing extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases, as well as the widespread derepression of AmpC β-lactamases and target site mutation for fluoroquinolones. Variation in the frequency of these resistant bacteria is monitored by several surveillance systems worldwide. These systems make use of a network of laboratory-generated antibiograms that are constructed on the basis of the cumulative antimicrobial susceptibility data from each hospital. Antibiograms are currently used to estimate the impact of changes in antibiotic usage and to determine infection control strategies and antibiotic usage policies. Furthermore, within the nosocomial setting, antibiograms are often taken into account to define a rational selection of the empirical
antimicrobial therapy for treating patients with hospital-acquired infections. Recently, a nationwide antibiogram analysis showed inconsistent susceptibility reports. As a consequence, a thorough review of antibiograms prior to distribution, by infectious disease specialists, clinical microbiologists and infection control personnel was suggested to help identify abnormal findings. However, with hospitalized patients there are other plausible biases that may be introduced into the design of the antibiograms, via the individual susceptibility data; these biases are difficult to remove once the antibiogram is conceived, such as history of antibiotic administration prior to sample collection, difficulty in determining the origin of the infection (e.g. community- or hospital-acquired) and inclusion of strains from either inappropriate samples or specimens from patients lacking infection criteria. These biases are beyond the laboratory reach and may limit the usefulness of the antibiogram in guiding the selection of an empirical antimicrobial therapy for treating patients with hospital-acquired infections. In this study, we approached this issue and performed a paired comparison between the antibiogram constructed with laboratory-based data alone and that formed at the department of infection control with data subjected to prior clinical validation, carried out in real time by a multidisciplinary team at the bedside of the hospitalized patients.

Methods

Setting

The Hospital San Martín is a 250 bed public teaching hospital for adult patients. It is located in Paraná, Argentina, a city of about 350,000 inhabitants. The hospital has a 10 bed intensive care unit and several surgical wards, including orthopaedic, abdominal, thoracic, gynaecological and neurological wards, but it lacks facilities for solid organ or bone marrow transplantation and cardiac surgery.

Strategy and data collection

Susceptibility testing was carried out by the disc diffusion method following the CLSI guidelines, including the interpretative breakpoint criteria. The presumptive presence of ESBL was routinely screened by the double-disc diffusion test with clavulanic acid and ceftriaxone and ceftazidime. Because our laboratory belongs to the WHONET programme, the individual susceptibility reports from all of the patients assumed by the laboratory as having nosocomial infections were entered into the WHONET microbiology laboratory database software. Between 2003 and 2005, the laboratory of microbiology printed in duplicate every individual susceptibility report corresponding to hospitalized patients and the copy was sent to the department of infection control. Every individual report was assessed in real time at the bedside of the patient by a team composed of seven physicians (infectious diseases and internal medicine specialists) and two clinical microbiologists. Assessments were performed for clinical significance and appropriateness of the specimen, as well as for the type, source and origin of the infection, hospitalization site and the underlying clinical condition of the patient. Nosocomial infection was defined following the guidelines of the Centers for Diseases Control and Prevention. Any individual report considered by the team as corresponding to colonization or to an inappropriately collected specimen was discarded. This process was, hence, assumed as a clinical validation of the susceptibility data. Subsequently, a clinical microbiologist entered the suitable data to the SIR system, homemade software designed by one of the authors (C. B.).

Data analysis and statistics

For comparison purposes, cumulative resistance rates were estimated at the laboratory by the WHONET software and at the infection control department by the SIR system. The antibiograms yielded by the WHONET software corresponded to all specimens passing through the laboratory and were designated as ‘laboratory-based’ data, whereas those yielded by the SIR system, corresponding to clinically significant specimens only, were designed as ‘clinically based’ data. To calculate bacterial resistance rates, the SIR system automatically eliminates multiple strains from the same patient if they display identical susceptibility pattern and if they are recovered within a 6 month period. This arbitrary period of time is already incorporated into the system to reduce the likelihood of data duplication. Furthermore, the software allows the estimation of resistance rates selecting by ward, source or type of infection, underlying disease or previous antibiotic administration.

In order to assess the differences between laboratory- and clinically based data, the following resistance phenotypes were selected: Escherichia coli, Enterobacter cloacae, Citrobacter freundii group, Klebsiella species, Proteus mirabilis and Pseudomonas aeruginosa resistant to broad-spectrum cephalosporins, as well as meticillin-resistant Staphylococcus aureus. Neither vancomycin-resistant enterococci nor imipenem-resistant P. aeruginosa or Acinetobacter species were considered for the analysis, as they had never been found in our hospital setting.

