Sustained reduction in antimicrobial use and decrease in methicillin-resistant Staphylococcus aureus and Clostridium difficile infections following implementation of an electronic medical record at a tertiary-care teaching hospital

Paul P. Cook1*, Shemra Rizzo2, Michael Gooch3, Michelle Jordan3, Xiangming Fang4 and Suzanne Hudson4

1Division of Infectious Diseases, Department of Medicine, Brody School of Medicine at East Carolina University, Greenville, NC, USA; 2Department of Biostatistics, University of California at Los Angeles, Los Angeles, CA, USA; 3Pitt County Memorial Hospital, Greenville, NC, USA; 4Department of Biostatistics, East Carolina University, Greenville, NC, USA

*Corresponding author. Tel: +1-252-744-5700; Fax: +1-252-744-3472; E-mail: cookp@ecu.edu

Received 4 July 2010; returned 10 August 2010; revised 27 September 2010; accepted 30 September 2010

Objectives: We evaluated the effect of implementation of an electronic medical record (EMR) on the use of antimicrobial agents and on the rates of infections with Clostridium difficile and methicillin-resistant Staphylococcus aureus (MRSA).

Methods: This was a retrospective, observational study conducted between 1 January 2005 and 31 December 2009. Antimicrobial drug use, rates of nosocomial C. difficile infection (CDI) and MRSA infection, the number of medical charts reviewed and number of antimicrobial recommendations made and accepted were compared before and after implementing the EMR utilizing interrupted time-series analysis.

Results: Compared with the 10 quarters prior to implementing the EMR, there was a 36.6% increase in the number of charts reviewed (P < 0.0001), a 98.1% increase in the number of antimicrobial recommendations made (P < 0.0001) and a 124% increase in the number of recommendations accepted (P < 0.0001). There was a 28.8% decrease in the use of 41 commonly used antibacterial agents (P < 0.0001). Nosocomial CDI decreased by 18.7% (P = 0.07) and nosocomial MRSA infections decreased by 45.2% (P < 0.0001) following implementation of the EMR.

Conclusions: Adoption of an EMR facilitated a significant increase in chart reviews and antimicrobial recommendations, which resulted in a sustained decrease in antimicrobial use. There were decreased nosocomial infections with MRSA and a trend towards decreasing CDIs following implementation of the EMR.

Keywords: antibiotic management, antibiotic resistance, nosocomial infections

Introduction

The use and overuse of antimicrobial agents has led to the development of antibiotic resistance in both the community and the hospital setting. Recommendations from various experts and organizations have promoted the prudent use of antimicrobial agents as a means of controlling resistance.1–3 Recent guidelines from the Infectious Diseases Society of America (IDSA) promote the concept of an electronic medical record (EMR) with computerized physician order entry (CPOE) as a means of facilitating the goals of an antimicrobial stewardship programme (ASP).1 Our hospital adopted an EMR with CPOE in July 2007. We examined the hospital use of antimicrobial agents before and after implementation of the EMR at our institution. We also determined the incidence of nosocomial infections with Clostridium difficile and methicillin-resistant Staphylococcus aureus (MRSA) during the same time period, as these infections are associated with antimicrobial use.2,4–8

Methods

Pitt County Memorial Hospital is an 861-bed, tertiary-care, teaching hospital affiliated with The Brody School of Medicine at East Carolina University. The hospital has a busy trauma unit, cardiothoracic surgery service, orthopaedic service, paediatric unit, oncology service and dialysis unit. Renal transplantsations are performed at the hospital, but there are no bone marrow transplantation or burn units. Ethics approval was not required for this study because we used only routine data collected on...
hospital wards. This was an observational study from 1 January 2005 until 31 December 2009. Our ASP was established in 2001 and has been described previously. Antimicrobial drug use was measured in defined daily doses per 1000 patient days (DDDs/1000 PDs) using the standards of the WHO (www.whocc.no/atcddd/).

Beginning in July 2007, Pitt County Memorial Hospital implemented an EMR (EPIC, Madison, WI, USA) with CPOE. Recommended dosing was built into the order screens for antibiotics following national guidelines. Reports for the ASP pharmacists were built into the EMR and were reviewed daily. The programme operated 5 days a week. The report listed all patients receiving antimicrobial agents continuously for at least 48 h. Information in the report included patient location, patient weight, allergies and ordering physician. The EMR allowed the ASP pharmacists to open an intervention on a patient and allowed documentation within the report on what recommendation was made. If a patient had cultures that had not been finalized, the intervention could be left open and a report run later listing the open interventions for follow-up. If a patient’s initial antibiotic regimen was deemed appropriate, but follow-up was desired to ensure the patient received the recommended time course of therapy, the intervention could also be left open for that purpose. Information entered into the intervention database stayed with the patient’s intervention record and could be seen if that patient came up for review at a later date. Reports were also available to calculate antibiotic usage overall, by unit and by service, allowing targeted education efforts.

