Infection Control and Antimicrobial Stewardship

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ABSTRACT

Infection Control measures can reduce the transmission of bacteria in the hospital. Reduction in the use of antibiotics via Antimicrobial Stewardship programs can reduce antibiotic resistance. The combination of Infection Control measures and Antimicrobial Stewardship can lead to a greater reduction in antibiotic resistant bacteria.

KEYWORDS: infection control, antimicrobial stewardship, antibiotic resistance, *Clostridium difficile*

Infection control involves preventing the transmission of infectious agents from patient-to-patient, patient-to-staff, staff-to-patient, visitor-to-patient, visitor-to-staff, etc. Commonly encountered infectious agents include viruses and bacteria. Among the bacteria some are antibiotic susceptible and others resistant. During the 1980s with concern for transmission of the HIV in healthcare settings, universal precautions was developed. The concept of universal precautions is such that any patient should be considered potentially infectious without having direct evidence of infection because patients may be asymptomatic yet seropositive.[1] Over time the concept of considering all patients as potentially infectious has evolved into the practice of Standard Precautions.[2]

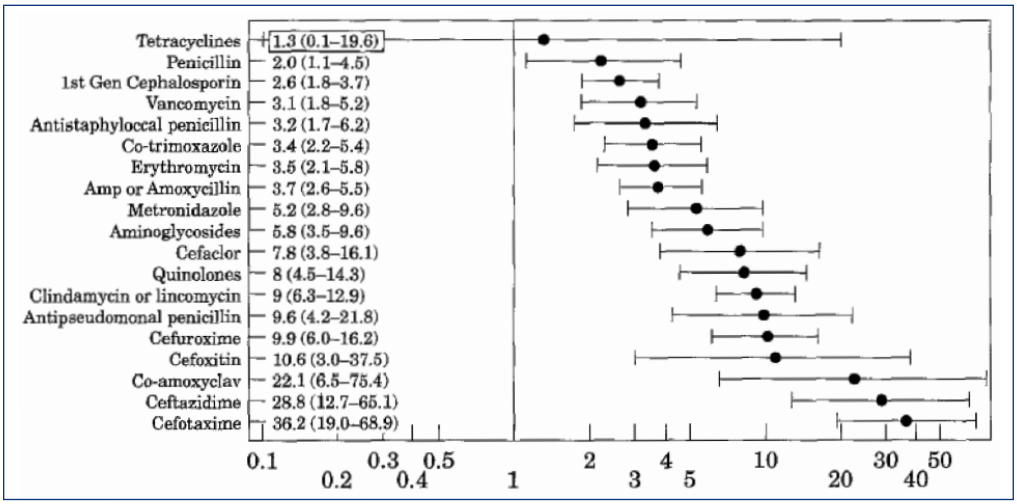
During the 1970s and 1980s methicillin-resistant *Staphylococcus aureus* (MRSA) started to emerge in the hospital setting. *S. aureus* is a gram-positive bacterium. About 30% of adults at any given time are colonized with *S. aureus*. Some people are transiently colonized, others are colonized for a prolonged period. *S. aureus* may be methicillin susceptible or methicillin resistant. One of the strategies to reduce the transmission of MRSA in hospitals is the use of Contact Precautions. Contact Precautions involves the use of gowns and gloves upon entry into the patient's room. Gowns and gloves protects healthcare workers from contaminating their hands or clothing. Gowns and gloves are removed when exiting a patient's room, hands are then cleaned; thus, preventing the transmission of bacteria from one patient to another.

During the late 1980s and early 1990s vancomycin resistant enterococcus (VRE) emerged. The use of Contact Precautions was recommended for the prevention of transmission of VRE. Additionally, the prudent use of vancomycin was recommended including situations in which vancomycin use should be discouraged.[3] This recommendation was probably based upon the concept that the use of antibiotics may drive antibiotic resistance.

Community-acquired MRSA emerged during the late 1990s. This was initially noticed among pediatric patients who had no predisposing risk factor for MRSA.[4] Treatment failure and deaths occurred among children empirically treated with a beta-lactam antibiotic.[5] Soon thereafter there was an emergence of community-acquired MRSA among children and adults in the United States. With the emergence of community-acquired MRSA there was an increase in the empiric use of vancomycin.

Hospital-acquired *Clostridium difficile* is a serious problem. A recent study using data from 10 geographically distinct areas in the United States showed that *C. difficile* is the most common hospital-acquired pathogen, more common than *S. aureus*.[6] Pseudomembranous colitis associated with antibiotic use was recognized during the 1950s and 1960s. *C. difficile* was identified as the causative agent of antibiotic-associated pseudomembranous colitis in 1978.[7] *C. difficile* is a gram-positive rod that produces two different toxins, toxin A and toxin B. It is the toxin that causes pseudomembranous colitis and the clinical symptom of diarrhea. Antibiotic treatment disrupts the normal flora of the intestinal tract allowing *C. difficile* to grow and produce toxins. Early on it was noted that pseudomembranous colitis due to *C. difficile* was associated with the use of clindamycin.[7] Since that time other antibiotics, including the third- generation cephalosporins and fluoroquinolones, were identified as a risk for the development of *C. difficile* infection. Third-generation cephalosporins, fluoroquinolones and clindamycin are associated with a higher risk while penicillin, tetracyclines, trimethoprim/sulfamethoxazole are associated with a lower risk of developing *C. difficile* infection (**See Figure 1**).[8] From an Antimicrobial Stewardship point of view, antibiotics with a lower risk of developing *C. difficile* are preferable to other antibiotics provided they have the same clinical efficacy. Hence, strategies to reduce *C. difficile* infection include reduction of the total use of antibiotics and when an antibiotic is necessary then choose an antibiotic that has a lower risk for the development of *C. difficile*. Infection Control practices used to reduce the transmission of *C. difficile* include Contact Precautions, daily room cleaning and using cleaning agents that are sporicidal, for example, sodium hypochlorite.

