Review

An overview of harms associated with β-lactam antimicrobials: where do the carbapenems fit in?

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Abstract

The US Institute of Medicine's focus on patient safety has motivated hospital administrators to facilitate a culture of safety. As a result, subcommittees of the pharmacy and therapeutics committee have emerged in many hospitals to focus on adverse events and patient safety. Antimicrobial harms have gained the attention of practicing clinicians and hospital formulary committees, because they top the list of drugs that are associated with adverse events and because of certain serious harms that have ultimately led to the withdrawal of some antimicrobial agents. In the near future, several antimicrobials in the late phase of development will become available for clinical use (ceftobiprole, ceftaroline, and telavancin), and others (doripenem and dalbavancin) have recently joined the armamentarium. Because new antimicrobials will become part of the treatment armamentarium, it is important to discuss our current understanding of antimicrobial harms in general. Although not thought of as traditional adverse events, *Clostridium difficile* infection and development of resistance during therapy are adverse events that occur as a result of antimicrobial exposure and therefore are discussed. In addition, a distillation of our current understanding of β-lactam specific adverse events will be provided. Finally, new methods of administration are being evaluated that may influence peak concentration-related antimicrobial adverse events.

Introduction

The safety of antibiotics has attracted attention lately in both the scientific and regulatory communities. For example, in 2001, the Interscience Conference on Antimicrobial Agents and Chemotherapy held a symposium entitled 'Antibiotics to die for'. In addition, the US Food and Drug Administration (FDA) recently mandated a second change in the labeling of telithromycin in less than a year because of safety concerns, and has updated the language of antimicrobials regarding the risk for *Clostridium difficile* infection [1]. Antibiotic safety is an important component of both patient care and formulary decision making. β-Lactams are typically considered to be among the safest classes of antibiotics available to clinicians

practicing today. Although these agents are generally safe, certain class effects exist that include serious hypersensitivity-related harms, bone marrow suppression, and seizures. These and other antimicrobial harms are discussed here.

General classification of adverse events

Type A events are predictable events that represent either an excess of the drug's primary pharmacologic effect (for example, hypotension with a vasodilator) or a secondary pharmacologic property (for example, anticholinergic effects with tricyclic antidepressants) [2]. These events are typically dose related, usually identified before marketing, and generally listed in the product's labeling. Although common and capable of producing significant morbidity, they are rarely fatal. In contrast, type B events are not an extension of the known pharmacologic properties of a drug. These events, which include idiosyncratic, immunologic/allergic, and carcinogenic/teratogenic events, are generally unpredictable, unrelated to dosing or route of administration, and are more or less a function of the patient's susceptibility to the effect rather than intrinsic drug toxicity. Type B events can present late, long after drug therapy has been discontinued, and consequently they may not be recognized or attributed to the drug because of the temporal disassociation. Although they are the least common, type B events are among the most serious and potentially life-threatening of the adverse events [2].

Adverse immunologic events can also be classified on the basis of their pathophysiology into types 1 through 4 and idiopathic events [3,4]. Type 1 events are immunoglobulin IgE-mediated, immediate hypersensitivity reactions that produce urticaria, hives, or anaphylaxis. Events of types 2 and 3 are IgG-mediated or IgM-mediated delayed reactions. Type 2 events present as anemia, cytopenia, or interstitial nephritis, whereas type 3 events present as serum sickness or drug

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CDI = *Clostridium difficile* infection; CYP = cytochrome P450; FDA = Food and Drug Administration; I_{Kr}, delayed rectifier potassium channel; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

fever. Type 4 events are T-cell-mediated, delayed reactions that present as contact dermatitis. All other events are deemed idiopathic. These idiopathic events can present as eosinophilia, a maculopapular rash, or Stevens-Johnson syndrome.

The type and severity of adverse events associated with a particular drug are influenced by a multitude of pharmacologic and clinical factors. These include the drug's pharmacokinetic properties (absorption, distribution, metabolism, and elimination); the dose, route, and duration of therapy; the patient's age and genetic composition; the presence of concomitant disorders; and concurrent drug administration.

Sources of information for antibiotic-associated adverse events

Data regarding a drug's safety profile can be difficult to obtain, because negative data are rarely published; moreover, there is typically a delay in the availability of published information for new drugs. Several sources can be explored, however, depending on where the drug is in its life cycle. Data can of course be found in the product labeling and from meeting abstracts at the time of drug approval. If an advisory committee hearing has taken place, then data may be found at the FDA's website [5]. This website is an underutilized source of data for the formulary decision maker and even for practicing clinicians who desire to know more about the drugs they prescribe. Good examples exist of presentations and accompanying discussions held at the FDA's Advisory Committee meetings, which are posted on the website in a downloadable format (PDF files and PowerPoint slides). Examples include the discussion of cardiac and renal concerns related to the cyclo-oxygenase-2 inhibitors and specific toxicities of voriconazole, telitromycin, moxifloxacin, and newer generation antipsychotics. Although some of this information has made its way into the published literature, some of it remains unpublished and is only available on the FDA's website. In addition, if the drug has already been approved in other countries, postmarketing studies may be available in those countries.

