Chapter 14. Impact of Changes in Antibiotic Use Practices on Nosocomial Infections and Antimicrobial Resistance – *Clostridium Difficile* and Vancomycin-resistant Enterococcus (VRE)

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Background

As discussed in the chapters on handwashing and barrier precautions (Chapters 12 and 13), hospital infection control has historically focused on preventing the transmission of nosocomial pathogens—either from patient to patient or from provider to patient. The potential role of overseeing hospital-wide antibiotic use as an infection control measure has also been recognized for many years.[1] With the widespread emergence of nosocomial antibiotic-resistant infections over the past 10-15 years, institutional efforts to control antibiotic use have become a priority for infection control.[2,3]

The practices reviewed in this chapter involve institutional efforts to control antibiotic use as a means of controlling complications of antibiotic overuse or misuse. In evaluating the potential benefits of these practices, the focus is on the impacts of antibiotic use on infections with vancomycin-resistant enterococci (VRE)[4] and *Clostridium difficile.*[5] These pathogens represent two of the most important nosocomial pathogens with relationships to inappropriate antibiotic use. Moreover, as suggested by recent evidence, infection with *C. difficile* may represent a risk factor for infection with VRE.[6]

Practice description

Interventions designed to limit the use of antibiotics may take many forms. Specific practices reviewed in the chapter include:

- *Infectious diseases physician approval*[7] – all requests for an antibiotic are discussed with an infectious diseases physician who decides whether use is appropriate
- *Monitoring of antibiotic use by pharmacy service*[8] – pharmacists monitor the use of certain antibiotics and make recommendations for changes to the prescriber
- *Guidelines for antimicrobial use*[8] – dissemination to physicians of guidelines describing appropriate and inappropriate use
- *Therapeutic substitution*[9] – use of one agent replaced by another agent with similar spectrum of activity
- *Computer-assisted prescribing*[10] – computer-based restriction of agent with extra prompts requesting documentation of indication for agent
- *Antibiotic-management program (AMP)*[11] – continuation of antibiotic after a specific duration requires approval from either an infectious diseases physician or pharmacist on the AMP

Prevalence and Severity of the Target Safety Problem

This chapter focuses on 2 of the most important nosocomial pathogens: VRE and *C. difficile*. VRE currently accounts for greater than 25% of all nosocomial enterococci[4] and confers an increased risk of death, independent of comorbid conditions that may have initially led to the infection.[12] VRE infections are also associated with significantly higher hospital costs than those due to vancomycin-sensitive enterococci (VSE)[12] (see Chapter 13). *C. difficile* represents the major, if not only, important infectious cause of nosocomial diarrhea.[5] Although death attributable to *C. difficile* occurs in less than 5% of patients,[17] the impact of *C. difficile* infection remains significant. Patients may require substantially longer lengths of hospital stay—upwards of 18-30 days,[18,19] with exploratory and therapeutic surgical procedures required in severe cases.[20] It has also been suggested that more debilitated patients (eg, in rehabilitation centers or long-term care facilities) may be at even greater risk for increased morbidity and mortality due to *C. difficile* infection.[21] The costs associated with *C. difficile* diarrhea, while not well described, are estimated to be as high as $10,000 per patient[22] (see Chapter 13).

Opportunities for Impact

Over half of all hospitalized patients are treated with antibiotics.[23] The antibiotics represent a significant portion of overall health care costs, accounting for between 20% and 50% of total hospital drug expenditures.[23] It has been estimated that 50% of all antibiotics prescribed are either at the wrong dose, the wrong drug, or taken for the wrong duration.[24,25] These findings suggest that there is significant room for improvement in antibiotic prescribing practices.

Most hospitals employ formulary restrictions for certain medications (particularly expensive agents, selecting one drug from a group of equivalent agents). However, only a minority of hospitals uses formulary restrictions to limit the use of entire antibiotic classes or specific agents. Those hospitals that do employ antimicrobial formulary restrictions most often do so as a means of controlling costs, rather than as an infection control measure.[26] Thus, there remain substantial opportunities to expand upon these existing formulary programs to control the emergence of antimicrobial resistance.

