“Collateral Damage” from Cephalosporin or Quinolone Antibiotic Therapy

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“Collateral damage” is a term used to refer to ecological adverse effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms. The risk of such damage can be assessed for different antibiotic classes by a variety of epidemiologic studies. Cephalosporin use has been linked to subsequent infection with vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing Klebsiella pneumoniae, β-lactam–resistant Acinetobacter species, and Clostridium difficile. Quinolone use has been linked to infection with methicillin-resistant Staphylococcus aureus and with increasing quinolone resistance in gram-negative bacilli, such as Pseudomonas aeruginosa. Neither third-generation cephalosporins nor quinolones appear suitable for sustained use in hospitals as “workhorse” antibiotic therapy.

Traditionally, studies of antimicrobial therapy have assessed clinical and bacteriological efficacy in the treatment of infection. This is intuitive and is clearly the most appropriate way to study the effectiveness of antibiotics. However, treatment of serious community-acquired and hospital-acquired infections with antibiotics that may be associated with “collateral damage”—that is, the selection of antibiotic-resistant organisms or Clostridium difficile and the unwanted development of colonization or infection with such organisms—also needs to be evaluated. Although such collateral damage has pertinence to the outpatient treatment of community-acquired pneumonia (CAP), here I concentrate on the effects of inpatient treatment with antibiotics commonly used for pneumonia and on the 2 antibiotic classes most commonly linked to collateral damage—cephalosporins and quinolones.

HOW CAN WE IDENTIFY COLLATERAL DAMAGE FROM ANTIBIOTICS?

Three types of epidemiological studies can potentially link antibiotic use with ecological adverse effects. The first type is case-control studies, which assess antibiotic use in persons infected with an antibiotic-resistant organism (case-patients) and in control subjects. There has been considerable recent discussion about the optimal design of such studies, especially with respect to selection of the control group [1–4]. The second type of study assesses accumulated data on antibiotic use (often expressed in defined daily doses per 1000 patient-days) in an institution and correlates them with rates of antibiotic resistance in that institution. Such studies may yield divergent results from those of studies with a case-control design that assess antibiotic use in individual patients [5]. The third type of study assesses an intervention aimed at limiting use of antibiotics of various classes to decrease selection pressure leading to antibiotic resistance. Animal colonization studies, such as those described by Donskey et al. [6], have also studied the effects of antibiotics on bacterial flora, but these are not assessed herein.

Each study design is subject to considerable degrees of bias. Unfortunately, few “scoring systems” are available that can assess the adequacy of conclusions derived from these types of studies.
from individual studies. Each study design has its own limitations. The literature is replete with examples in which the different study designs yield different results when assessing risk factors for certain infection types. Additionally, it must be recognized that the 2 antibiotic types under discussion here (cephalosporins and quinolones) may be used to treat infections other than CAP. With these important caveats, published studies that have assessed antibiotic use and subsequent collateral damage are reviewed here.

CEPHALOSPORINS

Gram-positive cocci. The cephalosporins commonly used in the treatment of CAP are cefuroxime, ceftriaxone, and cefotaxime. Cefepime is sometimes also used, especially in the treatment of nursing home–acquired pneumonia. Cephalosporins lack significant activity against enterococci. Before the emergence of vancomycin-resistant enterococci (VRE), it had been shown that cephalosporin use was associated with significant infections with enterococci [7]. In the era of VRE, a number of case-control studies have shown that use of third-generation cephalosporins may be a risk factor for infection with VRE. Dahms et al. [8], in a comparison of surgical inpatients with enterococcal infections due to vancomycin-resistant and vancomycin-susceptible strains, found that prior use of a third-generation cephalosporin was a risk factor for infection with VRE. Ostrowsky et al. [9], in a study that compared 35 patients colonized with VRE with 255 patients without VRE colonization at admission to 2 Boston surgical intensive care units (ICUs), found that prior receipt of a second- or third-generation cephalosporin was a risk factor for VRE colonization. Loeb et al. [10], in an assessment of risk factors for VRE colonization during a hospital outbreak, found that prior cephalosporin use was the only potentially modifiable risk factor. Finally, a review of 126 adult ICUs from across the United States showed that rates of third-generation cephalosporin use were associated with VRE prevalence [11].