Another factor has an impact on the availability of safety data. Companies sometimes seek initial FDA approval for two indications, particularly for antimicrobials. These indications are usually skin and skin structure infections, acute exacerbations of chronic bronchitis, acute bacterial sinusitis, or urinary tract infections - indications for which it is easy to enroll patients over a short period of time. Unfortunately, this often leaves the clinician without data on other infections for which the drug may be used. For example, tigecycline has been on the market for a couple of years, but its initial indications were for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections. Pneumonia studies have only recently been conducted. Although tigecycline may have been used off-label for the treatment of hospital-acquired pneumonia or ventilator-associated pneumonia (VAP), it failed to meet its

end-point of noninferiority compared with imipenem for patients with VAP [6]. Therefore, we can find ourselves feeling that we need to use a new antimicrobial for a particular indication before clinical studies support such a use. Having antibiotics available with enough data to support a wide range of indications to assess properly their utility for a yet wider range of indications does not necessarily go hand in hand in the current regulatory climate. Gone are the days when an antimicrobial came to the marketplace with 14 indications (for instance, trovafloxacin). The trend, especially for antimicrobials, is to request FDA approval for one or two indications and leave the clinician to determine whether the drug may or may not work for other infectious diseases. As we have learned (for example, from daptomycin and tigecycline), it should not be assumed that an antimicrobial approved for skin and skin structure infections will be effective for other indications. Clinicians typically must wait for 1 year for results from phase III trials to be published in a respectable peer-reviewed journal. Interestingly, about half of all drug withdrawals from the market occur within approximately 2 years of approval [7]. So, the first 2 years of the antimicrobial's time in the marketplace is very telling.

As mentioned above, antimicrobials lead all drug classes in terms of numbers of adverse events [8]. Some adverse events are class specific, but even within a class of antimicrobials some agents may not be associated with the adverse event at all. Examples include epileptogenic capabilities among the various β-lactams. All β-lactams have some potential to cause seizures, some more so than others. Among the carbapenems, imipenem is most frequently associated with seizures, whereas meropenem, ertapenem, and doripenem are at the opposite end of the spectrum in terms of risk for seizures. Similarly, macrolides/ketolides and fluoroquinolones are associated with QT liability, but azithromycin and ciprofloxacin stand out as not being associated with the potential for causing QT prolongation. For these reasons, new drugs should be viewed skeptically when they are first approved for use and introduced for formulary discussion.

For some antimicrobial classes, safety can be inferred from previously introduced class members. For example, the β-lactams have an established safety profile, with few if any surprises when a new class member is introduced for clinical use. Moxalactam is a well known exception to this long track record of safety. Other than the moxalactam example, which occurred several decades ago, the β-lactam family that includes the penicillins, cephalosporins, cephamycins, monobactams, and carbapenems has not had a class member withdrawn from the marketplace because of an unexpected and serious adverse event. For this reason, given adequate safety data during a clinical development program, novel β-lactams have been well accepted by hospital formularies upon their release to the market so long as other considerations, such as pricing and efficacy, are favorable

relative to existing class members. On the flip side, the opposite is true for the fluoroquinolones. In addition to the known class effects, unusual and serious adverse events with these agents have emerged shortly after their introduction to the market. Examples include drugs that were actually withdrawn from the market (for example, temafloxacin [hemolytic-uremic syndrome] and trovafloxacin [hepatotoxicity resulting in death or transplantation]). For this reason, formulary committees have been conservative in their adoption of new fluoroquinolones until a proven track record has been established.

Cardiac toxicity

Prolongation of the QT interval is an increasingly important adverse event that has led to the withdrawal of certain drugs from the market, many of them antimicrobials. Although prolonged QT interval rarely has consequences (such as life-threatening ventricular arrhythmias, specifically *torsades de pointes*), they are severe [9-11]. The fluoroquinolones (except for ciprofloxacin), macrolides/ketolides, and azoles have been shown to prolong the QT interval [9,11-13].

QTc prolongation occurs as a result of a drug's affinity toward binding to a particular potassium channel in the cardiac myocyte (delayed rectifier potassium channel; I_{Kr}). The prevalence and risk associated with this prolongation depends on drug-related and patient-related factors, including the dose and route of administration, the drug's individual propensity for binding to I_{Kr} channels, the number of channels present in an individual patient (reduced numbers exist in patients with congestive heart failure and in women), and genetic anomalies within these and other cardiac channels. In addition, organ dysfunction or the concomitant administration of other medications can increase this risk by delaying metabolism of the QT interval prolonging drug or enhancing drug exposure, or by causing electrolyte derangements [9,10]. Furthermore, concurrently administered medications may have direct effects of their own on these channels, augmenting the overall effect on the QT interval.

The affinity of various antibiotics for these channels varies substantially. For example, 50% inhibition of the I_{Kr} channel is produced by a 33 μmol/l concentration of clarithromycin, a 42.5 μmol/l concentration of telithromycin, a 72 μmol/l concentration of erythromycin, a 129 to 353 μmol/l concentration of moxifloxacin, and a 966 μmol/l concentration of ciprofloxacin [10]. In contrast, less than a 1 μmol/l concentration of sotalol or terfenadine is required to produce 50% inhibition [11].

