Restrictive reporting of selected antimicrobial susceptibilities influences clinical prescribing

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KEYWORDS
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Summary
Background: Cascade and restrictive reporting are useful strategies to enhance antibiotic stewardship programs.
Methods: We combined both strategies to improve the prescribing of antibiotics aimed at Gram-negative infections.
Results: For Enterobacter aerogenes, the susceptibility rates to amikacin increased from 10% to 100%; for third generation cephalosporins, these rates increased from 55% to 89%. The susceptibility rates of E. aerogenes to cefepime and piperacillin–tazobactam changed little, and the ampicillin susceptibility decreased from 30% in 2009 to 11% in 2010. For Proteus mirabilis, the susceptibility rates increased for third-generation cephalosporins (48% vs. 92%) and piperacillin–tazobactam (10% vs. 98%), with minimal changes for cefepime.

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Restrictive reporting of selected antimicrobial susceptibilities

(96% vs. 93%), ampicillin (69% vs. 73%) and amikacin (96% vs. 84%). For Pseudomonas aeruginosa, the susceptibility rates improved slightly for third-generation cephalosporins (81% vs. 91%) but reduced for piperacillin–tazobactam (99% vs. 59%). Hospital-acquired Clostridium difficile infections decreased from 0.11 to 0.07 per 1000 patient days.

Conclusions: Selective reporting helps physicians select the most appropriate antibiotics for their patients within a stewardship program, with reduced C. difficile infection.

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Introduction

The inappropriate use of antibiotics has societal consequences due to ecological effects on both patients and the environment [1,2]. These consequences include the emergence of antimicrobial resistance, which is a particularly ominous sign in the development of modern healthcare. Examples of this resistance include several pathogens, such as Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species, all of which may be multi-drug resistant [3,4]. Formulary restriction is already known to lead to significant and immediate reductions in antimicrobial prescribing and cost [5]. Controlling antibiotic consumption impacts the resistance rates and forms the main basis of antimicrobial stewardship programs. Additional requirements include the monitoring and reporting of antibiotic resistance following laboratory characterization. The Clinical and Laboratory Standards Institute (CLSI) has published guidelines for the analysis and presentation of cumulative antimicrobial susceptibility testing [6]. In one study, the use of a clinical syndrome-wise categorization of antimicrobial agents achieved stable susceptibility of nosocomial isolates [7]. Adherence to the principles of antibiotic use and effective monitoring were useful in halting bacterial resistance [8].

The selective or cascade reporting of antimicrobial susceptibilities may be employed in an antimicrobial stewardship initiative [9]. In cascade reporting, antimicrobial agents of each class are ranked based on a spectrum of activity, popularity or potential for the over-prescribing risk of drug resistance and cost. Thus, the reported antibiogram should include the most appropriate and least expensive drugs, provided the organism is susceptible. Higher risk agents are only released if alternative options are lacking. In selective reporting, the susceptibilities of broad-spectrum agents and those drugs at risk for over-prescription are deliberately withheld [5,9,10]. The CLSI guidelines specify antibiotics within categories that must be reported, e.g., group A and group B, which should be suppressed [11]. Group A is the suggested grouping of antimicrobial agents with FDA clinical indications that should be considered for routine testing and reporting on non-fastidious organisms by clinical microbiology laboratories in the United States. Group B represents the suggested grouping of antimicrobial agents with FDA clinical indications that should be considered for routine testing and reporting on fastidious organisms by clinical microbiology laboratories in the United States. The ultimate goal is to reduce antimicrobial consumption, particularly the use of broad-spectrum agents, to minimize the resistance potential. Selective reporting helps prescribers choose the most appropriate antimicrobial agent based on a susceptibility pattern. Additional strategies, such as antimicrobial order sheets, automatic stop orders and therapeutic substitution, are available to further enhance the best use of antibiotics [12]. We examined the effect of the selective reporting of selected broad-spectrum agents against pathogens with high resistance rates in our hospital.

