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Collateral damage and what the future might hold. The need to balance prudent antibiotic utilization and stewardship with effective patient management

David J. Weber*

Professor of Medicine, Pediatrics and Epidemiology, Schools of Medicine and Public Health, University of North Carolina, UNC Health Care System, CB# 7030 Bioinformatics Building, 130 Mason Road, Chapel Hill, NC 27599-7030, United States

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Summary Increased severity of illness among hospitalised patients and an ageing population have led to an increased incidence of hospital acquired infections and represent a significant challenge to the clinician in terms of managing infections. The collateral damage which can occur with antibiotic therapy is also an important consideration when initiating empirical antibiotic therapy, particularly in patients who are seriously ill or immunocompromised. Collateral damage is the term used to describe the adverse ecological effects of antibiotic therapy, such as the selection of drug-resistant organisms, and the adverse events associated with antibiotic therapy such as *Clostridium difficile* disease. Antibiotic use and ineffective infection control have been implicated in the development and spread of resistant Gram-positive and Gram-negative bacterial pathogens which are associated with increased mortality and morbidity, prolonged hospitalisation and increased costs. Carbapenem consumption and mechanical ventilation have been linked to colonisation or infection with problematic organisms including methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, while cephalosporin use has been associated with evolution of infections due to vancomycin-resistant enterococci (VRE) and Gram-negative bacilli producing extended-spectrum β-lactamases (ESBL), and to colonisation or superinfection with *Clostridium difficile*. The safety profile of antibiotics must also be taken into consideration when selecting therapy, and single broad-spectrum agents may provide excellent coverage with a low risk of adverse events. The use of single agents may be associated with lower costs, improved ease of administration and fewer drug–drug interactions. However, in an environment of increasing resistance, initial aggressive therapy may be required to avoid excessive mortality and morbidity. Ideally antibiotic therapy should be directed by culture and knowledge of local susceptibility patterns. Before culture results are available therapy may need to be initiated empirically to cover the likely pathogens. In neutropenic patients with fever the current guidelines recommend the use of empirical therapy at the onset of fever for all patients. Where no aetiology is identified, antibiotic therapy should continue for at least 2 weeks while aggressive attempts are made to define the source of fever. When the aetiology of infection has been identified, therapy should be adjusted to provide optimal treatment with the best safety profile and lowest cost. The principal of avoiding collateral damage provides a useful framework for selecting antibiotics for empirical therapy in today's changing environment.

* Tel: +1 919 966 2536; fax: +1 919 966 1451. E-mail: dweber@unch.unc.edu (D.J. Weber).

Background

Current challenges in the management of neutropenic patients and those in the intensive care unit (ICU) include the changing aetiology of infection (discussed elsewhere in this supplement), the changing hospital population and need for more vigilant infection control measures because of the rise in resistant organisms. Changes in the patient population in US hospitals include the following: (1) increased numbers of immunocompromised patients due to increases in patients with cancer, solid organ transplants, or infection with human immunodeficiency virus; (2) increases in patients with chronic diseases such as cystic fibrosis, diabetes mellitus, and autoimmune diseases such as lupus erythematosis, rheumatoid arthritis, and inflammatory bowel disease many of whom are also immunocompromised as a result of their underlying disease or therapy (e.g., corticosteroids): (3) more patients with multiple co-morbidities due to an aging population many of whom reside in care facilities and are therefore more likely to be colonized with antibiotic resistant pathogens; and (4) more severely ill patients because of the tendency to treat patients as out-patients.

In parallel with the increasing severity of illness in hospitalised patients, the number of hospital-acquired infections has also increased. The likelihood of developing a healthcare-associated infection increased between 1975 and 1995 from 7.2 per 1000 hospital days to 9.8 per 1000 hospital days [1]. Approximately 1 in 10 hospitalised patients will acquire an infection after admission, resulting in substantial economic cost [2]. Estimates of the cost of these infections, at 2002 prices, suggest that the annual economic burden is $6.7 billion per year in the USA and £1.06 billion (approximately $1.7 billion) in the United Kingdom [2], representing 0.06% and 0.10% of gross domestic product (GDP), respectively. Although in many instances length of hospitalisation has decreased, there has been an increase in the size and number of ICUs and in specialised facilities for transplants. Major challenges for the future include antimicrobial use and control of emerging resistant organisms, more intensive chemotherapy resulting in more severely immunocompromised patients, ineffective infection control (especially lack of compliance to hand hygiene recommendations), and development of evidence-based recommendations for infection control and prevention of nosocomial infections [3]. Other challenges include the need for sterilisation protocols to reduce the possibility of person-to-person transmission of prion agents following surgery, the possibility of an influenza pandemic in the near future (possibly due to an H5N1 strain), the potential for the intentional use of bioterrorism agents, and, in the future, the potential for zenotransplantation (i.e., use of animal organs in humans).