Overall duration of exposure also plays an important role [14]. Single doses of a drug are not likely to cause *torsades de pointes*; however, the probability that this particular adverse event will occur rises sharply when a full course of therapy is administered. In general, the median time to *torsades de pointes* is typically 4 to 5 days into therapy. β-Lactams, including the carbapenems, have not been associated with QT liability to date. In addition, preclinical screening tools are now used to detect the potential for QT liability, so that it can be assessed early in development (moxifloxacin) rather than waiting for postmarketing studies to elucidate this finding (droperidol).

Dysglycemias

Dysglycemias (hypoglycemia and hyperglycemia) are uncommon adverse events associated with some antimicrobials, including certain fluoroquinolones, particularly gatifloxacin [13,15]. Historically, quinine has been associated with dysglycemias. The quinolones, which are structurally related to quinine *vis à vis* quinoline rings, have a penchant to influence the release of insulin (gatifloxacin, temafloxacin, and clinafloxacin more so than others) [13,15]. Other antimicrobial classes appear to be devoid of the potential to disrupt glucose homeostasis. The purported pathophysiology of perturbations in glucose homeostasis (specifically hypoglycemia) is mechanistically similar to that observed with QT interval prolongation. A potassium channel exists within pancreatic β cells that is genetically similar to the one present in cardiac myocytes. Fluoroquinolones (particularly gatifloxacin, temafloxacin, and clinafloxacin) have a collateral affinity toward this channel, resulting in partial blockade and leading to an accumulation of intracellular glucose within these β cells, and insulin is secreted in response to this artificially elevated glucose concentration [16]. For example, clinafloxacin exposure resulted in a substantial increase in insulin release (from 165% to 235%) that triggered a reduction in blood glucose by 47% to 51% [13,15]. This is an extreme example within the fluoroquinolone class. Substantially smaller disturbances in blood glucose have been determined with other class members.

The reason why this is clinically unnoticed in patients is explained by the fact that the body is remarkable in its ability to compensate physiologically for small fluctuations in glucose regulation [13,15]. However, symptomatic hypoglycemia can develop in susceptible individuals who lack these compensatory mechanisms (for example, patients with underlying diagnosed or undiagnosed diabetes and those receiving corticosteroids) [15]. Gatifloxacin gained notoriety for complications that were detected in postmarketing studies. Clinafloxacin's proclivity for this rare but serious adverse event was determined during its clinical development program and may be among the reasons why its submission to the FDA was withdrawn by the company after completion of its phase III studies [13,15].

Clostridium difficile infection

C. difficile infection (CDI) is an emerging, complex, and important patient safety issue; it is an adverse event almost exclusively associated with antibiotic administration. Acquisition of CDI is a multifactorial process that involves antibiotic use, exposure to the organism, and a variety of host factors,

Figure 1
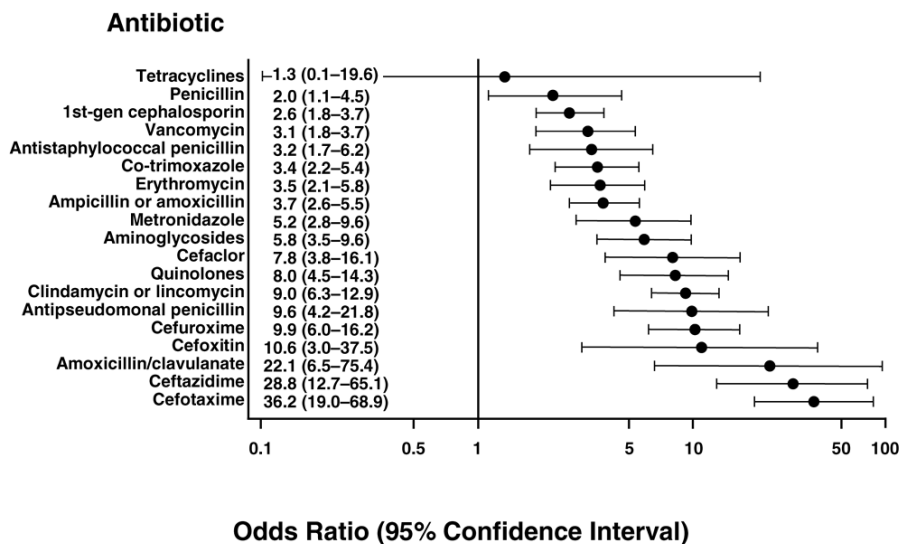
Pooled odds ratios and 95% confidence intervals for *Clostridium difficile* infection by antibiotic type. Adapted with permission from Bignardi. Reprinted with permission [23]. Copyright © 1998 The Hospital Infection Society.

including age, immune status, and gastric acid suppression [13,17]. Consequently, the risk for CDI can be substantially reduced through good antimicrobial stewardship, compliance with infection control practices, and appropriate environmental intervention [17,18]. A number of reasons for the increased incidence of CDI have been proposed and are discussed in detail elsewhere [19]. In brief, the appearance of a previously uncommon, toxin gene variant of *C. difficile* that possesses additional resistance characteristics (to fluoroquinolones) has emerged as a predominant cause of CDI throughout North America and as far away as Japan [20]. Because of the virulence associated with this new strain of *C. difficile*, careful attention to antimicrobial selection and duration of therapy has become an important tool in combating this infection.