Materials and methods

Hospital setting and infection control program

The Saudi Aramco Medical Services Organization (SAMSO) provides medical care for approximately 370,000 patients. The main hospital, Dhahran Health Center (DHC), is a 380-bed general hospital with five intensive care units (cardiac, medical, surgical, pediatric and neonatal). The hospital caters to a wide range of patients, including general medicine and surgery, intensive care and the management of hematological and solid organ malignancies. Over 36,000 patients are admitted
every year, with the total number of patient-days being 193,725 (the average length of stay was 5.3 days) [13]. A previous study in this hospital between 2006 and 2008 showed that ciprofloxacin was the most commonly used intravenous antibiotic (67.6% of total parenteral antibiotic consumption), followed by ceftriaxone (6%), cefazolin (5%) and imipenem–enzyme inhibitor (4.3%) [14]. From 2006 to 2008, the annual consumption rates of intravenous antimicrobial agents in defined daily doses (DDD) per 100 patient-days were the following: ciprofloxacin 82.643, ceftriaxone 7.447, cefazolin 6.166, imipenem–enzyme inhibitor 5.234 and levofloxacin 3.188 [14]. The annual incidence rates of *Clostridium difficile* infection in our hospital were 2.4 and 1.7 per 10,000 patient days in 2007 and 2008, respectively [15]. The most common organisms causing catheter-associated bloodstream infections between 2002 and 2006 were coagulase-negative staphylococci (23.7%), *Staphylococcus aureus* (11.1%), *Escherichia coli* (11.1%), candida (5%), *K. pneumoniae* (9%) and *P. aeruginosa* (7.3%) [16]. Nosocomial *Enterobacter cloacae* isolates were more resistant to ceftriaxone (17.5 vs. 5.5%), ciprofloxacin (9.5 vs. 4.7%) and ticarcillin–clavulanic acid (23 vs. 9.3%) than outpatient isolates [17].

**Design**

In May 2010, Clinical Laboratory Services and Pharmacy agreed to implement the selective reporting of tested antibiotics based on availability within the hospital antibiotic formulary. Additional antibiotics were tested for a cumulative susceptibility report but were excluded from the patient report. Reporting was also modified by offering antibiotics that can be administered at least two different ways, e.g., intravenous and oral administration.

We specifically targeted Gram-negative bacillus (GNB) susceptibility reporting for this initiative because 74% of all organisms isolated in our laboratory are GNB, specifically, *Enterobacter* spp., *Proteus* spp. and *P. aeruginosa*. Thus, the reporting of Enterobacteriaceae and Pseudomonas was modified, with at least four main antibiotics removed from the panels (Figs. 1 and 2). The reported susceptibility pattern was pertinent to valid clinical

**Modifications Enterobacteriaceae**

![Diagram of antibiotic panels for Enterobacteriaceae](image)

*Figure 1* Original and modified antibiotic panels for Enterobacteriaceae for patient reporting. Tables marked with X were the original panels that were merged into one modified panel (middle). Underlined antibiotics were removed, while the other antibiotics remained. ATM = aztreonam; CAZ = ceftazidime; TOB = tobramycin; C = chloramphenicol; TE = tetracycline; MZ = mezlocillin; PIP = piperacillin; CB = carbenicillin; Trimeth-Sulfa = trimethoprim–sulfamethoxazole.
isolate, linked with septic patients, non-duplicate and from hospitalized patients.

Antibiotic susceptibilities were chosen for release after considering local resistance rates, pharmacokinetic factors and recommendations from international organizations, e.g., the Infectious Disease Society of America (IDSA). If more than 20% of isolates were resistant to a specific antibiotic, this agent was excluded from the reporting panel. If susceptibility was confirmed, having a susceptibility result for that antibiotic/organism combination if clinically indicated. However, if the prevalence of resistance was >20%, the antibiotic in question should not be given as an empirical therapy.

The temporary freezing of selected antibiotics with high resistance rates (>20%) to GNB, such as amikacin, ampicillin and third generation cephalosporins, was instituted for Enterobacteriaceae when possible for most of the cephalosporins and when other agents were available. Broad-spectrum antibiotics known to have decreased susceptibility among local coliforms were also removed from the panel. The reporting of antibiotics within the same class, e.g., 3rd and 4th generation cephalosporins, was suppressed, with only one agent released in the report. The laboratory released additional antimicrobial susceptibilities if the patient was allergic to specified antimicrobial agents. The CLSI 2010 breakpoints were used, and Vitek 2 GNS-30 susceptibility cards were employed for MIC values. The breakpoints remained the same throughout the study.

We compared the antibiotic utilization as DDDS (per 1000 patient-occupied bed days) before and after the intervention. We also compared the antibiotic susceptibilities of selected organisms (E. aerogenes; P. mirabilis; P. aeruginosa) 6 months before and 6 months after the change in reporting.

No outbreaks occurred in the hospital during the study period. All patients with multidrug-resistant organisms (MDROs) are routinely placed on contact isolation, with en suite or designated bathrooms. An MDRO is defined as any organism that is resistant to at least three drugs within the following classes: β-lactams (piperacillin, piperacillin–tazobactam, ceftazidime, cefepime, ticarcillin, ticarcillin–clavulanate), carbapenems (imipenem, meropenem), aminoglycosides (gentamicin, tobramycin, amikacin) and fluoroquinolones (ciprofloxacin, levofloxacin) [16,17].