In the USA two million healthcare-associated infections are reported annually, with a cumulative incidence of ~10%, and are the sixth leading cause of death in the United States [4]. Over a 22-year period the frequency of sepsis has increased from 82.7 cases per 100,000 population in 1979 to 240.4 cases per 100,000 in 2000 [5]. Data from the National Nosocomial Infections Surveillance (NNIS) system managed by the Centers for Disease Control and Prevention (CDC) reported a 11% increase in 2003 relative to 1998–2002 in *Staphylococcus aureus* that are resistant to methicillin (i.e., MRSA) to approximately 60%, and a 47% increase in *Klebsiella pneumoniae* isolates resistant to 3rd-generation cephalosporins to over 20% [4]. The same reported noted a 12% increase in vancomycin-resistant enterococci (VRE) to 28.5%, a 15% increase in imipenem-resistant *Pseudomonas aeruginosa* to 21.1%, and a 20% increase in 3rd-generation cephalosporin resistant *P. aeruginosa* to 31.9%. In Europe the frequency of infections occurring in ICU patients has risen from 44.8% in 1995 [6] to 64.0% in 2002 [7]. The most common site of infection was the lung (68%) followed by the abdomen (22%), bloodstream (20%) and urinary tract (14%). In patients with sepsis, Gram-positive cocci were isolated from 40% of patients, Gram-negative bacilli from 38% and fungi from 17%. In contrast to neutropenic patients, exogenous flora are a major source of infection in the ICU, often being passed by healthcare workers and patients as a result of poor hand hygiene or inadequate infection control policies [8]. In addition ~15% of blood cultures yield *Candida* species, the most common infecting pathogen being *Candida albicans* [9].

Appropriate antibiotic selection

The importance of appropriate empirical antibiotic therapy has been clearly documented in the literature [10–15]. Empirical therapy also needs to consider the likelihood of the patient being infected with a resistant pathogen. As previously noted, NNIS has reported a 47% increase in extended-spectrum β-lactamase (ESBL) producing *K. pneumoniae* from 2003 compared with 1998–2002 with 20.6% of isolates being resistant to a 3rd-generation cephalosporin or aztreonam [4]. Over the same time period, resistance to cephalosporins, fluoroquinolones and carbapenems increased by 20%, 9% and 15%, respectively; and vancomycin-resistant enterococci increased by 12% with 28.5% of isolates being reported as resistant. The same data reported 59.5% of *S. aureus* as methicillin-resistant and 89.1% of coagulase-negative staphylococci as methicillin-resistant. Other data show that methicillin-resistant *S. aureus* (MRSA) has trebled in less than 20 years, rising from ~20% in 1987 to 63% in 2003 [16]. "Collateral damage" is a term used to refer to the adverse ecological effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted colonisation or infection with multidrug-resistant organisms [17].

A number of factors contribute to the spread of resistant isolates. Selection pressures for the development of resistance include antimicrobial prophylaxis, frequent empirical antibiotic use, polymicrobial therapy and prolonged exposure to antibiotic regimens. Hospitalised patients often have multiple co-morbidities, further increasing the risk of acquiring resistant pathogens or have intravenous lines in situ, or other indwelling catheters (e.g., endotracheal tubes, urinary catheters, etc.). The high use of broad-spectrum antibiotics in the ICU has also been associated with the emergence of virulent organisms, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

Table 1
Effect of mechanical ventilation and prior antibiotic use on the development of resistant pathogens