The individual risk associated with each antimicrobial is probably different. Studies to date have been unable to distinguish antimicrobial risk at the 'micro' level but they were able to elucidate differences at the 'macro' level. For example, the cephalosporins, fluoroquinolones, and variably clindamycin have topped the list of antimicrobials that have been associated with the emerging toxin gene variant strain of *C. difficile* known as BI/NAP1. This is due, in part, to the fact that the aforementioned drug classes possess no or variable activity against *C. difficile*. Antimicrobials with activity against *C. difficile* (for example, metronidazole, piperacillin-tazobactam, tetracyclines including tigecycline, and to some extent the carbapenems) have been associated with CDI less often than those classes of drugs to which *in vitro* resistance is routinely observed in clinical isolates [21,22]. In a review of the literature, the odds ratios for *C. difficile*-associated disease

ranged from 1.3 to 36.2, depending upon the antibiotic employed (Figure 1) [23]. Given the limitations inherent in meta-analyses of trials with vastly different protocols, these odds ratios are not listed for comparative purposes; however, they illustrate the fact that all antibiotics are associated with an increased risk for CDI [24]. Although carbapenems were not included in this analysis, recent data demonstrate that this class of antibiotics, like almost all others, carries a risk for CDI [25,26]. And, a review of the newer literature evaluating antimicrobial risk for CDI suggests that identified odds ratios fall within the previously identified range, including carbapenems [20]. Finally, it is important to remember that although the risk for CDI increases with increasing duration of antibiotic therapy, only a single dose is needed to increase this risk [20,25,27].

Metabolic liability

Drugs that rely on cytochrome P450 (CYP) enzymes for metabolism or inhibit these enzymes possess what is termed 'metabolic liability'. Of the various CYP isoenzymes, CYP 3A4 is the most important because it is responsible for the biotransformation of nearly 60% of all oxidized drugs [11]. Inhibiting the metabolism of a drug that relies on CYP 3A4 magnifies any associated toxicities inherent to that drug, because most are dose (exposure)-dependent (for example, hepatotoxicity, QT interval prolongation, and rhabdomyolysis). Because polypharmacy plagues patients with HIV disease and the elderly, the risk for drug interactions is increased significantly in these populations [28]. In addition, patients may be at risk for certain toxicities when they receive drugs that carry metabolic liability, even in the absence of a direct drug-drug interaction. The reason for this is that some

patients are characterized genetically as poor metabolizer phenotypes (typically more common with CYP 2C9 and CYP 2C19, which have specific impacts on the azole antifungals). Patients with these poor metabolizer phenotypes are at risk for dramatically reduced drug clearance when they are given drugs that are metabolized through these CYP isoforms [11]. In general, antimicrobials that carry metabolic liability include macrolides, ketolides, imidazole/triazole antifungals, and (to a lesser degree) trimethoprim-sulfamethoxazole and ciprofloxacin. To date, β-lactams, most fluoroquinolones, clindamycin, and aminoglycoside antimicrobials do not possess metabolic liability, making them safe to use in patients receiving concurrent CYP P450 inhibitors and substrates.

A recent example demonstrates the ongoing importance of unrecognized metabolic liability. A large population of outpatients in a Medicaid claims database were evaluated [29]. Patients who were receiving an antimicrobial (erythromycin) concurrently with CYP 3A4 inhibitors were compared with patients receiving CYP 3A4 inhibitors and/or β-lactam antibiotics. A fivefold increase in cardiac sudden death was reported in patients taking erythromycin-CYP 3A4 combinations compared with recipients of CYP 3A4 inhibitors and/or amoxicillin.

Immune-mediated adverse events

Immune-related antimicrobial harms are a common complication of many antibiotics, including β-lactams, fluoroquinolones, glycopeptides, and sulfa drugs [4,13,30,31]. Hypersensitivity reactions producing rash, pruritus, and/or urticaria are the most frequent and occur in up to 8% of patients who receive a penicillin and up to 3% of patients who receive a cephalosporin [32,33]. In contrast, anaphylaxis develops in only 0.004% to 0.015%, and fatality due to this anaphylaxis occurs in only 0.001% to 0.003% of penicillin treatment courses [4].

Cross-reactivity occurs within the various classes of antibiotics. For example, patients who have had an allergic reaction to penicillin have a fourfold to sixfold increased risk for a reaction upon exposure to other β-lactams [4]. Thus, a history of an allergic reaction to penicillin has traditionally been sufficient to exclude further therapy with all members of the β-lactam class [4]. However, recent evidence suggests that this broad-based exclusion is too conservative and prevents patients from receiving first-line therapy, and often results in the patient receiving a marginally effective therapy. It is important to remember that patients should receive the most effective agent, not a second-line or third-line treatment (unless absolutely necessary). In some cases (for example, in patients with cystic fibrosis) there are no second-line therapies for certain pathogens; in these situations desensitization protocols are used to facilitate the use of a first-line antimicrobial [34].

