Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting

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Received 3 March 2008; returned 2 April 2008; revised 21 April 2008; accepted 7 May 2008

Objectives: Antibiotic stewardship is important, but the ideal strategy for providing stewardship in a hospital setting is unknown. A practical, sustainable and transferable strategy is needed. This study evaluates the impact of a novel computerized antimicrobial approval system on antibiotic-prescribing behaviour in a hospital. Effects on drug consumption, antibiotic resistance patterns of local bacteria and patient outcomes were monitored.

Methods: The study was conducted at a tertiary referral teaching hospital in Melbourne, Australia. The system was deployed in January 2005 and guided the use of 28 restricted antimicrobials. Data were collected over 7 years: 5 years before and 2 years after deployment. Uptake of the system was evaluated using an in-built audit trail. Drug utilization was prospectively monitored using pharmacy data (as defined daily doses per 1000 bed-days) and analysed via time-series analysis with segmental linear regression. Antibiograms of local bacteria were prospectively evaluated. In-hospital mortality and length of stay for patients with Gram-negative bacteraemia were also reported.

Results: Between 250 and 300 approvals were registered per month during 2006. The gradients in the use of third- and fourth-generation cephalosporins ($+0.52, P<0.01$), glycopeptides ($+0.27, P=0.09$), carbapenems ($+0.12, P=0.21$), aminoglycosides ($+0.15, P=0.27$) and quinolones ($+0.76, P=0.08$) all fell after deployment, while extended-spectrum penicillin use increased. Trends in increased susceptibility of Staphylococcus aureus to methicillin and improved susceptibility of Pseudomonas spp. to many antibiotics were observed. No increase in adverse outcomes for patients with Gram-negative bacteraemia was observed.

Conclusions: The system was successfully adopted and significant changes in antimicrobial usage were demonstrated.

Keywords: computer, antibiotics, antibiotic stewardship, decision support, approval

Introduction

Antibiotic stewardship is important to address the problem of multi-resistant pathogens.1–3 It encompasses many strategies designed to optimize antibiotic use in a given setting, that is, to avoid under-treatment of infection, while minimizing overuse of antibiotics that might contribute to the selection of antibiotic-resistant pathogens. Methods for stewardship vary, but can usually be broadly categorized as ‘persuasive’ (provision of education and feedback about drug use) or ‘restrictive’ (requiring approval for use of particular drugs).4

The evidence for efficacy of restrictive strategies on reducing multi-resistant bacteria has generally been related to limiting use of specific antibiotics to address an outbreak of a
particular pathogen.\textsuperscript{5–7} The effect of restricting a larger group of antibiotics over a longer time period has been less well examined.

The rationale for antibiotic restriction is generally accepted by clinicians,\textsuperscript{8–10} but, in practice, this acceptance depends on how the restriction is implemented. If antibiotic restriction impedes clinicians’ workflow and consumes their valuable time, then it is unlikely to be widely supported. In an ideal system, approvals must be easy to access at all times of the day and communication between the authorizer, the prescriber and the pharmacist needs to be facilitated.

Based on these requirements, computerized antimicrobial approval systems (cAASs) have been developed. Some computerized systems addressed approval for individual antibiotics,\textsuperscript{11,12} and others were intended for use by the approver rather than the prescriber.\textsuperscript{13} There have clearly been some very successful systems used at hospitals with a history of well-integrated comprehensive computerization.\textsuperscript{14}

The overall aim of the study was to evaluate the impact of a cAAS in an Australian hospital setting using multiple methods of evaluation. The specific aims were to examine the uptake and the effects on prescribing behaviour, to monitor for any changes in antibiotic resistance patterns in local bacteria and to follow the outcomes of patients with bacterial infections.

**Methods**

**Description of the intervention**

This study was carried out in the Royal Melbourne Hospital, a 365 bed adult tertiary referral and teaching hospital in metropolitan Melbourne. The Drug and Therapeutics Committee of the hospital had already specified an antibiotic formulary with a list of ‘restricted antimicrobial agents’. For these antimicrobials, it was expected that clinicians would obtain an approval to prescribe the drug. The list included aciclovir, amphotericin, azithromycin, aztreonam, ceftriaxone, cefotaxime, ceftazidime, cefepime, ciprofloxacin, colistin, ertapenem, famciclovir, gentamicin, imipenem, itraconazole, linezolid, meropenem, moxifloxacin, piperacillin/tazobactam, posaconazole, quinupristin/dalfopristin, rifampicin, ticarcillin/clavulanate, telcooxacillin, tobramycin, valaciclovir, vancomycin and voriconazole. For the purposes of this paper, only the major classes of antibacterial drugs were evaluated; these include third- and fourth-generation cephalosporins, carbapenems, glycopeptides, aminoglycosides, quinolones and extended-spectrum penicillins.