Organisms	Number (percentage) responsible for 135 VAP episodes classified according to duration of mechanical ventilation (MV) and prior antibiotic therapy (ABT)			
	Group 1 (n = 22) MV < 7, ABT = no	Group 2 (n = 12) MV < 7, ABT = yes	Group 3 (n = 17) MV ⩾ 7, ABT = no	Group 4 (n = 84) MV ⩾ 7, ABT = yes
Multiresistant bacteria	0*	6 (30)	4 (12.5)†	89 (58.6)
P. aeruginosa	0	4 (20)	2 (6.3)	33 (21.7)
A. baumannii	0	1 (5)	1 (3.1)	20 (13.2)
S. maltophilia	0	0	0	6 (3.9)
MRSA	0	1 (5)	1 (3.1)	30 (19.7)
Other bacteria	41 (100)	14 (70)	28 (87.5)	63 (41.4)

*P < 0.02 versus Group 2, 3 or 4; †P < 0.0001 versus Group 4. Adapted from Trouillet 1998 [22].

De-escalation, which consists of initial treatment with broad-spectrum antibiotics to cover the most probable causative pathogens, followed by antibiotic streamlining driven by microbiological findings (isolation by culture with susceptibility testing of pathogens) is thought to provide maximum benefit for the individual patient, while reducing the selection pressure for resistance [18,19]. The correlation between antibiotic use and resistance is well documented in the literature, and reducing antibiotic use may result in a decline in the levels of resistance. Lepper et al. [20] reported a correlation between the consumption of imipenem and resistance in isolates of *P. aeruginosa*. Interestingly these investigators did not find a correlation between levels of resistance and consumption of either ceftazidime or piperacillin-tazobactam. Carbapenem consumption [21] and mechanical ventilation [22,23] have also been linked to colonisation or infection with *Acinetobacter* spp., MRSA, *P. aeruginosa* and *S. maltophilia* (Table 1).

Antibiotic use has also been implicated in the spread of VRE. In an extensive review of the literature VRE colonisation and infection were found to occur predominantly in patients with severe underlying disease, extended length of hospital stay, and previous antibiotic exposure [24]. This meta-analysis reported that the most consistently recognised antibiotic agents inducing or facilitating the acquisition of VRE colonisation or infection were vancomycin, cephalosporins, and anti-anaerobic agents. The total number of antibiotic agents and the duration of antibiotic treatment or prophylaxis were also identified as important risk factors for the acquisition of VRE. In an animal model comparing the effects of different antibiotics on persistence and density of VRE intestinal colonization [25], vancomycin, clindamycin, piperacillin-tazobactam, ticarcillin-clavulanic acid, metronidazole, cefotetan, ampicillin, and ampicillin-sulbactam promoted persistent high-density VRE colonisation. Cefepime, ceftriaxone, aztreonam, and ciprofloxacin promoted VRE to a lesser degree or not at all. These investigators concluded that antimicrobial activity against anaerobes was the most important factor for promoting persistent high-density VRE stool colonisation.

Resistant pathogens are associated with escalating costs due to prolonged hospitalisation, the need for increased infection control procedures, including isolation (which may negatively impact on the psychological well being of the patient), and in most studies, increased mortality. Two recent meta-analyses [26,27] and data from the Centers for Disease Control (CDC) [28] report a significant increase in the mortality associated with methicillin-resistant *S. aureus* or VRE infections ($p < 0.001$). In the presence of ESBL-producing *E. coli* and *K. pneumoniae*, intermediate susceptibility (MIC ⩾ 8 μg/mL) has been associated with 100% failure of cephalosporins [29].

Adverse events associated with antibiotic therapy

In critically ill or at risk patients, such as those with neutropenia, the safety profile of an antibiotic is an important therapeutic consideration. Adverse reactions occurring with antibiotic use (Table 2) are usually the result of (1) dose or duration related toxicity (e.g., renal toxicity due to an aminoglycoside, thrombocytopenia due to linezolid) , (2) an immunologic reaction to the drug or its metabolites (e.g., anaphylaxis to penicillin), or (3) an idiosyncratic effect of the compound or its metabolites (e.g., tendon rupture due to a fluoroquinolone). Most antibiotic-related adverse reactions are predictable and are unwanted toxicities inherent in the antibiotic compound or its metabolites. Such events are often dose- or duration-dependent and can be avoided by appropriate dosage adjustments or limiting the duration of therapy. Unpredictable reactions may occur independent of the dose and route of administration and reflect such factors as drug intolerance, allergy, and other idiosyncratic responses, including aplastic anaemia associated with chloramphenicol, tendon rupture with the fluoroquinolones and liver toxicity with trovafloxacin. The choice of an antibiotic for empirical therapy is based on considerations of efficacy, safety, and cost. Estimation of efficacy is based on the nature of the presumed infection (site), spectrum of the antibiotic(s), epidemiology (age, location of patient such as ICU), host defences (especially immunocompromising disorders), and the local antibiogramme. Safety concerns include frequency of dose- and duration-dependent toxicity (this may depend on underlying renal and/or hepatic impairment) and idiosyncratic reactions.