The results of these studies imply that reduction in the use of second- and third-generation cephalosporins might result in a reduction in the occurrence of VRE. Of interest is a recent evaluation of the effects of restriction of third-generation cephalosporin use [12]. Despite an 85.8% decrease in the use of third-generation cephalosporins during the evaluation period, the prevalence of VRE increased steadily. This result might be construed to mean that reduction in third-generation cephalosporin use is completely ineffective in the control of VRE. However, the prevalence of VRE is affected by multiple factors, including concurrent infection-control interventions and concurrent trends in the use of antibiotics with antianaerobic bacterial activity [12, 13]. In the treatment of fever in neutropenic patients, the replacement of ceftazidime by piperacillin/tazobactam for first-line empirical therapy was associated with a decrease in the prevalence of VRE [14]. More institutions need to publish their experience with alteration in cephalosporin use and its effect on VRE prevalence in order for a clearer understanding of this relationship to emerge.

Third-generation cephalosporin use has also been associated with infection with methicillin-resistant Staphylococcus aureus (MRSA) in some case-control studies [15]. A formulary change that decreased the use of cephalosporins and increased the use of β-lactam/β-lactamase inhibitor antibiotics resulted in a small but statistically significant reduction in MRSA infections [16].

Gram-negative bacilli. In contrast to the scenario with gram-positive organisms, there does appear to be a clear-cut relationship between the use of third-generation cephalosporin antibiotics and colonization or infection with certain multidrug-resistant gram-negative bacilli. This has been demonstrated in studies correlating total hospital antibiotic consumption with hospital-wide antibiotic resistance rates, in case-control studies, and in studies assessing the effects of limitation of cephalosporins on hospital-wide antibiotic resistance rates.

Quale and Landman and their colleagues [17–20] have published a number of significant papers assessing outbreaks of multiresistant gram-negative bacilli in multiple hospitals in Brooklyn, New York. Total hospital consumption of a variety of antibiotic classes was related to the prevalence of extended-spectrum β-lactamase (ESBL)–producing Klebsiella pneumoniae and multiresistant Acinetobacter baumannii and Pseudomonas aeruginosa in 15 hospitals. Furthermore, total hospital use of cephalosporins plus aztreonam was directly correlated with the prevalence of ESBL–producing K. pneumoniae and multiresistant A. baumannii but not multidrug-resistant P. aeruginosa [17–20]. Several case-control studies have also shown a relationship between prior use of third-generation cephalosporins and subsequent colonization or infection with ESBL-producing organisms [21–25]. Studies that have not shown this association have generally been underpowered or have examined a focal monoclonal outbreak, associated with poor infection control [26].

Several studies have used education of prescribers as a means of reducing cephalosporin use and have observed reductions in the rates of ESBL production by gram-negative organisms [27, 28]. More forcefully, Rahal et al. [29] used extensive class restriction of cephalosporins as a means of controlling ESBL–producing Klebsiella infections. Following restriction, neither ceftriaxone nor cefuroxime was used for CAP in their institution, and the use of a cephalosporin for any condition other than pediatric infection, meningitis, gonococcal infection, or spontaneous bacterial peritonitis was allowed only after approval from the hospital’s infectious disease service. The use of all cephalosporins decreased by 80%. This was accompanied
by a 44% reduction in the incidence of ESBL-producing Klebsiella infections. Although it has been widely noted that imipenem resistance in P. aeruginosa became more common during the period of cephalosporin restriction, the P. aeruginosa isolates, unlike the Klebsiella infections, were not multidrug-resistant.

**C. difficile.** A plethora of case-control studies have associated C. difficile infections with prior use of cefotaxime, as opposed to piperacillin/tazobactam, was associated with a significantly increased incidence of C. difficile infection [34]. Restriction of use of injectable third-generation cephalosporins (resulting in a 92% reduction in use of these antibiotics) was associated with a halving of cases of C. difficile-associated diarrhea in 1 particular center [39].

**QUINOLONES**

**Gram-positive cocci.** There is a potential connection between prior quinolone use and colonization or infection with MRSA. Several case-control studies have shown that prior receipt of a quinolone was associated with subsequent MRSA infection [40–43]. In a study of 10 urban teaching hospitals across the United States over a prolonged period, an overall decrease in susceptibility of S. aureus to methicillin was observed [44]. This coincided with an increase in quinolone use in 9 of the 10 institutions. It is noteworthy that the majority of MRSA strains are now also quinolone-resistant, and hence selection of such strains by quinolone use is biologically plausible. It is interesting that exposure of clinical isolates of MRSA to subinhibitory concentrations of quinolones induces the production of fibronectin-binding proteins and increases the adhesion of staphylococci to fibronectin-coated surfaces [45, 46].