Between 5% and 20% of patients claim to have a history of an allergic reaction to penicillin [3,4]. However, much of this

Figure 2
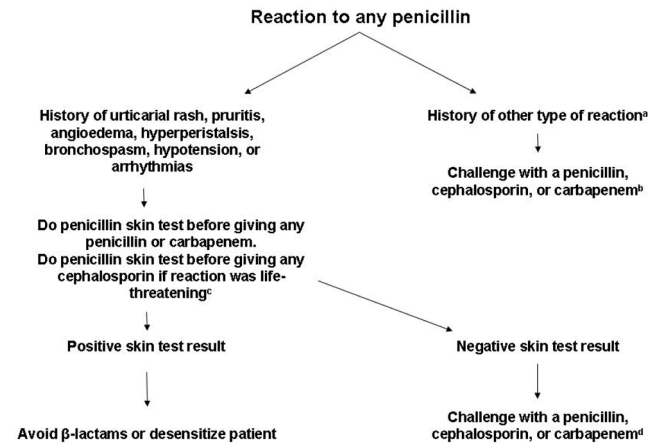
Approach to antibiotic selection in patients with a history of penicillin allergy. [a]It is often difficult to obtain an accurate history; if in doubt, assume that reaction could have been an urticarial rash. [b]Avoid use of first-generation cephalosporins. Stevens-Johnson syndrome and toxic epidermal necrolysis are not IgE mediated. If the suspected drug reaction was either of these, then avoid skin testing and use of penicillins. [c]Skin testing with amoxicillin is sometimes used if the reaction was to amoxicillin, but the incidence of false negatives is unknown. [d]If the reaction was serious, then one may challenge in a supervised setting using a 'graded challenge' with escalating oral doses followed by intravenous administration, if applicable. Reprinted with permission [3]. Copyright © 2002 the Infectious Diseases Society of America.

historical information is in error; only 10% to 20% of patients reporting a penicillin allergy are truly allergic based on skin testing [35]. Most of these 'alleged' allergic reactions to penicillin represent predictable side effects of the drug or are due to the infectious agent itself rather than the drug and do not represent true type 1 hypersensitivity reactions [3,36]. Penicillin skin testing has a negative predictive value in excess of 99% and is a safe and effective means of determining which of these reactions represent a true IgE-mediated response. In more than 2,000 patients who stated that they were allergic to penicillin but had a negative skin test, no life-threatening immediate reactions occurred during penicillin therapy [36]. In 2002, Robinson and coworkers [3] reported a useful algorithm to guide antibiotic selection in patients with a history of penicillin allergy (Figure 2). When using this algorithm it must be remembered that skin testing is predictive only of IgE-mediated events; a negative skin test does not decrease the probability of non-IgE-mediated events [3]. However, these non-IgE-mediated events are frequently related to side chains on the β-lactam ring [3], and so affected patients may be less susceptible to cross-reactivity with other members of the class or other classes of β-lactams.

Cross-reactivity between penicillins and carbapenems would be expected on the basis of structural similarity. However,

data evaluating the frequency of hypersensitive reactions in penicillin allergic patients who receive a carbapenem are limited to skin testing and retrospective evaluations [35]. In three separate chart reviews, the prevalence rates of carbapenem hypersensitivity in patients with a history of penicillin allergy were 9.5% [37], 11% [38], and 9.2% [39]. However, in only one of these evaluations [38] was this risk significantly increased relative to patients without a history of penicillin allergy. Because precise and complete documentation is essential to differentiate between allergic and nonallergic reactions and to establish the temporal relationship of these reactions to therapy, the retrospective nature of these evaluations substantially influences the accuracy of these risk assessments.

Pending more definitive data, patients with a self-reported history of a penicillin allergy that is not IgE mediated are assumed to be at moderate risk for an associated adverse event. These patients may receive a cephalosporin or carbapenem if other treatment options are lacking and a cephalosporin or carbapenem is deemed the most appropriate option. Skin testing can be considered in patients with suspected IgE-mediated penicillin allergy. In general, patients with a positive skin test or other documented type 1 hypersensitivity to penicillin should avoid carbapenems unless justified by the clinical circumstances. In the setting of administering a cephalosporin or carbapenem to a patient with a documented anaphylactic reaction to penicillin, the patient should be desensitized using a published protocol in the intensive care unit setting [3,35].

For example, my colleagues and I reported the successful treatment of an acute pulmonary exacerbation due to multi-drug-resistant *Burkholderia cepacia* and methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with cystic fibrosis [34]. We documented hypersensitivity by skin testing to multiple antibiotics, including carbapenems, and a clinical history of hypersensitivity after receiving imipenem. We utilized a regimen of meropenem, tobramycin, and vanco-mycin after meropenem desensitization using a 12-dose escalation protocol. A number of our patients with cystic fibrosis and histories of serious and life-threatening carba-penem or penicillin hypersensitivities have been desensitized to carbapenems. Desensitization has worked in these patients with little trouble. In some cases the patient reacted upon receiving the third or fourth escalating desensitization dose; we returned to the previous concentration of drug to which the patient did not react and infused that dose over a longer time period (for example, from >20 to >40 minutes) and then continued with 40-minute consecutive infusions rather than the standard 20-minute infusions. It is important that the patient does not miss any of the doses and that the dose is administered on time (and not late). We often supply extra doses on the nursing unit in case something happens to one of the doses. Another important caveat is that patients with Stevens-Johnson syndrome or exfoliative reactions should not be challenged via desensitization.

