International Journal of Antimicrobial Agents 45 (2015) 262–267

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Long-term effects of an antimicrobial stewardship programme at a tertiary-care teaching hospital

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ARTICLE INFO

Article history:
Received 3 September 2014
Accepted 5 November 2014

Keywords:
Antimicrobial stewardship
Meticillin-resistant *Staphylococcus aureus*
Multidrug-resistant *Pseudomonas aeruginosa*
Clostridium difficile

ABSTRACT

Antimicrobial stewardship has been shown to reduce unnecessary antibiotic use, but there are few data on the long-term benefits of such a programme. Antimicrobial use over a 13-year period since implementing an antimicrobial stewardship programme (ASP) at our institution was examined. Nosocomial rates of *Clostridium difficile* infection (CDI) and antimicrobial susceptibility patterns of common nosocomial micro-organisms over the same period were also reviewed. Total antimicrobial use decreased by 62.8% ($P < 0.0001$). There were decreases in use of aminoglycosides (−91.3%; $P < 0.0001$), cephalosporins (−68.3%; $P < 0.0001$), extended-spectrum penicillins (−77.7%; $P < 0.0001$), macrolides (−27.2%; $P = 0.002$), clindamycin (−95.9%; $P < 0.0001$) and quinolones (−78.7%; $P < 0.0001$). Antifungal use decreased by 71.0% ($P < 0.0001$). There were increases in the use of carbapenems (+736%, $P < 0.0001$) and anti-MRSA drugs (+73.3%; $P < 0.0001$). There was a 56.7% ($P = 0.007$) reduction in nosocomial MRSA infections. Nosocomial CDI rates decreased by 42.6% ($P = 0.005$) between 2003 and 2010 and then increased to near baseline levels following implementation of more sensitive testing for detection of CDI in 2011. There were decreases in the rate (−71.9%; $P = 0.001$) and percentage (−51.4%; $P < 0.0001$) of quinolone-resistant *Pseudomonas aeruginosa*. There were decreases in the rate ($P < 0.0001$) and percentage ($P = 0.02$) of carbapenem-resistant *P. aeruginosa* following implementation of a policy restricting ciprofloxacin use. We have demonstrated sustained reductions in both antimicrobial use and drug-resistant organisms following implementation of an ASP.

1. Introduction

The beneficial effects of antimicrobial stewardship are many and have been reviewed previously [1–3]. Antimicrobial stewardship is a concept that has many forms, but the basic tenets are common to most antimicrobial stewardship programmes (ASPs). The core concepts include reduction of unnecessary antimicrobial use as well as promotion of the correct drug at the proper dose for the appropriate duration. An ASP was implemented at our institution in 2001. Over the years there have been many changes to the programme. The purpose of this study was to describe antimicrobial use at our institution over the 13-year period since implementing the ASP and to discuss the methods that were implemented to limit the unnecessary use of these drugs. Nosocomial rates of *Clostridium difficile* infection (CDI), which is associated with antimicrobial use, were also examined. Finally, the antimicrobial susceptibility patterns of common nosocomial micro-organisms over the same time period were examined.

2. Materials and methods

2.1. Antimicrobial stewardship implementation

Vidant Medical Center is a 904-bed, tertiary-care teaching hospital affiliated with the Brody School of Medicine at East Carolina University (Greenville, NC). The hospital has a busy trauma service, orthopaedic service, cardiovascular surgery service, paediatric unit and oncology service. Renal transplantations occur at the hospital, but there are no liver, lung or heart transplantations. Bone marrow transplantations ceased in 2005. The hospital does not have a burn unit. Ethical approval was not required for this study because only routine data collected on hospital wards were used. This was an observational study from 1 January 2001 to 31 December 2013. The ASP was established in 2001 and has been described previously [4,5].

The programme was formed by the Antimicrobial Utilization & Stewardship Subcommittee and was approved by the Pharmacy

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http://dx.doi.org/10.1016/j.ijantimicag.2014.11.006
0924-8579/

Table 1
Antimicrobials classified as restricted and controlled by the antimicrobial stewardship programme.

Restricted[a]	Controlled[b]
Amphotericin B lipid complex	Amikacin
Ciprofloxacin	Ampicillin/sulbactam
Clindamycin	Azithromycin
Colistimethate (or colistin)	Aztreonam
Daptomycin	Cefepime
Fidaxomicin	Cefotaxime
Linezolid	Ceftaroline
Micafungin	Ceftriaxone
Posaconazole	Ertapenem
Tigecycline	Fluconazole
Voriconazole	Ganciclovir
Non-formulary antibiotics	Meropenem
	Moxifloxacin
	Piperacillin/tazobactam
	Tobramycin
	Vancomycin

[a] Restricted antimicrobial agents required prior approval by the infectious diseases clinicians.
[b] Controlled antimicrobial agents could be prescribed without infectious diseases approval, but the appropriateness of their use was reviewed by the antimicrobial stewardship programme after 48 h of use.