The ASP pharmacists entered their recommendations as a progress note and then entered an order for antimicrobial monitoring. This triggered a pop-up screen whenever a physician, nurse practitioner or physician’s assistant entered that particular patient’s record, directing them to the recommendation in the progress note. The physician had to acknowledge seeing the record at the time. It was possible for the pharmacists to determine whether the pop-up had been triggered and who had seen it.

The antimicrobial management programme reviewed 49 antimicrobial agents used at the hospital (Table 1). Broad-spectrum antibiotics were divided into seven classes. Extended-spectrum penicillins included ampicillin, amoxicillin, ampicillin/sulbactam, piperacillin and piperacillin/tazobactam. Cephalosporins included cefazolin, cefadroxil, cefalexin, cefuroxime, cefotetan, ceftriaxone, cefazidime and cefepime. The quinolone class included moxifloxacin and ciprofloxacin.

### Table 1. List of antibacterial and antifungal agents that were monitored as part of the ASP

<table>
<thead>
<tr>
<th>Antibacterial agents</th>
<th>Antifungal agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>amikacin, amoxicillin, amoxicillin/clavulanate, ampicillin, ampicillin/sulbactam, azithromycin, aztreonam, cefaclor, cefadroxil, cefazolin, ceftazidime, ceftiraxone, cefuroxime, cefalexin, ciprofloxacin, clarithromycin, clindamycin, daptomycin, doripenem, doxycycline, ertapenem, erythromycin, gentamicin, imipenem, linezolid, meropenem, metronidazole, moxifloxacin, nafcillin, piperacillin, piperacillin/tazobactam, sulfamethoxazole/trimethoprim, telithromycin, tetracycline, tigecycline, tobramycin, vancomycin</td>
<td>amphotericin B, anidulafungin, caspofungin, fluconazole, itraconazole, miconazole, posaconazole, voriconazole</td>
</tr>
</tbody>
</table>

Carbapenems included ertapenem, doripenem, imipenem and meropenem. Macrolides included azithromycin, erythromycin, clarithromycin and telithromycin. Aminoglycosides included amikacin, gentamicin and tobramycin. Tetracyclines/glycylcyclines included tetracycline, doxycycline and tigecycline. Clindamycin, aztreonam, vancomycin, nafcillin, linezolid, daptomycin, metronidazole and trimethoprim/sulfamethoxazole were examined separately.

Stool samples were tested for the presence of *C. difficile* toxin using a standard cell culture cytotoxicity assay with MRC-5 lung fibroblast cells and antibiotin from TechLab (Blacksburg, VA, USA). Clinical cultures for *S. aureus* included blood, CSF, wounds, respiratory specimens, pleural fluid, tissue specimens and urine. Surveillance cultures were not included. In vitro bacterial susceptibilities were determined using the MicroScan system (Dade Behring). The nosocomial *C. difficile* and MRSA datasets were created by querying MedMined (CareFusion, Birmingham, AL, USA).

In an effort to limit the analysis to nosocomial infections, only cultures or stool specimens from patients who were in hospital more than 3 days following admission were included for evaluation. Duplicate positive test results from the same patient within a 3 month period were counted only once. Rates of nosocomial *C. difficile* and MRSA infections were expressed as cases per 10 000 patient hospital days.

In evaluating the effect of implementation of EMR on the use of antibiotic agents and on the rates of infections with *C. difficile* and MRSA, we adopted interrupted time-series models to control for the serial correlation among the data. It turned out that an interrupted AR(1) model (where AR stands for autoregressive) was able to sufficiently account for the autocorrelation and thus was selected for our final analysis. The model can be formulated as follows:

$$ Y_t = \phi Y_{t-1} + \beta_0 + \beta_1 \times \text{Intervention} + \varepsilon_t $$

where $Y_t$ is the response value at time $t$, $\phi$ is the lag 1 coefficient of the AR(1) model, $\beta_1$ is the measurement error and Intervention is an indicator variable whose value is 0 for timepoints before EMR was implemented and 1 for timepoints after EMR was implemented. Due to the fact that our time-series data are fairly stationary both before and after the introduction of EMR, we did not include a linear trend in the model above. Thus $\beta_1$ is $(1-\phi)$ times the mean response before EMR was implemented and $\beta_2$ is the change in $(1-\phi)$ times the mean response due to the implementation of EMR. As a result, testing on the effect of EMR is equivalent to testing on the significance of $\beta_1$. This interrupted AR(1) model was fitted using the ARIMA procedure in SAS 9.2. This statistical method was used to compare antibiotic use, number of charts reviewed, number of recommendations made, number of recommendations accepted, demographic data and rates of *C. difficile* infection (CDI) and MRSA infection with $P<0.05$ as the level of significance. Linear regression was used to assess hand washing compliance rates over the 5 year period of the study. Spearman’s rank correlation coefficient was used to correlate antimicrobial use with rates of CDI and MRSA infection.