Table 2
Adverse events associated with antibiotics

Adverse event	Examples
Dose and/or duration related	Aminoglycosides (renal dysfunction, dose and duration dependent) Linezolid (hematologic toxicity, duration >2 weeks) Penicillins (seizures, doses >40–60 million U/d) Vancomycin (Red man's sydrome, rapid infusion) Gemifloxacin (rash, therapy >7 days) Ethambutol (optic neuritis, dose >15 mg/kg) 5 flucytosine (leukopenia)
Idiosyncratic reactions	Chloramphenicol (aplastic anemia) Fluoroquinolones (tendon rupture) Sulfonamides (aseptic meningitis) Isoniazid (liver toxicity)
Allergic reactions	Anaphylaxis (all drugs)
Collateral damage [a]	Overgrowth (e.g., *C. difficile*) Induction of resistance (e.g., *P. aeruginosa*) Selection for resistant pathogen (e.g., MRSA)

[a] See text for more complete discussion.

Finally, everything else being equal, we should choose the least expensive antibiotic regimen. Many times a single broad-spectrum agent will provide excellent coverage with a low risk of adverse events. The advantages of using a single broad-spectrum agent include the ability to ascribe toxicity, ease of administration, reduced likelihood of drug–drug interactions, and lower cost.

A classical and clinical important example of collateral damage from antibiotic therapy is the precipitation of *Clostridium difficile* associated disease (CDAD). CDAD is increasing worldwide, and occurs almost entirely in patients who have received previous antimicrobial treatment. Pepin et al. [30] reported an increase of 35.6 per 100,000 population in 1991 to 156.3 per 100,000 in 2003. Among patients aged 65 years or more, it increased from 102.0 to 866.5 per 100,000. The annual cost of CDAD in the United States has been estimated at >$1.1 billion (2002 prices) [31]. Severe pseudomembranous colitis, toxic megacolon and fulminant CDAD are life-threatening complications of *C. difficile* infection. In an early study of patients undergoing elective surgical procedures who had not received prior antibiotic treatment nor reported any diarrhoeal disease during at least the preceding 3 months, patients received prophylaxis with a cephalosporin or mezlocillin or no antibiotic prophylaxis [32]. The incidence of *C. difficile* and cytotoxin after injection of a single dose of cephalosporin was 23%. Of patients receiving cefoperazone, significantly more (43.7%, $P = 0.04$) were colonised with *C. difficile* than with other cephalosporins. Of patients receiving prophylaxis with mezlocillin only 3.3% were colonised, and of patients receiving no prophylaxis none were colonised.

Antibiotics are not equal in terms of developing CDAD. CDAD rates significantly decrease when clindamycin or third-generation cephalosporin use is reduced. More recently, increased CDAD risk has been associated with fluoroquinolone use. The risk of antibiotic-associated CDAD increases when *C. difficile* is antibiotic-resistant, with high-level fluoroquinolone-resistance as an identified risk factor. In 2005, *C. difficile* hyperproducing toxins A and B was associated with an outbreak of CDAD [33]. Isolates belonging to one restriction-endonuclease analysis (REA) group (BI) and having the same pulsed-field gel electrophoresis (PFGE) type (NAP1) were identified in specimens collected from patients. BI/NAP1 isolates were of toxinotype III, and were positive for the binary toxin CDT, and contained an 18-bp tcdC deletion. Fluoroquinolone-resistance was more common in BI/NAP1 isolates than in non-BI/NAP1 isolates (100% vs. 42%, $P < 0.001$), whereas the rate of resistance to clindamycin was the same in the two groups (79%). These resistant clones have been associated with an increased severity of disease [34]. A multivariate analysis of risk factors showed that second-generation cephalosporins were associated with the highest increase risk for developing CDAD (OR = 6.0, 95% CI: 2.1–17.5) (Table 3).