Study Designs

A structured search of the PubMed database (including MEDLINE) and review of the bibliographies of relevant articles identified 10 studies that have examined methods to change antibiotic use with respect to VRE and/or *C. difficile* infection (Table 14.1). All of these studies were before-after observational cohort studies (Level 3) in which baseline data regarding incidence of VRE or *C. difficile* were obtained during an observational period and compared with a second time period after an intervention had been implemented. Data on baseline comparability of the before and after groups were not reported in 6 studies.[8-11,21,27] Two studies only reported similar admission and census rates during the before and after time periods,[7,28] while 2 studies compared patients in the 2 time periods on the basis of numerous variables.[29,30]

Study Outcomes

All of the studies reviewed reported changes in the clinical incidence or prevalence of either VRE or *C. difficile* as a result of antibiotic practice interventions (Level 1). Studies investigating *C. difficile* measured clinical infections. Studies investigating VRE examined VRE infection[11] or VRE colonization.[8-10,27]

Evidence for Effectiveness of the Practice

Of the 10 studies listed in Table 14.1, all but 3[8,11,21] showed significant reductions in the incidence of *C. difficile* or VRE following practice changes. Several possibilities may explain the negative findings of these 3 studies. First, the interventions analyzed might not have produced significant alterations in antibiotic use, so that infection rates with the target pathogens remained unchanged. Second, it is possible that patient-to-patient spread of these pathogens limited the efficacy of the interventions, as this mode of transmission is well known to occur for both VRE and *C. difficile*, usually via the hands of health care workers (see also Chapter 13).[31,32] Third, since environmental contamination occurs with both these pathogens, successful control of these organisms may require enhanced disinfection procedures in some cases.[33,34] Targeting antibiotic use may not be sufficient to reduce incidence of these pathogens since a significant number of infected or colonized patients may serve as reservoirs. Under this scenario, the argument for barrier precautions as an adjunct measure to prevent spread of organisms from patient to patient becomes more persuasive (see Chapter 13). Indeed, although changes in antibiotic use practice were the primary intervention in all of the studies reviewed here, one study included a component of enhanced barrier precautions in the intervention.[21] Future studies should investigate the impact of such multifaceted interventions, both for VRE and *C. difficile* as well as for other nosocomial pathogens.

Other Potential Benefits

Although not the focus of this chapter, the practices reviewed here may have a beneficial impact on other emerging nosocomial pathogens strongly associated with inappropriate antibiotic use, such as extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae.*[35] In addition, although we have focused on control of VRE as an end in itself, a primary motivation to achieve this goal is the need to delay the emergence of vancomycin-resistance in *Staphylococcus aureus*.[36,37] As *S. aureus* represents the most common nosocomial infection,[38] the development of high-level vancomycin resistance among staphylococci would constitute a public health disaster.[39]

Thus, practices that decrease the prevalence of VRE may play an important, albeit indirect, role in preventing or delaying this occurrence.

Potential for Harm

Few of the reviewed studies reported any assessment of possible harm as a result of the antibiotic use practice interventions. One potential result of interventions designed to reduce the use of one antibiotic, or antibiotic class, is the subsequent increase in the use of another class of agents to compensate. In fact, one reviewed study[7] noted an increase in the use of other anti-anaerobic agents as clindamycin use decreased. Whether changes in antibiotic use results in changes in antimicrobial susceptibilities, either in the pathogen under study (eg, VRE, *C. difficile*) or in other nosocomial pathogens, it is a fertile ground for future study.

Finally, efforts to decrease use of certain antibiotics might increase infection rates due to inappropriate withholding of appropriate antibiotics. However, one reviewed study [10] noted no increase in rates of surgical site infections following decrease in the use of vancomycin for preoperative prophylaxis (see also Subchapter 20.1).