and Therapeutics Committee and the medical staff executive committee. The ASP initially had one pharmacist; an additional pharmacist was added in 2004. The ASP operated 6 days per week. The physician director, an infectious diseases (ID) clinician, had a contract with the hospital (Vidant Medical Center) and was compensated for his time. The Department of Pharmacy of the hospital provided the pharmacist positions for the programme. All antimicrobials were classified as unrestricted, controlled or restricted (Table 1). Restricted antimicrobials required prior approval by the ID staff before the drugs could be dispensed by the pharmacy. Any adult patient receiving one or more of the controlled or restricted antimicrobials for ≥48 h triggered a chart review by the ASP. The pharmacist reviewed a computer-generated report of all patients receiving controlled and restricted drugs. Patient charts were reviewed 2 days after the initial order for the antimicrobial drug. Based on microbiology culture results, radiology reports and the working diagnosis, the pharmacist, with input from the ID practitioner, made recommendations to change or stop the controlled antimicrobial agents. From 2001 to 2007, the ASP pharmacists walk-rounded through the hospital and left a pre-printed form in the progress note section of the chart outlining recommendations and the rationale behind them. In July 2007 the hospital converted to the comprehensive electronic health record (EHR) software EPIC (Epic, Verona, WI). In order to communicate in a paperless chart, a unique form of electronic communication was devised. First, an electronic progress note with the ASP recommendation was entered into the EHR. The ASP pharmacist then entered a unique order into the system entitled 'Antimicrobial management'. This order was linked to the progress note. Whenever a physician or other provider logged into a patient's chart, the EHR automatically opened a new window with a message from the ASP to the provider. This communication window alerted the provider that the ASP had left a recommendation in the EHR. The provider then had 24 h to respond to (i.e. accept or reject) the recommendation per medical staff guidelines.

Antimicrobial drug use was measured in defined daily doses per 1000 patient-days (DDD/1000 PD) according to World Health Organization (WHO) standards (http://www.whocc.no/atcddd/). Antimicrobial agents were divided into nine different categories. Extended-spectrum penicillins included ampicillin, amoxicillin, ampicillin/sulbactam, piperacillin and piperacillin/tazobactam (TZP). Cephalosporins included cefazolin, cefadroxil, cefalexin, cefoxitin, cefuroxime, cefotetan, ceftriaxone, ceftazidime, cefotaxime and cefepime. Quinolones included moxifloxacin and ciprofloxacin. Carbapenems included ertapenem and the group 2 (antipseudomonal) carbapenems (doripenem, imipenem and meropenem). Macrolides included azithromycin, erythromycin and clarithromycin. Aminoglycosides included amikacin, gentamicin and tobramycin. Tetracyclines/glycylcyclines included tetracycline, doxycycline and tigecycline. Vancomycin, daptomycin, linezolid, tigecycline and ceftaroline were grouped as anti-meticillin-resistant *Staphylococcus aureus* (anti-MRSA) drugs. Antifungal drugs included amphotericin B deoxycholate, amphotericin B lipid complex, itraconazole, posaconazole, voriconazole and micafungin. Clindamycin, aztreonam, nafcillin, metronidazole and trimethoprim/sulfamethoxazole were examined separately. Antiviral agents [human immunodeficiency virus (HIV) medications, acyclovir, valaciclovir, ganciclovir, valganciclovir and famciclovir] were not included in the analysis.

2.2. Surveillance definitions

Nosocomial Gram-negative and Gram-positive data sets were created by querying MedMined® (CareFusion, Birmingham, AL). Because the hospital's MedMined database began in 2003, no data were available for nosocomial infections for the first 2 years of the ASP. All clinical care unit specimens (blood, sterile fluid, sputum, urine, wounds and anaerobic specimens) with test results that were positive for *Pseudomonas aeruginosa* and *S. aureus* between 1 January 2003 and 31 December 2013 that had been collected at Vidant Medical Center (formerly Pitt County Memorial Hospital) were included in the database. Results of surveillance and environmental sample cultures were excluded. Only nosocomial cases, defined as specimens from patients who had been in the hospital for >3 days, were included in this study. Duplicate isolates collected from the same patient within the same hospital stay were counted only once. Percent resistance was defined as the percentage of total isolates that were resistant to the selected antimicrobial. Intermediately susceptible isolates were classified as resistant. Rates of nosocomial MRSA, quinolone-resistant *P. aeruginosa* (QRPA), carbapenem-resistant *P. aeruginosa* (CRPA) and *C. difficile* cases were expressed as the number of isolates per 10 000 patient-days.

2.3. Laboratory methods

In vitro bacterial susceptibilities were determined using a MicroScan system (Dade Behring, Deerfield, IL). Between 2001 and 2010, 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 antitoxin from TechLab Inc. (Blacksburg, VA). Beginning in 2011, the microbiology laboratory began using a more sensitive enzyme immunoassay (EIA) for detection of glutamate dehydrogenase (GDH) and *C. difficile* toxins A/B (C. Diff Quik Chek Complete®; TechLab Inc.). Stool samples that were GDH-positive but toxin A/B-negative underwent confirmatory testing by nucleic acid amplification testing (NAAT) (Xpert® *C. difficile*; Cepheid, Sunnyvale, CA).

2.4. Statistics

Statistical analysis was performed using GraphPad Prism v.6.0d (GraphPad Software Inc., La Jolla, CA). Linear regression was used to examine antimicrobial use as well as rates and/or proportions of infections with *C. difficile*, MRSA, QRPA and CRPA. A *P*-value of <0.05 was considered as the level of significance. Spearman's rank correlation coefficient was used to correlate antimicrobial use with rates of MRSA infection and *P. aeruginosa* susceptibilities.