### Results

#### Effect of EMR on chart reviews

There were statistically significant increases in the number of charts reviewed, number of antimicrobial recommendations made and number of accepted recommendations following implementation of the EMR (Table 2). Compared with the 10 quarters prior to implementing the EMR, there was a 36.6% increase in the number of charts reviewed ($P<0.0001$), a 98.1% increase in the number of antimicrobial recommendations made ($P<0.0001$) and a 124% increase in the number of recommendations accepted ($P<0.0001$). Recommendations for antimicrobial changes were made on 23.6% of the charts.
Antibacterial drug use
For the 41 antibacterial drugs monitored, there was a 28.8% decrease in use following implementation of the EMR (Figure 1 and Table 3). There were significant decreases in use of extended-spectrum penicillins, cephalosporins, clindamycin, quinolones, macrolides, metronidazole, vancomycin and aminoglycosides. The use of cefazolin, the drug of choice for surgical prophylaxis, decreased by 53% (81 DDDs/1000 PDs to 38 DDDs/1000 PDs) following implementation of the EMR (P<0.0001). There were no significant changes in use of nafcillin, daptomycin, tetracyclines/glycylcyclines, trimethoprim/sulfamethoxazole or linezolid. Carbapenem use increased by 51.3% (P<0.0029).

Antifungal drug use
Total antifungal use decreased by 17.8% (P=0.01) following implementation of the EMR.

MRSA rate
There were 807 nosocomial MRSA infections during the study period. Nosocomial MRSA infections decreased by 45.2% (P<0.0001) following implementation of the EMR (Figure 1). There was a correlation of MRSA infection with total antibacterial agent use; the correlation was strongest with use of quinolones, followed by cephalosporins, then extended-spectrum penicillins (Table 4). Because of the known association of MRSA infections with poor hand hygiene, we examined hand hygiene compliance rates over the 5 year period of the study. The monthly mean compliance rate was 83.7%. Over the course of the study...
porins and, to a lesser extent, quinolones (Table 4).

The mean rate of nosocomial CDI prior to implementation of the antimicrobial stewardship.3 There are very few data regarding that an EMR be adopted by institutions to facilitate the process of CDIs, the correlation was highest with cephalosporin use. For MRSA infections, the correlation was highest with quinolone use. For

Quinolones 0.70 (P=0.0002) 0.35 (P=0.13)
Cephalosporins 0.66 (P=0.001) 0.61 (P=0.004)
Quinolones 0.70 (P=0.0006) 0.43 (P=0.055)
Total antibacterial agents 0.62 (P=0.003) 0.38 (P=0.10)

For MRSA infections, the correlation was highest with quinolone use. For CDIs, the correlation was highest with cephalosporin use.

period, linear regression analysis revealed a slight, but statistically significant (P=0.02), decrease in hand hygiene compliance hospital-wide.

**CDI rate**

There were a total of 394 nosocomial C. difficile toxin-positive cases during the study period. There were no significant differences in the average length of stay of all patients before and after implementation of the EMR and there were no significant differences in the ages of patients with CDI in the period before and after implementation of the EMR (data not shown). Similarly, there were no differences in the two groups with regard to time in hospital prior to the first positive C. difficile toxin-positive stool (data not shown). The hospital rates for CDI per quarter are shown in Figure 1. There was an 18.7% decrease in the rate of CDI following implementation of the EMR (P=0.07). The mean rate of nosocomial CDI prior to implementation of the EMR was 3.9 cases/10,000 PDs; after the EMR was implemented, the mean rate of nosocomial CDI was 3.2 cases/10,000 PDs. The rate of nosocomial CDI correlated best with the use of cephalosporins and, to a lesser extent, quinolones (Table 4).

**Discussion**

The IDSA has recommended that hospitals adopt an ASP as a means of controlling unnecessary and inappropriate antibiotic use within hospitals.7 That same organization has recommended that an EMR be adopted by institutions to facilitate the process of antimicrobial stewardship.8 There are very few data regarding the effect of computerized programmes on antibiotic use and outcomes.10,11 Our hospital instituted an ASP in January 2001 and we previously reported significant reductions in antimicrobial use following implementation of that programme.9 In July 2007 our institution implemented an EMR with CPOE. Our programme involved feedback to the provider once microbiology cultures and susceptibility data were available. The present study demonstrates significant reductions in antimicrobial use following the implementation of this programme.