Figure 1. Pooled Odds Ratio with 95% CI for each antibiotic in relation to the main outcome of interest (*C. difficile* diarrhoea).[8]



MRSA and VRE are classic examples and continue to be a concern for transmission of antibiotic-resistant bacteria in the hospital. Over the past two decades, gram-negative rods resistant to extended spectrum beta-lactams, such as third- and fourth-generation cephalosporins, have increased. More recently common gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae* have become resistant to carbapenems (imipenem and meropenem). Common gram negative bacteria are resistant to beta-lactam antibiotics because they produce a beta-lactamase. Beta-lactamases are enzymes produced by resistant bacteria that break the beta-lactam ring, hence inactivating the beta-lactam antibiotic. There are more than 1000 beta-lactamases. When an *Enterobacteriaceae* is resistant to carbapenems they are referred to as CRE (carbapenem- resistant *Enterobacteriaceae*). There are different beta-lactamases that confer resistance to carbapenems. KPC is a carbapenemase that inactivates carbapenems; it is the most commonly found mechanism for carbapenem resistance in the United States. NDM (New Delhi metallo-beta-lactamase) is another carbapenemase that inactivates carbapenems and is less common in the United States.

The emergence of antibiotic-resistant bacteria is associated with the use of antibiotics. When antibiotics were introduced into clinical medicine during the 1940s, common bacteria such as *S. aureus*, *E. coli* and *Streptococcus pneumoniae* were not antibiotic resistant. Once an antibiotic-resistance mechanism (mutation or gene) entered these organisms there was spread of these antibiotic-resistant strains of bacteria due to the selective pressure exerted by the use of antibiotics. If there was no use of antibiotics (no selective pressure of antibiotics) then there would not be spread of the antibiotic-resistant bacteria. Thus, when asked "does use of antibiotics lead to antibiotic resistance?" the answer is "yes." However, it has not been fully elucidated whether there is a quantitative association between antibiotic use and antibiotic resistance. From a conceptual point of view, it seems plausible that a very low use of an antibiotic would not drive antibiotic resistance and a very high use of an antibiotic could lead to high rates of resistance.

Reducing the use of an antibiotic can reduce the rate of resistance to that antibiotic. In one hospital, an 80% reduction of third-generation cephalosporin use was associated with a 44% reduction of the rate of ceftazidime resistance among *K. pneumoniae*.[9] In Finland, the outpatient reduction in the use of macrolide antibiotics (erythromycin, azithromycin, clarithromycin, roxithromycin) was associated with a reduction in the rate of macrolide resistance among Group A streptococci.[10] Hence, reduction in use of a specific antibiotic or class of antibiotic can lead to a reduction in the rate of resistance. However, in the ceftazidime-resistant *K. pneumoniae* study, there was an increase in the use of imipenem, a carbapenem, that was associated with an increase in the rate of imipenem resistance among *Pseudomonas aeruginosa*, and in the macrolide- resistant group A streptococcus study the reduction in the use of macrolide antibiotics was compensated for by using other antibiotics.[9,10] Hence, reducing antibiotic use may lead to a decrease in resistance; however, this reduction should not be compensated for by using another antibiotic.

The exact magnitude of the impact of the use of infection control practices such as contact precautions involving the use of gowns and gloves on the transmission of certain bacteria including MRSA, VRE and ESBL has not been fully elucidated. Additionally, it seems as if transmission, albeit at a lower rate, still occurs despite these efforts. Another or an additional approach would be to decrease the amount of antibiotic use that occurs in healthcare settings. By decreasing and possibly eliminating the use of antibiotics may help decrease the transmission of resistant bacteria in the hospital.

The rate of prescription of antibiotics for acute respiratory tract infections in the outpatient setting decreased from 1995 to 2006.[11] There was a 36% reduction in antibiotic prescription for acute respiratory tract infections in those less than 5 years and an 18% reduction among those 5 years of age and older. Although among adults there was an overall decrease in antibiotic prescription, the prescription of quinolones increased 5-fold. A Blue Cross Blue Shield report showed an overall 9% reduction in outpatient antibiotic prescription fill rate during the period 2010 to 2016.[12] There was a 22% reduction among infants, 16% reduction among

children and a 6% reduction among adults. Hence, there is some data showing a reduction in the use of antibiotics in the outpatient setting. A report from the CDC showed that 55.7% of hospitalized patients in that study received an antibiotic during their hospitalization. It was also shown that there could be a 37% improvement in the use of antibiotics in two specific areas, one area was selected urinary tract infections and other was the use of intravenous vancomycin.[13] They also showed, using mathematically modeling, that a 30% reduction in the use of broad-spectrum antibiotics would lead to a 26% reduction in *C. difficile* infection.

A recent systemic review and meta-analysis showed that antimicrobial stewardship programs reduced the incidence of multidrug resistant gram-negative bacteria, ESBL producing gram-negative bacteria, MRSA and *C. difficile*. The combination of antimicrobial stewardship and infection control was more effective than antimicrobial stewardship alone.[14]

SUMMARY

Infection control measures can reduce the transmission of infectious agents such as multidrug-resistant bacteria and *C. difficile* in the hospital. Antimicrobial stewardship can reduce the unnecessary or inappropriate use of antibiotics leading to a reduction in the prevalence of antibiotic resistance. Together, infection control measures and antibiotic stewardship can lead to a further decline in *C. difficile* and multidrug-resistant bacteria.

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