For each restricted drug, the cAAS listed standard indications, chiefly derived from *Therapeutic Guidelines: Antibiotic* (an independent regularly updated source of antibiotic-prescribing advice widely used in Australia) with some hospital-specific modifications.\textsuperscript{18} A specified duration of approval for the use of restricted antibiotics was nominated by the ID unit for each indication. The prescriber could obtain approval to use the restricted drug for these standard indications via any networked computer workstation throughout the hospital. A typical initial approval duration for empirical therapy might be 3 days, with a view to de-escalating therapy as the patient improved or microbiology results were obtained. For any indications that fell outside the standard indications, the prescriber could obtain 24 h of approval via the computer after documenting the indication as free text. The ID registrars (equivalent to an ID fellow) would review these patients within 24 h to determine the need for ongoing therapy and to specify the duration of approval. Alternatively, the prescriber could make telephone contact with the ID registrar for individualized approval at any time. The ID registrar was able to extend or discontinue existing approvals electronically, whenever required. For serious infections, such as bacterial meningitis, the approval triggered a visual alert for the ID registrar to review the patient. The approvals were stored in the system’s database and could be viewed in real-time (and printed) by the clinical and pharmacy staff.

Pharmacists did not withhold therapy from patients, but if an approval was not obtained within 24 h, they would contact the ID registrar to follow-up the patient. Restricted drugs were removed from the ‘after hours’ drug cupboards on most wards. In the intensive care unit (ICU), however, the restricted drugs were still available to patients without approval. A formal feedback was provided to units regarding their compliance with the approval system over time.

A pilot system addressing third-generation cephalosporins was released in January 2001, and the complete system covering all restricted antimicrobials was deployed in January 2005.

**Assessment of the impact of the cAAS**

**Uptake.** An in-built audit trail kept track of the number of times the approval system was used for each drug, as well as the units, doctors using the system and the particular indications that were nominated. The approvals were divided into standard indications (approvals obtained directly from the computer), non-standard indications (entered as free text by the prescriber) and telephone approvals (obtained after a call to the ID registrar and later electronically recorded).

**Drug consumption.** The consumption of the restricted drugs was evaluated using data from hospital pharmacy records. This included all drugs prescribed to inpatients, outpatients and patients presenting to the emergency department, both individual patient dispensing and drugs used from ward stock. Data were reported as the number of defined daily doses (DDDs) per 1000 bed-days per month from January 2000 to December 2006. The DDDs used were those specified by the World Health Organization,\textsuperscript{19} and the bed-days were calculated from the hospital administration records. Time-series analysis was used to assess the trends in drug consumption over time. Segmented linear regression techniques were applied to compare the patterns of prescribing in the time periods before and after the intervention, taking account of trends over time. This provided a P value describing the difference observed between the pre- and post-intervention time periods.\textsuperscript{20,21}

**Antibiotic resistance.** The antibiotic resistance profiles of common pathogens were evaluated by constructing antibiograms using data from the hospital microbiology laboratory. Bacterial pathogens with
more than 100 isolates per quarter (Staphylococcus aureus, coagulase-negative staphylococci, enterococcal spp., Escherichia coli, Klebsiella spp. and Pseudomonas spp.) were evaluated to look at the changes in antibiotic susceptibility profiles over time. Screening isolates were excluded from the analysis. Repeated isolates of the same bacterial species from the same patient were excluded if they occurred within 7 days for sterile site isolates and within 30 days for non-sterile site isolates. For the purposes of this study, intermediate susceptibility was reported as ‘resistant’. The rate of susceptibility to each antibiotic of interest for the most common bacterial pathogens was calculated as a percentage of the number of isolates of that species per quarter (3 monthly intervals) from 1 January 2000 to 31 December 2006.