Hepatotoxicity has been associated with amoxicillin/clavu-lanate, oxacillin, and trovafloxacin [40-43]. In a series of patients being treated as outpatients with intravenous therapy, oxacillin was associated with a significantly increased prevalence of hepatotoxicity (22%) as compared with nafcillin (0%), clindamycin (1.4%), or other antimicrobials (1.4%; all $P < 0.001$ versus oxacillin) [41]. Trovafloxacin was removed from the market secondary to several deaths related to hepatotoxicity [13,44].

Bone marrow suppression resulting in thrombocytopenia, anemia, and/or neutropenia can develop when IgG or IgM antibodies bind to antimicrobial antigens on the surface of circulating cells, leading to lysis or opsonization of these cells [4]. β-Lactams, including imipenem, linezolid, and glyco-peptides, have all been associated with various forms of bone marrow suppression [30,41,45,46].

Central nervous system adverse events

β-Lactams, fluoroquinolones, and isoniazid are associated with increased risk for seizures [13,47,48]. In fact, β-lactams are frequently used to induce seizures in animal models [49]. At high enough doses, all β-lactams can induce seizures. However, because the problem is recognized and because of use of appropriate dosing regimens, seizures as a complica-tion of β-lactam use had almost fallen into obscurity before the launch of imipenem [50]. Because high-dose (4 g/day) imipenem was thought to be more effective than a 2 g/day dosing regimen in certain infections, and because early clinical trails suggested that 4 g/day was safe [51,52], the higher dosing regimen was evaluated. As a result, imipenem was approved by the FDA for use at a dose of up to 4 g/day (1 g every 6 hours). However, subsequent analysis of phase III dose-ranging studies showed that imipenem was asso-ciated with a dose-dependent risk for seizures, with a risk of 3.6% associated with daily doses exceeding 2 g/day [47]. In addition, a trial for the treatment of bacterial meningitis had to be halted prematurely when 33% of the patients receiving imipenem developed seizures [53]. This risk for seizure has led to extensive revision of the recommended dosing regimen for imipenem. The new scheme, which involves type and severity of infection, susceptibility of the organism, six cate-gories of patient size, and five categories of renal function, is among the most complicated for any pharmaceutical agent approved for use in the USA [54]. This complicated dosing regimen, coupled with a fear of inducing seizures, has resulted in the underdosing of imipenem in clinical settings, 'just to be safe'. Suboptimal dosing of imipenem may reduce its efficacy for difficult infections and contribute to the rapid emergence of resistance in *Pseudomonas aeruginosa*, which is of particular concern for carbapenems (see below).

Although FDA-approved labeling warns of a seizure risk with all carbapenems, this risk appears to be most significant with imipenem. The seizure rate in pivotal trials of newer carbapenems is reported to be 0.7% or less [55,56]. The

epileptogenic activity of β-lactams occurs as a direct result of their ability to bind to and competitively inhibit the γ-aminobutyric acid receptor in the brain [57], and the affinity of imipenem for this receptor is substantially greater than that of meropenem. In an animal model, the concentration of meropenem required to achieve 50% inhibition of γ-aminobutyric acid receptors in cerebral cortical membranes was more than 20-fold greater than that required with imipenem (Figure 3) [57]. Consistent with this, intracerebroventricular injection of 100 μg of imipenem into dogs induced facial spasms, twitching, falling back, and clonic convulsions, whereas a similar dose of meropenem had no effect on behavior [57]. Ertapenem and doripenem appear to behave similarly to meropenem rather than to imipenem. The central nervous system safety of meropenem can be highlighted by the fact that it is approved for the treatment of meningitis, whereas for imipenem one-third of all patients with meningitis suffered from seizures.

Other, and sometimes subclinical, neurologic effects can be elicited by beta-lactams. This has been noted for nearly if not all members of this class. Of late, a paper or two has highlighted these effects with the use of the now generic cefepime. While true, cefepime can cause subclinical and clinical neurologic effects which may manifest as delirium, psychosis, aphasia, somnolence, and insomnia, a myriad of other causes for these effects can be culprits. In one case report and review of the literature, cefepime was concluded to be similar to ceftazidime with respect to neurologic adverse events [58]. One common theme tying together these case reports were the fact that nearly all of the patients unequivocally had kidney disease or were on some form of hemodialysis or filtration modality, yet were given unadjusted doses of cefepime. In modern times, we would call these "medical errors". Unlike most institutions where renal dosing takes place, one paper reported extreme overdoses, so much so it is not any wonder why the patients did not demonstrate frank seizures resulting in litigious action [59]. One of these patients with end stage kidney disease received, on average, almost 9 grams per day for five days [59]! The only cephalosporin, monobactam, or carbapenem that does not require attention to renal dosing is ceftriaxone. For all other aforementioned antimicrobial classes, the clinician needs to be cognizant of renal dosage adjustment in the context of the infection being treated [60]. Otherwise, one can be castigated, at minimum, for such a great responsibility which cannot be ignored, as happened in the paper in question. It also should be remembered that the fluoroquinolones exhibit neurologic adverse events as well, manifesting similarly to beta-lactams [61]. A heightened awareness of this issue is warranted for these classes of drugs.