Costs and Implementation

The costs of implementing a program to alter antibiotic use practices must be balanced against potential cost savings. Sources of savings may be reduced antibiotic use, use of less expensive agents rather than the more expensive newer agents, and potentially, reduced costs due to decreased incidence of nosocomial infections as a result of interventions. Although several studies reported cost savings due only to decreased antibiotic use,[10,11,29] analyses taking into account costs related to subsequent infections (or infections prevented) have been sparse. One study noted that cost savings from decreased use of clindamycin offset the expenditures due to increased use of other antibiotics.[7] The authors suggested that if each case of *C. difficile* resulted in a cost of $2000, the savings to the hospital of the intervention could approach $162,000 annually based on the number of cases averted.[7]

Another cost of antibiotic use interventions is the expense of ongoing monitoring of antibiotic use and antimicrobial susceptibilities of nosocomial pathogens. Effective recommendation of certain antimicrobial agents over others requires access to (and financial and logistic support for) routine antimicrobial susceptibility testing. Monitoring institutional resistance patterns is vital in order to make required formulary changes in response to emerging resistance patterns and to determine the most effective agents given prevailing susceptibility patterns.

Comment

Given the strong association between antibiotic use and subsequent infection (demonstrated for both *C. difficile* and VRE), it is not surprising that changes in antibiotic use practices can reduce the incidence of infection with these 2 pathogens. The majority of reviewed studies demonstrated a significant reduction in the incidence of VRE or *C. difficile* following interventions to change antibiotic use practice. While these studies all demonstrated short-term success, future studies should confirm the efficacy of such interventions over the long term. In addition, the effectiveness and feasibility of combining antibiotic practice strategies with efforts to enhance barrier precautions (Chapter 13) should be investigated. Finally, the cost-effectiveness of such strategies (taking into account both the costs associated with monitoring and maintaining sound antibiotic use practices and the costs associated with nosocomial antibiotic-resistant infections) should be investigated.

Table 14.1. Before-after studies of practices to improve antibiotic use*

Study Setting and Intervention	Outcomes	Results: before vs. after practice
Elderly care unit of a large teaching hospital in England, 1984-85; Changes in empiric antibiotic regimens[29]	Level 1	*C. difficile* infections decreased from 37 to 16 cases (p=0.002).
Chronic care facility in Baltimore, 1985-86; multifaceted intervention[21]	Level 1	Patients with *C. difficile* toxin decreased from 28% to 24% (p=NS); Patients with *C. difficile* culture increased from 33% to 42% (p=NS)
Veterans Affairs Medical Center in Arizona, 1990-92; restriction of clindamycin use[28]	Level 1	*C. difficile* infections decreased from 7.7 to 1.9 cases/month (p<0.001)
660-bed Veterans Affairs hospital in California, 1992-94; removal of antibiotic restrictions[30]	Level 1	Monthly incidence of *C. difficile* infections per 1,000 admissions increased from 3.4 to 6.2 (p<0.05)
703-bed Veterans Affairs Medical Center in Virginia, 1993-94; restriction of clindamycin use[7]	Level 1	*C. difficile* infections decreased from 11.5 to 3.33 cases/month (p<0.001)
557-bed academic medical center in Maryland, 1994; restriction of vancomycin use[8]	Level 2	Mean monthly prevalence of VRE decreased from 26% to 25% (p=NS)
35-bed hematologic malignancy unit in a large medical center in England, 1994-95; sequential antimicrobial formulary changes[9]	Level 2	VRE colonization for phases 1, 2, and 3 were 57%, 19%, 36%, respectively (p<0.001 for phase 1 vs. 2; p=0.08 for phase 2 vs. 3)
Large academic medical center in Virginia, 1994-95; computer-based restriction of vancomycin use[10]	Level 2	VRE colonization decreased (p<0.001, test for trend)
310-bed Veterans Affairs medical center in New York, 1995; restriction of multiple antibiotics[27]	Level 2	Point prevalence of VRE decreased from 42% to 15% (p<0.001)
725-bed teaching hospital in Philadelphia, 1995-96; restriction of vancomycin use[11]	Level 2	Incidence of VRE was unchanged at 30% (p=NS)

* NS indicates not statistically significant; VRE, vancomycin-resistant entercocci.

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