Patient outcome. In an effort to evaluate the impact of antimicrobial restriction on patient outcomes, a review of all patients with a positive blood culture for a Gram-negative bacillus during a 2 year period before the deployment of the system (1 January 2003–31 December 2004) was compared with those identified in a 2 year period after deployment (1 January 2005–31 December 2006). This patient group was chosen because it was reasonable to assume that these positive cultures were likely to be clinically significant (not contaminants), would require directed antibiotic therapy (often with a restricted antibiotic) and might have a high mortality if not appropriately treated. The pre-determined outcomes of interest were the in-hospital mortality rate of these patients and the length of hospital stay. General data regarding the species of Gram-negative bacilli isolated and the hospital units that treated these patients were also collected.

Results

Uptake

Figure 1 illustrates the number of approvals per month for all restricted antimicrobial drugs. The cAAS uptake increased in 2005 and reached a plateau at 250–300 new approvals per month during 2006. The pharmacists reported unapproved prescriptions (for the ID registrar to follow-up) at a rate of <5 per month hospitalwide. Audits showed that approval was obtained for 80% to 100% of doses of restricted drugs used for general medical and surgical inpatients. Information regarding the high levels of user acceptance of the system has been reported elsewhere.17

Drug consumption

Figure 2 illustrates changes in the consumption of the most commonly prescribed restricted antibiotic classes over time. Importantly, the fall in third- and fourth-generation cephalosporin use in 2001 corresponds to the introduction of the pilot cAAS as described previously.11 The effect of this intervention appears to have been sustained. The trend in the rate of consumption of glycopeptides, carbapenems, aminoglycosides, quinolones and third- and fourth-generation cephalosporins was reduced after January 2005 compared with that before 2005 (Table 1). An expected increase in consumption of extended-spectrum penicillins occurred after January 2005 in the light of changes to hospital guidelines (refer to the Discussion section).

Antibiotic susceptibility profiles

Figure 3 shows the antibiotic susceptibility profiles of S. aureus and E. coli that represented, respectively, the most common Gram-positive and Gram-negative isolates at the hospital. Pseudomonas spp. are also described as the most common Gram-negative isolate that would be likely to have been nosocomially acquired. A trend towards increased susceptibility of S. aureus to methicillin and increasing susceptibility of Pseudomonas spp. isolates to both carbapenems and aminoglycosides was observed, particularly after the 2001 intervention. The percentage of E. coli isolates susceptible to cefazolin increased after 2005. In all other isolates examined, resistance rates to common antibiotics remained stable. Figure 4 presents the rate of new bacterial isolates per 1000 bed-days per quarter for these bacterial species. Of interest, the rate of E. coli isolates
Figure 2. Consumption of restricted antibiotics reported as the number of DDDs/1000 patient bed-days per month. Trend lines established by linear regression before (continuous lines) and after (broken lines) deployment of a computerized approval system (in January 2005) are shown. Arrows indicate time of deployment of approval system. Note: For third-generation cephalosporins, pilot computerized approval programme deployed in January 2001 and permanent system deployed in January 2005. The figures in boxes represent the gradients of the trend lines in each time period assessed by linear regression.
Figure 2. Continued
increased steadily over time, but the rates of *Pseudomonas* spp. and *S. aureus* in hospitalized patients remained stable.

**Patient outcome**

One hundred and eighty-four patients with Gram-negative bacteria were identified over a 4 year period (2 years before and 2 years after the introduction of cAAS). Haematology/oncology patients accounted for 67.5% of these patients, the remainder being 15% medical, 10% surgical and 7.5% emergency department patients. Of the organisms identified, 27% were *E. coli*, 25% *Klebsiella*, 15% *Pseudomonas*, 8% *Acinetobacter* and 25% other pathogens. Comparing the periods before and after the introduction of cAAS, the 30 day mortality rate and the length of stay remained similar (Table 2).

**Discussion**

This study describes a multifaceted evaluation of the effects of the deployment of a computerized approval system for antibiotic stewardship in an Australian hospital that led to reduced consumption of broad-spectrum antibiotics. It demonstrates that a user-friendly system designed by clinicians can be incorporated and used to facilitate the usual workflow, thus re-enforcing longer-term sustainability. As previous authors have suggested, the challenge with antibiotic stewardship is to find strategies that will work in a hospital setting. Our system operated without the backup of sophisticated, well-integrated computer systems (the hospital did not have electronic medical records or a computerized prescribing system) and without the employment of additional staff, which distinguishes it from successful interventions described at other sites. Pharmacists and ID clinicians promoted the use of the system and helped to educate other staff on an ongoing basis as part of their normal duties. The ID clinicians continued to provide individualized consultation for patients who were prescribed restricted drugs whenever required, particularly for unusual or complex clinical situations, or where prolonged antibiotic therapy was required. Indeed, the system helped to streamline the activities of the ID service.

