Antibiotics in anesthesia and critical care

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: P Moine; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: Sepsis is life-threatening organ dysfunction due to a dysregulated host response to an underlying acute infection. Sepsis is a major worldwide healthcare problem. An annual estimated 48.9 million incident cases of sepsis is reported, with 11 million (20%) sepsis-related deaths. Administration of appropriate antimicrobials is one of the most effective therapeutic interventions to reduce mortality. The severity of illness informs the urgency of antimicrobial administration. Nevertheless, even used properly, they cause adverse effects and contribute to the development of antibiotic resistance. Both inadequate and unnecessarily broad empiric antibiotics are associated with higher mortality and also select for antibiotic-resistant germs. In this narrative review, we will first discuss important factors and potential confounders which may influence the occurrence of surgical site infection (SSI) and which should be considered in the provision of perioperative antibiotic prophylaxis (PAP). Then, we will summarize recent advances and perspectives to optimize antibiotic therapy in the intensive care unit (ICU). Finally, the major role of the microbiota and the impact of antimicrobials on it will be discussed. While expert recommendations help guide daily practice in the operating theatre and ICU, a thorough knowledge of pharmacokinetic/pharmacodynamic (PK/PD) rules is critical to optimize the management of complex patients and minimize the emergence of multidrug-resistant organisms.

Keywords: Antibiotics; surgical prophylaxis; microbiota; septic shock; pharmacokinetic/pharmacodynamic (PK/PD)

Submitted Nov 09, 2022. Accepted for publication Nov 06, 2023. Published online Dec 13, 2023.
doi: 10.21037/atm-22-5585
View this article at: https://dx.doi.org/10.21037/atm-22-5585

Introduction

Sepsis is life-threatening organ dysfunction due to a dysregulated host response to an underlying acute infection (1-3). Sepsis is a major worldwide healthcare problem (1,3). An annual estimated 48.9 million incident cases of sepsis is reported, with 11 million (20%) sepsis-related deaths (1).

Administration of appropriate antimicrobials is one of the most effective therapeutic interventions to reduce mortality (3). The severity of illness informs the urgency of antimicrobial administration (3). Nevertheless, even used properly, they cause side effects and contribute to the development of antibiotic resistance (4). Both inadequate and unnecessarily broad empiric antibiotics are associated with higher mortality and also select for antibiotic-resistant germs (4,5). In this narrative review, we will first

discuss important factors and potential confounders which may influence the occurrence of surgical site infections (SSIs) and which should be considered in the provision of perioperative antibiotic prophylaxis (PAP). Then, we will summarize recent advances and perspectives to optimize antibiotic therapy in the intensive care unit (ICU) (6).

Surgical antibiotic prophylaxis (AP)

In Europe and the USA, SSI are one of the most common causes of hospital-acquired infections (7,8). They occur in up to 5% of patients who had surgery, and increase significantly hospital length of stay, morbidity and mortality, and costs of hospitalization (7-9). These infections are largely preventable and application of evidence-based strategies may prevent approximately 50% of SSIs (*Table 1*) (7-18).

SSIs are therefore a quality indicator and a pay-for performance P4P metric in the United States (19). The Surgical Care Improvement Project (SCIP) performance has promoted three perioperative antibiotic recommendations: (I) appropriate timing: prophylactic antibiotic (PA) received within 1 hour prior to surgical incision; (II) drug selection: appropriate PA selection consistent with published guidelines; (III) duration: PA discontinued within 24 hours after surgery end time (48 hours for cardiac patients) (4-10,19-23). Wherefore, SSI prevention guidelines are published by major scientific and professional organizations (10-12,18), and are periodically revisited (12,23). PAP, among other evidence-based recommendations, is one of the most effective strategies for preventing SSIs, and considered a standard of care (7,8,10,11,13,18,19,24,25). Nevertheless, these SCIP recommendations failed to provide improved surgical outcomes (26). These best practice measures may be too general and other potential contributing factors, both patient-specific and non-specific, might require some considerations in clinical practice (*Table 2*). Nonetheless, these considerations would concern both surgery and critically ill patients.

Effectiveness of selected antibiotic agents according to type of surgery

A fundamental question underlying the selection of antibiotics for PAP is whether the choice of specific intravenous antibiotics according to the type of surgery truly matters. The optimal choice of antibiotic for different types of surgery has not yet been definitively established (14). Current recommendations regarding choice of PAs are the result of consensus among multidisciplinary panels of experts and based on very limited evidence concerning relatively few agents, rather than based on high-quality evidence concerning true comparisons of various antibiotic options (14). However, evaluations of the association between appropriate antibiotic selection and SSI rates have identified trends approaching statistical significance; in addition, individual studies have shown significant differences in the occurrence of SSI between specific comparator antibiotics (27-30). For example, in orthopedic procedures, vancomycin as a sole agent was significantly and independently associated with higher SSI rates, compared to cefazolin, clindamycin, or vancomycin-cefazolin combination (26,31). Likewise, in a RCT comparing prophylactic ertapenem and cefotetan in colorectal surgery (CRS), significantly lower rates of SSIs were reported with ertapenem (32).