Before the launch of the reporting initiative, an educational program was delivered to prescribers during hospital grand rounds and as additional seminars on antibiotic stewardship. The program introduced cascade reporting, the benefits and disadvantages of such reporting and the concept of restrictive reporting in general. Specific examples were shared with prescribing physicians to justify the restrictions. These examples included the reasons for removing amikacin, ampicillin, cefazolin and cefuroxime and retaining gentamicin, ceftriaxone, ciprofloxacin and one carbapenem on the reporting panel for Enterobacteriaceae.

After the educational program began, the infectious disease specialist and microbiology laboratory technicians experienced increasing calls from physicians regarding the proposed changes. Many physicians were comfortable only with prescribing familiar antibiotics. We were able to alleviate concerns via further discussion and the provision of published support for the intervention. In addition, we held small group meetings with the main in-patient prescribers, which were also attended by key and influential physicians. The physicians eventually agreed to support the stewardship initiative.

Statistical analyses

Statistical analyses were performed using the SPSS statistical software, version 10.1 (SPSS). The antibiotic utilization was calculated as DDDS and expressed per 1000 patient-days before and after the intervention. The antibiotic susceptibilities of selected organisms were reported as percentage
susceptible. The change in DDD/1000 patient-days was computed. Differences in susceptibility testing results were compared using the Chi-square test, and a P value of ≤0.05 was considered statistically significant.

Results

The numbers of tested isolates of *E. aerogenes* were 104 and 75 in 2009 and 2010, respectively. The *P. mirabilis* isolate numbers were 168 and 116, and the *P. aeruginosa* isolates were 481 and 414 in 2009 and 2010, respectively. The cumulative susceptibilities to specific organism—antibiotic combinations improved following the introduction of restrictive reporting (Figs. 3–5). For *E. aerogenes*, the susceptibility rates to amikacin and third-generation cephalosporins improved from 10% to 100% (*P < 0.001*) and from 55% to 89% (*P = 0.0001*), respectively (Fig. 3). The changes in the susceptibility rates to cefepime and piperacillin–tazobactam were 93–97% (*P = 0.126*) and 93–91% (*P = 0.23*), respectively (Fig. 3). The ampicillin susceptibility decreased from 30% in 2009 to 11% in 2010 (*P = 0.0018*) for this organism.

For *P. mirabilis*, the susceptibility rates improved for third-generation cephalosporins (48% vs. 92%, *P < 0.001*) and piperacillin–tazobactam (10% vs. 98%, *P < 0.001*), with little change for cefepime (96% vs. 93%, *P = 0.26*), ampicillin (69% vs. 73%, *P = 0.46*) and amikacin (96% vs. 84%, *P < 0.005*) (Fig. 4).

The susceptibility rates for third-generation cephalosporins somewhat improved for *P. aeruginosa* (81% vs. 91%, *P < 0.001*) (Fig. 5). However, the susceptibility to piperacillin–tazobactam significantly reduced (99% vs. 59%, *P < 0.001*), which was presumed to be the result of the overall increase in the consumption of this agent (Fig. 6). The susceptibility rates for cefepime, levofloxacin, tobramycin or amikacin did not change.

As shown in Fig. 6, the uses of amoxicillin and ampicillin, piperacillin–tazobactam, ticarcillin–clavulanic acid, ceftriaxone and amoxicillin–clavulanic acid increased throughout the hospital, with small increases for levofloxacin and ceftazidime. The utilization rates of cefepime and amikacin markedly decreased, with smaller decreases for cefuroxime and cefazolin. The annual *C. difficile* rate reduced from 0.11 to 0.07 per 1000 patient days in 2009 and 2010, respectively (*P < 0.001*).

Discussion

The introduction of selective reporting resulted in a measurable diminution of resistance for some organism–antibiotic combinations, excluding *P. aeruginosa*. The overall impact was less than
hoped, and prescribers are assumed to not necessarily support the policy for all patients. Clinical instances in which patients required treatment with a restricted agent due to extreme-drug resistance are also suspected. In addition, the increased use of one member of an antibiotic class will select for resistance to other members of the same class as well as for unrelated agents. This selection may explain the differences in resistance rates between the three species of organisms studied. The universal restriction of amikacin and cefepime has been noted to significantly reduce consumption, but increased susceptibility was not universally demonstrated among the organisms studied. Once an organism gains resistance, it apparently is not easily lost [2]. Continuous antibiotic exposure, even to agents belonging to unrelated classes, will maintain a certain level of resistance in a confined area, such as a hospital.

Despite the absence of any identified outbreaks during the study, the restricted reporting initiative is potentially confounded by infection control deficits, e.g., infection clusters, localized infection control problems, the role of carriers, etc. The hand hygiene rate increased from 40% to 85% in 2004 and 2011, respectively [18]. Device-associated infection prevention bundles were introduced in 2006 for ventilator-associated pneumonia (VAP), in 2008 for central line-associated blood stream infections (CLABSI) and in mid-2010 for catheter-associated urinary tract infections (CAUTI) [19]. The latter intervention may have impacted the study reported here.