In this hospital, the deployment of cAAS was associated with changes in the pattern of consumption of a broad range of restricted drugs. The limited durations of approval would have encouraged clinicians to more carefully evaluate the need for restricted antibiotics, to select narrower-spectrum antibiotics where possible and to shorten durations of therapy. In the case of cephalosporins, 6 years of follow-up after deployment of the pilot system were available and demonstrated a sustained reduction in the use of this class of antibiotic. For the other broad-spectrum antibiotics evaluated, changes in the pattern of consumption have been maintained over at least 2 years.

Other factors would have influenced prescribing patterns. In the case of carbapenems, it should be noted that an outbreak of *Acinetobacter* spp. occurred in the ICU in the second half of 2005, which was likely to be responsible for a sharp peak in carbapenem use at that time. The increase in the use of extended-spectrum penicillins after 2005 was expected. It is likely that the change in the institutional protocol for empirical therapy for patients with febrile neutropenia from cefepime to piperacillin/tazobactam largely explains both the increase in extended-spectrum penicillin use and the decline in cephalosporin use after 2005. A hospital policy to discourage prolonged use of aminoglycosides, beyond 72 h, was also released in late 2003 in an effort to limit potential for aminoglycoside toxicity. For patients requiring prolonged therapy, extended-spectrum penicillins or cephalosporins were suggested as alternative agents. cAAS was used to promote these new guidelines and directed clinicians towards recommended antibiotics at the time of antibiotic prescription. No other guidelines or protocols specifically affecting the use of restricted antibiotics were deployed over the study period.

The patterns of resistance of the common pathogens remained relatively stable in the 2 year period post-deployment of cAAS, which supports the findings of previous authors. The changes in *Pseudomonas* spp. susceptibility are of particular interest though, and might be associated in time with the sustained reduction in third- and fourth-generation cephalosporin use after 2001, as an association between carbapenem-resistant *Pseudomonas* spp. and the use of extended-spectrum cephalosporins has previously been described. Similarly, the trend in increased methicillin susceptibility in *S. aureus* might also be associated in time with the reduction in cephalosporin use, but a more detailed study of the correlation is required. Past studies have also associated changes in the susceptibility of these two bacteria with other drugs such as quinolones. It should be acknowledged that the increased rate of susceptibility of

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### Table 1. Changes in patterns of drug consumption over time; gradients assessed using linear regression.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Gradient DDDs/1000 bed-days versus time before pilot intervention</th>
<th>Gradient DDDs/1000 bed-days versus time before intervention</th>
<th>Gradient DDDs/1000 bed-days versus time after intervention</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins (third- and fourth-generation)</td>
<td>+0.52</td>
<td>−0.05</td>
<td>−0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>not applicable</td>
<td>+0.27</td>
<td>−0.53</td>
<td>0.09</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>not applicable</td>
<td>+0.12</td>
<td>−0.24</td>
<td>0.21</td>
</tr>
<tr>
<td>Quinolones</td>
<td>not applicable</td>
<td>+0.76</td>
<td>+0.11</td>
<td>0.08</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>not applicable</td>
<td>+0.15</td>
<td>−0.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extended-spectrum penicillins</td>
<td>not applicable</td>
<td>+0.16</td>
<td>+1.16</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*P* values represent comparisons of gradients in the time periods before compared with after deployment of the system, taking time into account.
S. aureus to methicillin might permit less use of glycopeptides and could explain some of the reduction in consumption of this class of drug.

Clearly many factors other than antibiotic consumption patterns will affect the number and resistance patterns of bacteria identified from clinical isolates. In particular, changes in infection control procedures that might affect transmission of resistant organisms are important and have not been considered here. There were, however, no major changes in isolation facilities or policies, and no routine screening or eradication policy for resistant pathogens was in place over the study period. Details of relevant infection control activities are provided in Table 3.