Emergence of resistance

Although not typically thought of as an adverse event, emergence of resistance is a major adverse sequela of antibiotic use [62]. In a retrospective review of 173 studies

Figure 3
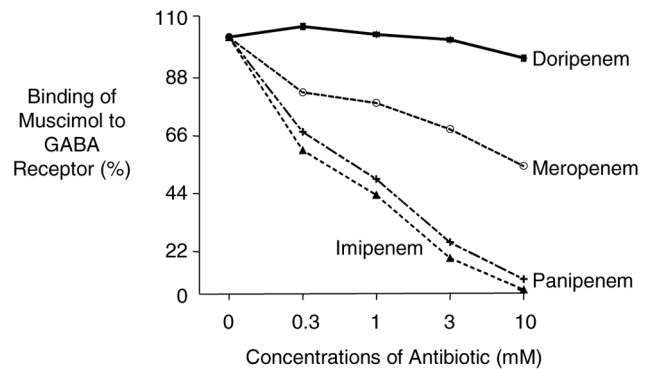
Concentrations of various penems and their displacement of GABA from their receptor sites. Illustrated is the concentration-dependent displacement of muscimol by meropenem, panipenem, and imipenem at the γ-aminobutyric acid (GABA) receptor in mouse cerebral cortical membranes [66].

involving more than 14,000 patients and 225 individual treatment regimens, emergence of resistance occurred in 4% of all organisms and complicated 5.6% of all infections treated [63]. Emergence of resistance was greatest for *P. aeruginosa* infections and appeared to be associated with β-lactams, aminoglycosides, and fluoroquinolones [63]. Currently, carbapenems retain a broad spectrum of activity that includes most β-lactamase producing organisms [64]. However, preserving this activity will require good antimicrobial stewardship that involves using them appropriately, at the correct dose, and for the correct duration [24]. For example, studies have demonstrated that VAP can be treated for as few as 7 to 8 days of therapy, as long as the patient initially received effective antimicrobials (specifically, the pathogen eventually isolated turns out to be susceptible to the initially selected empirical treatment choice) [65]. It is important to note that patients with life-threatening infections, such as health care associated pneumonia or sepsis, must receive initially appropriate therapy, because observations in clinical practice have demonstrated that this does not routinely occur in some centers. One can take the recommended approach that reflects a Chinese menu, whereby one selects a drug from column A (carbapenem, piperacillin-tazobactam, or cefepime) and one from column B (an aminoglycoside or an antipseudomonal fluoroquinolone) plus or minus one from column C (an anti-MRSA treatment option). The individual choices should be dictated by the hospital's anibiogram. These broad-spectrum regimens will ensure that the patient receives adequate therapy initially.

Although some are fearful of this broad-spectrum approach, the key is to de-escalate therapy on day 3, when the results of the culture return, and to stop therapy in 7 to 8 days as long as the patient has clinically responded to the regimen.

Figure 4
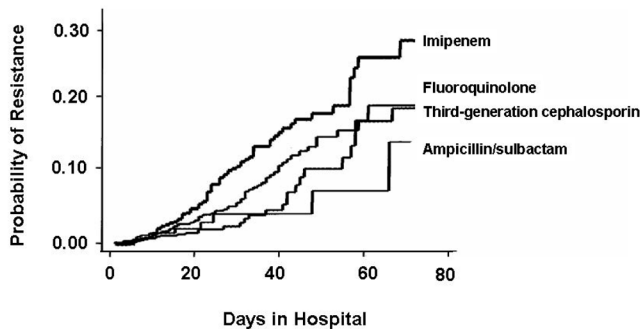
Cumulative risk for emergence of Gram-negative resistant organisms by treatment and duration of hospitalization. Adapted with permission [70]. Copyright © 2001 the Infectious Diseases Society of America.

Therapy for *P. aeruginosa* or *Acinetobacter* spp. may be extended for up to 10 days, but the longer the patient receives antimicrobials, the more likely the patient is to develop resistance to the antimicrobials being administered. Unfortunately, clinical guidelines that some clinicians consider a 'bible' for antimicrobial information contain 'random' and non-evidence-based statements. For example, for pneumonias caused by *P. aeruginosa* or other Enterobacteriaceae, the Sanford Guide 2007 [66] recommends '21 days, often up to 42 days' as the duration of therapy. Discrepancies between quick pocket guides and randomized controlled trials sometimes contribute to confusion in the trenches.

Numerous evaluations have demonstrated that imipenem can select for emergence of resistant Gram-negative organisms such as *P. aeruginosa* (Figure 4) [67-72]. In an early meta-analysis [67], 18% of *P. aeruginosa* isolates developed resistance to imipenem during therapy for a variety of infections. Furthermore, the incidence was 32.8% (41/125) in respiratory tract infections. In a cohort evaluation, the hazard ratio for the emergence of resistant *P. aeruginosa* was greater for imipenem therapy (44; $P = 0.001$) than for piperacillin (5.2; $P = 0.01$), ciprofloxacin (9.2; $P = 0.04$), or ceftazidime (0.8; $P = 0.7$) therapy [68]. In a subsequent, open-label prospective evaluation [69], this hazard ratio was greater for imipenem therapy (7.8; 95% confidence interval 3.4 to 18.1) than for piperacillin-tazobactam (3.9; 95% confidence interval 1.3 to 11.9) or cefotaxime (9.3; 95% confidence interval 2.9 to 30.2) therapy.