Our data show that the EMR was a tool that allowed our pharmacists (M. G. and M. J.) to review more charts and to make more recommendations. Following implementation of the EMR, the majority of ASP recommendations were accepted within a few hours. Also, the antibiotic order sets that were built into the EMR did not allow inappropriately high doses of antimicrobial agents, as sometimes occurred before the EMR was implemented. By reviewing more charts and having their recommendations accepted sooner, the pharmacists were able to discontinue unnecessary antimicrobial agents in more patients, thus accounting for the large decrease in antimicrobial use.

There were large decreases in the use of cephalosporins, extended-spectrum penicillins and quinolones, agents that are highly associated with both MRSA infections and CDIs.7,8,12–16 Use of cefazolin, the drug of choice for surgical prophylaxis, decreased by 53% following implementation of the EMR. We suspect that the EMR facilitated the appropriate dose and duration of antibiotic use for surgical cases, and eliminated prolonged courses of unnecessary antibiotic prophylaxis in this patient population. With regard to quinolones, ciprofloxacin use was restricted at our institution beginning in July 2007. Quinolones accounted for approximately 15% of the total antibacterial agent use prior to the implementation of the EMR, but that use decreased to 6.5% following implementation of the programme. Our data show a high correlation of quinolone use with MRSA infection, and, to a lesser extent, CDI. Furthermore, our results demonstrate a high correlation of cephalosporin use with both C. difficile and MRSA infections. We speculate that reduced cephalosporin and quinolone use contributed to the decreased nosocomial infection rates of both C. difficile and MRSA.

We suspect that the increase in carbapenem use following implementation of the EMR was a result of our efforts to reduce the use of both quinolones and antipseudomonal penicillins (primarily piperacillin/tazobactam) at the hospital. In other words, carbapenems became an alternative agent to quinolones and piperacillin/tazobactam. Despite the large increase in carbapenem use, the total use of these drugs remained less than the use of both the extended-spectrum penicillins and the quinolones (Table 3).

There are several limitations associated with an aggregate data study such as this. The duration of antibiotic use for individual patients was not assessed. Also, it is not clear whether all of the C. difficile or MRSA infections began in hospital or prior to hospital admission. We tried to account for this possibility by only including specimens positive for C. difficile toxin or MRSA from patients who had been in hospital for more than 3 days. Antibiotics are only one of many risk factors for the development of CDI or MRSA infection.17–22 Factors such as renal insufficiency, malignancy, gastrointestinal surgery, use of proton pump inhibitors, previous antibiotic exposures and enteral feeding were not evaluated in this study. Also, nosocomial spread of C. difficile or MRSA was not assessed. Nevertheless, our assessment of compliance with hand washing demonstrated a slight decrease in hand hygiene compliance over the course of the study period, suggesting that the improvements in CDI and MRSA rates were not completely related to improvements in infection control policies. Finally, our hospital began a programme to identify all incoming patients with MRSA colonization of the nares in February 2007. As part of this programme, all patients who screened positive for MRSA were placed in private rooms with strict contact isolation infection control measures. There is no question that infection control policies play a major role in the rates of nosocomial MRSA as well as CDIs. Our data support the concept that programmes that promote both infection control surveillance and antimicrobial stewardship are more likely to be effective than either measure alone.4

### Table 4. Correlation of antibacterial class use with MRSA infections (p MRSA) and CDIs (p CDI)

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>p MRSA</th>
<th>p CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended-spectrum penicillins</td>
<td>0.65( P=0.002)</td>
<td>0.35 (P=0.13)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>0.66( P=0.001)</td>
<td>0.61 (P=0.004)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>0.70( P=0.0006)</td>
<td>0.43 (P=0.055)</td>
</tr>
<tr>
<td>Total antibacterial agents</td>
<td>0.62( P=0.003)</td>
<td>0.38 (P=0.10)</td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/jac/article-abstract/66/1/205/724918 by guest on 13 March 2019
Infections with MRSA and C. difficile are associated with an increase in hospital length of stay, high mortality and increased hospital costs. Our data support the use of an EMR with CPOE as a means of reducing unnecessary antimicrobial use. Reduction in antimicrobial drug use facilitated by the EMR can indirectly lead to decreased rates of infection with both MRSA and C. difficile.

Acknowledgements
Portions of this work were presented at the IDSA Meeting, Philadelphia, PA, 2009.

We thank Delores Nobles and Kathy Cochran for help with the MedMined queries and hand hygiene data and Joy Barwick for her assistance with the C. difficile data.

Funding
No specific funding. Data for this manuscript were collected as part of routine surveillance of the hospital antibiotic management programme.

Transparency declarations
P. P. C. is a member of the speakers’ bureau of Pfizer, Astellas and Merck. P. P. C. has received research funding from GlaxoSmithKline, Merck, Gilead, Pfizer and Bristol-Myers Squibb. All other authors: none to declare.

References