Preventing collateral damage

The CDC's Campaign to Prevent Antimicrobial Resistance in Healthcare Settings has identified 4 strategies to prevent the spread of resistant pathogens: (1) preventing infection; (2) preventing transmission; (3) effective diagnosis and treatment of infection; and (4) optimising the use of antimicrobials. Key interventions for infection control include effective hand hygiene using alcohol-based antiseptics or handwashing products such as those containing chlorhexidine [3], surveillance systems to monitor and identify key pathogens and contact precautions including gloves and gowning for patients with multidrug-resistant pathogens (e.g., MRSA, VRE, *C. difficile*), and appropriate environmental disinfection (especially important with *C. difficile*). We also isolate cases colonised or infected with multidrug resistant Gram negative bacilli if the are susceptible to less than 2 classes of antimicrobial agents.

Successful interventions to reduce resistance also include reduction in overall use of antibiotics, especially third-generation cephalosporins [35]. The extensive

Table 3
Multivariate model of risk factors for developing CDAD [34]

lIncreased risk	Odds ratio (95% CI)	No increased risk	Odds ratio (95% CI)
Any cephalosporin	3.8 (2.2–6.6)	Clindamycin	1.6 (0.5–4.8)
1st cephalosporin	2.4 (1.2–4.6)	Aminoglycosides	0.7 (0.3–1.9)
2nd cephalosporin	6.0 (2.1–17.5)	Macrolides	1.3 (0.6–2.9)
3rd cephalosporin	3.0 (1.4–6.8)	IV vancomycin	1.3 (0.5–3.1)
Any fluoroquinolone	3.9 (2.3–6.6)	Penicillins	0.7 (0.3–2.9)
Ciprofloxacin	3.3 1.8–5.4)	Carbapenems	1.4 (0.3–6.3)
Gatifloxacin/moxifloxacin	3.4 (1.5–7.7)	Penicillin with β-lactamase inhibitor	1.2 (0.7–2.3)
		Levofloxacin	0.6 (0.2–1.9)

Table 4
Cephalosporin replacement and reduction in ESBLs

Year	Reference	Agent	Reduction in cephalosporin use	Replacement agent	Intervention successful (Yes/No)
1993	Meyer [39]	Ceftazidime	73%	Imipenem-cilastatin	Yes
1996	Rice [40]	Ceftazidime	50%	Piperacillin-tazobactam	Yes
1998	Pena [41]	3rd-Generation cephalosporin	83%	Piperacillin-tazobactam Imipenem-cilastatin	Yes
1998	Rahal [42]	All cephalosporins	80%	Imipenem-cilastatin	Yes
1999	Landman [43]	Ceftazidime Ceftazidime	89% 66%	Ampicillin-sulbactam Piperacillin-tazobactam	Yes
2000	Patterson [44]	Ceftazidime	Hosp. A – 71% Hosp. B – 27%	Piperacillin-tazobactam	Yes

use of third-generation cephalosporin antibiotics has played an important role in the worldwide emergence of ESBLs in Gram-negative bacteria [17,36–38]. Table 4 summarises publications reporting the effect of replacing cephalosporins with imipenem-cilastatin, ampicillin-sulbactam or piperacillin-tazobactam on the levels of resistance. In all these studies, replacing cephalosporins with alternative agents resulted in a reduction in the incidence of ESBLs. When these measures are combined with the active promotion of prescribing guidelines, appropriate use of antibiotics increases and costs and duration of hospitalisation decreases [45,46]. The use of a computer program that provides guidelines may also aid the decision process and has been associated with significant reductions in orders for drugs to which the patients had reported allergies (35, vs. 146 during the pre-intervention period; $p < 0.01$), excess drug dosages (87 vs. 405, $p < 0.01$), and antibiotic-susceptibility mismatches (12 vs. 206, $p < 0.01$) [45]. Evans and co-workers [45] also noted marked reductions in the mean number of days of excessive drug dosage (2.7 vs. 5.9, $p < 0.002$) and in adverse events caused by anti-infective agents (4 vs. 28, $p < 0.02$). They also reported improved outcomes (i.e., shorter hospital stay) and reduced cost.