A single mutation in *P. aeruginosa* confers resistance to imipenem; in contrast, resistance to newer carbapenems, such as meropenem, requires two separate and distinct mutations [62,73]. As a result, emergence of resistant *P. aeruginosa* appears to be less likely with the newer carbapenems than with imipenem [74]. The clinical significance of this may vary from center to center, and the percentage susceptibility of each carbapenem to various problematic pathogens should dictate which one is selected for an individual formulary.

Prolonged infusion as a means to optimize patient safety and enhance potential efficacy

Carbapenems are characterized pharmacodynamically as time-dependent killers. In other words, bacterial killing is optimized when the duration of time that the antibiotic concentration exceeds the minimum inhibitory concentration (MIC) of the infecting pathogen for a given period of the dosing interval [24]. The time above MIC requirements for optimal efficacy of carbapenems varies by pathogen and happens to be the least amount of time required compared with other β-lactam antimicrobials [75]. Certain adverse events are dose-dependent or concentration-dependent, including seizures, nausea, and vomiting. Consequently, extending the duration of the carbapenem infusion can maximize time above MIC and can be a particularly useful tool when dealing with pathogens such as *P. aeruginosa*, which have higher MIC values but remain within the susceptible or potentially intermediate resistant breakpoint range. In some cases, in which high MIC values are noted for the infecting organism, both increasing the dose and prolonging the infusion interval can result in an optimized time above MIC and improve the probability of a clinical response. Selecting a drug within the class that possesses the lowest MIC value for a particular pathogen also helps in resolving the pharmacodynamic equation, in simple terms, because lower MIC values require less drug to maintain an adequate time above MIC. This is commonly done in clinical practice, but for concentration-dependent killing agents such as the aminoglycosides. Tobramycin typically possesses twofold to fourfold lower MIC values than gentamicin for strains of *P. aeruginosa*. In this case, the magnitude of the ratio between the peak concentration and the MIC value is an important determinant of bacterial killing. Given that tobramycin and gentamicin have identical pharmacokinetic properties and achievable peak concentrations, simply choosing the aminoglycoside with the lowest MIC can double or quadruple the ratio of peak concentration to MIC.

Monte Carlo simulations have been performed for various carbapenem-pathogen combinations and dosing regimens. Meropenem 500 mg infused over a 3-hour period every 8 hours yielded a time above MIC comparable to 1 g meropenem infused over 1 hour every 8 hours or 500 mg imipenem infused over 1 hour every 6 hours [76]. In addition, the blunted peak concentrations observed with prolonged infusion times have been shown to be beneficial in terms of reducing the gastrointestinal adverse effects associated with imipenem therapy [72,77]. Prolonged or extended infusion of β-lactam therapy is preferred to continuous infusion, because intravenous therapy can be administered more frequently and the intravenous catheter is not tied up for the entire 24-hour day.

The ability to extend infusion durations in the clinic can be impeded by the duration of stability once the solution is

prepared. In this regard, imipenem is slightly less stable than meropenem, limiting its practical utility in clinical practice. In a comparative evaluation of the stability of both carbapenems in aqueous solution at room temperature, 10% degradation occurred after only 3.5 hours with imipenem, as compared with 5.15 hours with meropenem [78]. Future carbapenems would optimally have even longer stability in aqueous solution, improving the ability to extend infusion durations and increasing the number of indications for which extended infusions are approved. But these pharmacodynamic concepts are not new at all. Harry Eagle [79] demonstrated that continuous versus discontinuous administration of penicillin was an efficient and effective method of optimizing beta-lactam therapy in the late 1940s. Perhaps some 60 plus years later, we can take advantage of his observations at the bedside.

Conclusion
One of the chief concerns in prescribing antimicrobial therapy or selecting agents for hospital formularies is a drug's potential to cause harm. The harm can be a class effect or uniquely associated with a particular class member. No unexpected harms have been reported for FDA approved β-lactams for decades, since moxalactam caused serious complications associated with bleeding events. This is not to say we should be complacent about sensitivity to the potential for harms within this class. In contrast, drug classes such as the fluoroquinolones have been subjected to a great deal of scrutiny, given the checkered history of unexpected toxicities and withdrawals from the market. New methods for optimizing the pharmacodynamics of β-lactams with short half-lives (for example, prolonged infusions) have the potential not only to increase the time above MIC for pathogens with higher MIC values, potentially leading to enhanced efficacy, but also to blunt peak concentration-related toxicities. Because of their activity against a broad spectrum of resistant pathogens such as *P. aeruginosa* and extended-spectrum β-lactamase producing Enterobacteriaceae, the carbapenems are increasingly being incorporated into first-line therapy protocols and pathways for the treatment of serious health care associated infections. Ultimately, as with other drug classes, the carbapenems must be used judiciously. Antimicrobial stewardship programs can ensure that this class of antimicrobials, along with others, is used at the appropriate doses and, importantly, for the shortest possible time.

Competing interests
The author declares that they have no competing interests.

Acknowledgements

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