Selective and/or cascade reporting allows the microbiology laboratory to take a more active role in antimicrobial stewardship [20]. In this study, we used a modified approach to cascade reporting by releasing not the least expensive but the most effective drug based on the antibiogram. In a survey of selective reporting for urinary tract infections, this technique improved the appropriateness of antibiotic prescriptions from 7% to 14% [21]. As anticipated, the routine reporting of ampicillin, ticarcillin—clavulanic acid and piperacillin—tazobactam resulted in increased consumption. A previous study showed that the routine reporting of rifampicin susceptibility increased the use of rifampicin [22]. The hospital turnover increased markedly during the study, and our attempts to curtail piperacillin/tazobactam were unsuccessful. Clinicians were predisposed to select this agent because cephalosporins and amikacin were also restricted. We believe that without the study, the consumption of piperacillin—tazobactam would have reached a much greater level, given the trend witnessed previously at our hospital. In addition, piperacillin—tazobactam was being released for use in patients with serious pseudomonal infections. The antibiotics considered for selective reporting should reflect clinical need, the local prevalence of resistance, approved indications and clinical guidelines [23]. While selective reporting

![% Change](image)

**Figure 6** The percentage change of DDDs/1000 patient-days of selected antibiotics; the comparison of usage before and after the change in the reporting of susceptibility pattern (December 2009—May 2010) compared to that after the change (June 2010—December 2010).
alters the prescribing rates of different antibiotics, the strategy may not necessarily be associated with a better choice of antibiotic therapy [24]. *E. aerogenes* is naturally ampicillin resistant due to a chromosomal AmpC beta-lactamase. Therefore, the reported change in susceptibility from 30% to 10% may be attributed to other factors, such as varying AmpC expression. The literature and guidelines (e.g., EUCAST Expert Rules) discourages the use of third-generation cephalosporins for *E. aerogenes* [25]. The reason for this is the induction of the chromosomal AmpC and selection of constitutively overexpressing mutants. Thus, finding that abandoning the use of cefepime influenced third-generation cephalosporin susceptibility can be anticipated on this basis.

In conclusion, the restrictive reporting of antibiotic susceptibilities for key pathogens influenced clinical prescribing and permitted a laboratory-based contribution toward an antimicrobial stewardship program. Some notable improvements in the susceptibility rates for selected Enterobacteriaceae were observed, and the increased awareness of prudent prescribing may have also contributed to a decreased rate of *C. difficile* infection. Predicting further long-term benefits on resistance rates from this type of study is difficult, but the current concern for increasing resistance justifies an attempt to improve the local use of antibiotics.

We would have preferred to collect data on all hospital pathogens isolated in the microbiology laboratory but lacked the resources to do so. We decided to focus on the most common pathogens isolated in our laboratory, particularly those that showed the highest rates of resistance. We could not remove imipenem from routine reporting, as clinicians were adamant about availability; it was also needed for pan-resistant isolates, but the educational component of the program highlighted the adverse effects resulting from the frequent use of this drug. The study was supported by ward-based pharmacists who identified patients that received restricted or broad-spectrum agents, including imipenem, and approached clinicians who aimed to stop or change prescribed drugs to a less powerful agent. Ongoing support is required for prescribers whenever an antibiotic stewardship initiative is implemented. Clinicians should be provided with advice at all stages of any intervention, including ward visits, seminars, telephone teaching and after-hours discussion. Repeated educational or policy methods and the implementation of such activities in future studies would increase support among healthcare personnel. Similarly, having an educational and initial teaching for undergraduate medical students, who are the prescribing doctors of the future, is important [26].

The limitations of the current study include the following: difficulties in persuading colleagues to prescribe specific agents or combinations of agents, relevant microbiology not always sent, laboratory break points not necessarily reflecting the clinical situation, no incentive for prescribers to choose more appropriate antibiotics and the reduced consumption of one antibiotic class leading to the increased consumption of another, which will also influence antimicrobial susceptibilities in the hospital. Antimicrobial selection pressures are expected to constantly undermine the stewardship initiative. Regarding the strengths of this study, it represented an opportunity for the microbiology laboratory and its staff not only to highlight the importance of increasing antimicrobial resistance to clinicians but also to implement a strategy to tackle this resistance. The study also forged relationships between clinicians and microbiologists and provided a focus on antimicrobial resistance for the hospital, with further opportunities to implement stewardship initiatives.

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Conflict of interests

In the past, S.J.D. has received nonrecurring, lecture or conference fees from Pfizer, Novartis and Janssen-Cilag. The other authors have no relevant conflicts of interest to declare.

Ethical approval

Not required.

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Restrictive References