Selecting antibiotics for empirical therapy to which the likely infecting organisms are susceptible is associated with a much greater chance of clinical success and improved patient outcomes than an inappropriate choice. Ideally, antibiotic therapy should be based on the accurate identification and susceptibility testing of bacteria responsible for the infection. However, this may take up to 72 hours due to limitations in current diagnostic methods. The dilemma for the clinician faced with an infected patient is that increased multi-resistant organisms mean that broad-spectrum antibiotics should ideally be used sparingly, yet prompt aggressive antibiotic treatment is required to avoid morbidity and mortality. Clinical decisions regarding empirical antibiotic treatment must be made when the need to treat is greater than the need to wait for microbiological confirmation. In clinical practice, this occurs with most critically ill patients who become febrile. In the ICU setting, several studies have shown that mortality in patients who receive inappropriate or inadequate initial antibiotic therapy is almost double that seen in those who receive adequate antimicrobial treatment [13,14]. In an ICU-based analysis, inadequate antimicrobial treatment was the most important independent determinant of hospital mortality [19]. Risk stratification studies have shown that previous antibiotic use, particularly broad-spectrum antibiotics, and prolonged use of a mechanical ventilator, significantly contribute to increasing patient risk of developing resistance [22]. For this reason, risk needs to be assessed for each patient before treatment decisions are made.

Similarly, the Infectious Disease Society of America (IDSA) 2002 Guidelines for the management of neutropenic

fever recommend empirical antibiotic therapy for all neutropenic patients at the onset of fever [47] (see elsewhere in this supplement). In selecting the initial antibiotic regimen, the type, frequency of occurrence, and antibiotic susceptibility of bacterial isolates recovered from other similar patients in the same hospital should be considered. The use of certain antibiotics may be limited by special circumstances, such as drug allergy or organ (e.g. renal or hepatic) dysfunction. Cisplatin, amphotericin B, cyclosporine, vancomycin and aminoglycosides should be avoided in combination because of their additive renal toxicity. Drug plasma concentrations should be monitored when they are helpful in predicting therapeutic success and toxicity (e.g. aminoglycosides). Catheter-associated bacteraemia due to *Bacillus* species, *P. aeruginosa, S. maltophilia, Corynebacterium jeikeium*, or VRE, and candidaemia, often respond poorly to antimicrobial treatment, and prompt removal of the catheter is recommended, whenever possible. Established infections with *Acinetobacter* species also often require removal of the infected catheter.

Several studies have shown no significant differences between monotherapy and multi-drug combinations for empirical treatment of uncomplicated episodes of fever in neutropenic patients [48–54]. A third- or fourth-generation cephalosporin (ceftazidime or cefepime), piperacillin-tazobactam, or a carbapenem (imipenem-cilastatin or meropenem) may be used successfully as monotherapy). However, ESBLs have reduced the utility of ceftazidime for monotherapy. Cefepime, imipenem-cilastatin, and meropenem, unlike ceftazidime, have excellent activity against viridans streptococci and pneumococci. Piperacillin-tazobactam has also been found to be effective as monotherapy [50,54]. Patients must be monitored closely for non-response, emergence of secondary infections, adverse effects, and the development of drug-resistant organisms. In particular, the spectrum of drugs usually used as monotherapy does not usually cover coagulase-negative staphylococci, MRSA, VRE, some strains of penicillin-resistant *S. pneumoniae*, and viridans streptococci.

Summary

Inappropriate antibiotic use and overuse are the main driving factors for the development of antibiotic resistant pathogens. Appropriate choice of empiric antibiotics is associated with decreased mortality, and the choice of empirical therapy should be guided by the epidemiology of infection, infecting flora, and local antimicrobial susceptibility patterns. Appropriate infection control and antibiotic use can decrease the likelihood of patients developing antibiotic resistant pathogens. Empirical management of neutropenic fever has been challenged by the emergence of resistance. When selecting antibiotics for managing these patients, three factors should be taken into consideration: spectrum of activity, the potential to induce future antibiotic resistance, and adverse events or toxicity. Antibiotics posseing a tailored spectrum of activity (i.e., coverage of likely pathogens including antibiotic-resistant strains) can improve treatment outcomes while avoiding collateral damage. Also, the use of an antibiotic with chemical properties that may minimize the risk of developing resistance should be considered. These principles provide a useful framework for the empirical choice of antibiotics. This approach should provide improved clinical and microbiological outcomes while decreasing the risk for collateral damage.

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