Rates were analysed by comparison of proportions with the \( \chi^2 \) or Fisher’s exact tests using the software Statistix for Windows, ver. 2.0 (Analytical Software co., 1985, 98). A \( P \) value of \( \leq 0.05 \) was regarded as significant.

Results

In total, 2305 individual susceptibility reports, assumed by the laboratory as corresponding to patients with hospital-acquired infection, were assessed. Only 1429 (62.0%) were considered as clinically significant by the multidisciplinary team, and 868 of these (60.7%) corresponded to patients with hospital-acquired infections, as ascertained in real time by the team. Table 1 shows the difference between laboratory- and clinically based frequencies of the resistant phenotypes selected for the analysis. Apart from P. aeruginosa, resistant pathogens were significantly more frequent in the clinically based rates (\( P \leq 0.03 \)). To further illustrate the potential clinical impact of the differences between the laboratory and clinical setting of data generation, the laboratory constructed an antibiogram for E. coli using the WHONET software, focusing on ‘abdominal fluid’ as the microbiological specimen and on ‘hospitalized patient’ as the origin of the infection. This should represent an example of the highest discriminative reach of the laboratory-based antibiogram (i.e. focusing on specimen and origin of infection). Results were compared against those of two types of abdominal infections that could be discriminated by the SIR program with data validated in real time by the team, such as community- and hospital-acquired peritonitis. Therefore, whereas the laboratory-based data represented the source of the specimen, the clinically based data represented the type and, hence, the actual origin of the infection. Data are given in Table 2. Resistance rates to
ampicillin/sulbactam, cefalotin, gentamicin and ciprofloxacin were significantly higher in hospital-acquired peritonitis than in both abdominal fluid and community-acquired peritonitis ($P < 0.05$). In addition, resistance rate to ciprofloxacin was higher in abdominal fluid than in community-acquired peritonitis ($P = 0.04$).

**Discussion**

Although antibiograms are used for multiple purposes, one of their most common uses is to assist clinicians in the design of empirical therapies for suspected infections within a hospital setting. Surprisingly, the reliability of antibiograms to be used for this purpose has rarely been assessed. Indeed, many issues regarding the generation of these reports, such as handling duplicate isolates, incorporation of only select sites of cultures, or isolates from only confirmed infections have been pointed out. In addition, to better aid in empirical therapy decisions for hospitalized patients, separate summary reports would be needed for hospital- and community-acquired infections. Such reports would be difficult to generate for many clinical microbiology laboratories. Our results demonstrate that laboratory-based data underestimate the frequency of most of the resistant organisms in patients with hospital-acquired infection, with the exception of *P. aeruginosa*. Fridkin et al. found similar results for methicillin-resistant staphylococci when they assessed this issue in patients with nosocomial-acquired infection in 166 intensive care units in the United States. However, they did not observe this phenomenon with other pathogens, as we did. Differences may be explained by the fact that our study was hospital-wide; hence, laboratory-based data from our hospitalized patients were more likely to be affected by the inclusion of strains from community-acquired infections. To elucidate this issue, we compared a laboratory-based antibiogram for *E. coli*, focusing on abdominal fluid as the microbiological specimen with that of an infection discriminated, in real time by clinical assessment, as community- and hospital-acquired peritonitis. Results confirmed that resistance rates yielded by laboratory-based data are ‘diluted’ by the inclusion of more susceptible strains, probably coming from the community setting. This bias is beyond the laboratory reach and is probably the reason for underestimation of resistance rates in patients with hospital-acquired infections by the laboratory-based data. Therefore, we believe that real-time clinical validation of the routine hospital susceptibility report would increase confidence level among clinicians that laboratory-based data can guide empirical therapy for patients with hospital-acquired infections, as the frequency of antimicrobial resistance among isolates from patients with infections acquired in the healthcare setting may be different from that of all isolates processed by the clinical microbiology laboratory.

In summary, this study shows that laboratory-based data underestimate the frequency of several major resistant organisms in patients with hospital-acquired infection. Real-time clinical validation of the individual susceptibility reports, performed by a multidisciplinary team prior to data entering, seems to be a suitable strategy to get more reliable data to guide the rational selection of antimicrobial empirical therapy in patients with hospital-acquired infections.

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