No change in the pattern of drug consumption should be presented without data that indicates that patient outcomes did not suffer. This is, however, difficult to demonstrate without acknowledging the many possible confounders that influence patient outcomes. In this study, we chose to use mortality from Gram-negative bacteraemia as a broad surrogate marker for patient outcomes from infection in general. Our concerns were that delayed access to broad-spectrum drugs (by requiring ...
clinicians to seek approval to prescribe these drugs after the initial 24 h of unrestricted use) might lead to poorer outcomes for patients requiring broad-spectrum agents. Although patient numbers were not large, no decline in patient outcomes was observed in this cohort.

This study has important limitations. The approval system was not enforced in the ICU, where a significant percentage of broad-spectrum antibiotics is used. Movement of patients from the ICU to the wards is an important potential source of transmission of resistant nosocomial pathogens. A twice-weekly ward round by ID consultants, however, did attempt to ensure that the use of restricted antimicrobial agents in the ICU was reviewed and approved. As discussed previously, the change in the hospital protocol for management of patients with febrile neutropenia in 2005 did potentially confound interpretation of the results, but such changes were judged to be important by local experts and could not be avoided. In this study, it was not possible to differentiate community-acquired from nosocomial infections, so some changes in hospital ecology might have been masked by a large number of community-acquired bacteria also being isolated. The increase in the rate of E. coli isolated from patients over the 7 years of follow-up is of interest, and perhaps somehow correlates with the increased number of patients with Gram-negative bacteremia managed at the hospital over time. This might suggest some change in the nature of patients; for example, maybe more patients are being exposed to more potent immunosuppressive therapies, leading to more frequent presentation with infections.

Overall, this study provides a comprehensive evaluation of a novel, clinician-led, sustainable system for providing antibiotic stewardship in a busy hospital environment. It showed that a cAAS could be successfully implemented in hospitals and can influence antibiotic-prescribing habits. More detailed studies over longer periods will be required to demonstrate an impact on the desired outcome of reducing the rising prevalence of rates of multidrug-resistant pathogens and improving patient outcomes.

**Figure 4.** Rate of new bacterial isolates per 1000 bed-days per quarter (3 month period).

<table>
<thead>
<tr>
<th>Date</th>
<th>Site</th>
<th>Infection control activity</th>
</tr>
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<tbody>
<tr>
<td>February 2000</td>
<td>ICU</td>
<td>move from old to new ICU ward</td>
</tr>
<tr>
<td>November 2004</td>
<td>ICU</td>
<td>employment of two infection control nurses to work specifically in ICU</td>
</tr>
<tr>
<td>April 2005</td>
<td>hospitalwide</td>
<td>hand hygiene campaign promoting the use of alcohol-based handrub</td>
</tr>
<tr>
<td>October 2005 (for 3 months only)</td>
<td>ICU</td>
<td>screening and isolation of patients colonized with Acinetobacter in ICU and use of plastic gowns and gloves for all nurses in direct contact with ICU patients</td>
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</thead>
<tbody>
<tr>
<td>Number of patients with Gram-negative bacteremia</td>
<td>43</td>
<td>39</td>
<td>43</td>
<td>59</td>
</tr>
<tr>
<td>Mortality, 30 day; n (%)</td>
<td>5 (11.6)</td>
<td>6 (15.3)</td>
<td>4 (9.3)</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>Length of stay, days; median (range)</td>
<td>12 (1–62)</td>
<td>15 (1–117)</td>
<td>15 (1–176)</td>
<td>13 (1–112)</td>
</tr>
</tbody>
</table>

**Table 2.** Patients with Gram-negative bacteremia: comparison of patient groups 2003–06

**Table 3.** Description of major hospital interventions in infection control over the study period
but this study suggests that there may be a positive impact on these parameters.

Acknowledgements

We thank Medseed computing, Ms Renukadevi Shanmugasundaram (software developer Melbourne Health), and the clinicians and pharmacists of the Royal Melbourne Hospital.

Funding

The National Health and Medical Research Council of Australia provides funding for the Centre for Clinical Research Excellence in Infectious Diseases. The Guidance DS project was initially funded by a grant from the Biotechnology Innovation Fund from the Commonwealth Government of Australia. Ongoing funding was provided by Melbourne Health.

Transparency declarations

The computerized approval system evaluated in this study is a commercial product owned by Melbourne Health. The authors are employed by Melbourne Health, but declare no other direct personal financial interest in the system. The funding bodies had no influence on the study design, data collection and analysis, or the interpretation and writing of this manuscript. The authors declare no competing interest with regard to the material published in this article.

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