There are few data on the relationship between prior quinolone use and colonization or infection with VRE. However, Lautenbach et al. [12] found a borderline association between VRE prevalence and quinolone use (P = .07).

**Gram-negative bacilli.** There is little doubt that patients who develop an infection with a gram-negative bacillus and who have previously received a quinolone will have an increased risk of infection with a quinolone-resistant strain. This has been demonstrated in patients who have received quinolones as prophylaxis against infections with gram-negative bacilli while neutropenic and while receiving quinolones as prophylaxis against spontaneous bacterial peritonitis [47–49]. Additionally, prior quinolone use is a risk factor for subsequent infection with quinolone-resistant, ESBL-producing organisms [50, 51].

The multihospital studies in Brooklyn did not find a relationship between hospitals’ rate of use of quinolones and the number of infections with ceftazidime-resistant K. pneumoniae, ceftazidime-resistant A. baumannii, carbapenem-resistant A. baumannii, or carbapenem-resistant P. aeruginosa [17, 18]. However, case-control studies have identified prior quinolone use as a risk factor for infection with ESBL-producing Klebsiella species and *Escherichia coli* in nursing homes and nosocomial *Acinetobacter* infections in an ICU [52, 53].

A major concern worldwide has been the increasing resistance of *P. aeruginosa* to multiple antibiotics. Quinolones represent an important option for treatment of *P. aeruginosa* infection [54]. However, increasing quinolone use for indications other than *P. aeruginosa* infection is likely to reduce the susceptibility of *P. aeruginosa* to quinolones [55]. Zervos et al. [44], in their multihospital study, have shown that as quinolone use rises in an institution, susceptibility of *P. aeruginosa* to quinolones deteriorates. Of note, in the single institution in which there was a reduction in quinolone use over time, there was also an improvement in the quinolone susceptibility of isolates.

**C. difficile.** For many years, quinolone use has been regarded as creating little risk of C. difficile infection [56]. However, recent case-control studies have concluded that use of quinolones may indeed be a risk factor for nosocomial C. difficile infection [37, 57–59]. It remains to be seen whether quinolones with enhanced antianaerobic bacterial activity increase or decrease the risk of nosocomial C. difficile infection [58, 59].

**CONCLUSIONS**

No two hospitals are alike in the intensity of antibiotic use or adequacy of and adherence to infection control procedures. Numerous confounding factors may make extrapolation of results from one particular hospital or region to another misleading. Differences in the variety of surgical services offered, the extent of environmental bacterial contamination, baseline prevalence of antibiotic-resistant organisms, the “colonization density” of drug-resistant organisms, the age of the population served, and even the nurse-to-patient ratio may lead to differ-

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**Table 1. Summary of potential “collateral damage” from use of cephalosporins and quinolones.**

<table>
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<tr>
<th>Class of agent, pathogen(s) selected for</th>
<th>Third-generation cephalosporins</th>
<th>Extended-spectrum β-lactamase–producing Klebsiella species</th>
<th>β-lactam–resistant Acinetobacter species</th>
<th>Clostridium difficile</th>
<th>Quinolones</th>
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<td>Vancomycin-resistant enterococci</td>
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<td>Methicillin-resistant Staphylococcus aureus</td>
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<td>Quinolone-resistant gram-negative bacilli, including <em>Pseudomonas aeruginosa</em></td>
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ences in risk factors for infections with multiresistant organisms.

With these caveats in mind, of the major antibiotic classes, aminoglycosides, β-lactam/β-lactamase inhibitor combinations, and macrolides appear least frequently to be associated with subsequent infection with multiresistant organisms. In contrast, cephalosporin and quinolone use has been linked more frequently to collateral damage (in the form of antibiotic-resistant superinfections) (table 1). Such infections include those with multiresistant gram-positive and gram-negative bacteria as well as C. difficile. Intervention studies in an individual hospital showing that sustained reduction in rates of infection with multiresistant organisms coincides with reduction in the use of certain antibiotic classes (assuming that other variables, such as infection-control interventions, are kept constant) may be the closest thing to proof of the concept that certain antibiotic classes are less suitable than others as “workhorse” antibiotic therapy.

References

30. Nelson DE, Auerbach SB, Balch AL, et al. Epidemic Clostridium dиф-