The above findings suggest that the agent selected for prophylaxis may indeed be important. Significant variations in effectiveness among the approved and accepted agents for SSI prophylaxis in colorectal and orthopedic surgeries have been reported (14,26,30,31). Such variability in reported efficacy is likely multifactorial and may be explained in part by the antibiotic spectrum of antimicrobial activity against bacteria most likely to contaminate the surgical site (SS), as well as by the potential development of antibiotic resistance over time. Furthermore, differences among antibiotics in terms of their pharmacokinetic (PK) and pharmacodynamic (PD) properties within different types of surgical patient populations may also explain observed variability in prophylactic effectiveness. Related to these PK/PD properties, differences in tissue penetration of antibiotics, the use of antibiotic loading doses, weight-based (or alternative) dosing strategies, and timely antibiotic redosing during prolonged surgical procedures may each play a role in antibiotic effectiveness; however, the interplay among all of these potential factors remains to be fully understood (33). PA effectiveness may also be explained by specific factors at the site of potential SSI, such as bacterial load, phase of bacterial growth, pH, or the presence or absence of oxygen at contaminated SSs (34). To compound the issue, other confounders such as surgical technique, specific patient factors such as age and obesity or comorbidities, and disease presentations likely influence the occurrence of SSIs (30). This issue is particularly relevant when patients report a β-lactam allergy. Several studies have suggested that the use of an alternative to β-lactam antibiotics in AP, such as clindamycin or vancomycin, is associated with an increased risk of SSIs and hospital length of stay (35-37). A β-lactam

Table 1 Evidence-based recommendations for the prevention of surgical site infections (7,8,10-18)—recommendations provided for adults[†]

Antibiotic prophylaxis[†]

- Indications
  - Operative procedures with a high incidence of SSIs, or when foreign materials are implanted—Altemeier II (15)
  - High morbidity attributable to SSI
- Optimal selection
  - Antibiotics effective against the pathogens most likely to be encountered during the surgery with a good diffusion in the targeted tissues (14)
  - Preferred β-lactams: first- and second-generation cephalosporins
  - Primarily agents not commonly used in curative antibiotic therapy
- Route
  - Intravenous administration
- Optimal timing
  - Before the surgical incision or within 60 minutes prior surgical incision
  - Vancomycin and fluoroquinolones within 60–120 minutes prior to incision
  - Timed such that a bactericidal concentration of the agent is established in the serum and tissues when the incision is made (10,12)
  - "At induction of anesthesia"
- Dosing
  - Single dose of prophylactic antimicrobial agent (12)
- Obese patients and weight-adjusted dosing
  - No recommendation/unresolved issue[‡]
- Intraoperative redosing during prolonged procedures
  - Re-dosing should be based on the half-life of the antibiotic [redosing after two half-lives of the drug (16,17)] and excessive blood loss (>1,500 mL)[§]
- Postoperative AP optimal duration
  - Surgical antibiotic prophylaxis should not be prolonged after completion of the operation or for less than 24 hours
  - "In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial agent doses after surgical incision is closed in the operating room, even in presence of drain" (10)

Other evidence-based recommendations

- Preoperative showering on at least the night before the operative day (soap or antiseptic agent)
- Decolonization with mupirocin ointment in nasal carriers of *S. aureus* undergoing cardiothoracic and orthopedic surgery
- Hair should either not be removed (use a clipper if absolutely necessary)
- Alcohol-based skin preparation
- Surgical hand preparation: scrubbing with antimicrobial soap and water or using alcohol-based hand rub
- Enhanced nutritional support
- Perioperative normothermia
- Blood pressure control/adequate volume replacement—goal-directed fluid therapy suggested
- Perioperative glucose control <200 mg/dL (between 110 and 150 mg/dL)
- Increased intraoperatively and post-extubation 80% FiO_2 (challenged) (13)

[†], each institution should develop guidelines/protocols for the proper surgical prophylaxis to standardize practices. [‡], randomized controlled trials to evaluate the benefits and harms of weight-adjusted parenteral antimicrobial prophylaxis dosing and its effect on the risk of SSI were not identified in the literature (10). It is recommended to increase the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in obese and morbidly obese patients: for cefazolin 3.0 g if >120 kg; for aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight; vancomycin should be dosed at 15 to 30 mg/kg (10,17). [§], randomized controlled trials to evaluate the benefits or harms of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of SSI were not identified in the literature (10). SSI, surgical site infection; AP, antibiotic prophylaxis; OR, operating room.

Table 2 Factors which likely contribute to surgical site infections and are not targeted by SCIP measures

Selection of perioperative antibiotics according to effectiveness in specific types of surgery
Variability in antibiotic pharmacokinetics within various type of surgical patients/populations
Antibiotic concentrations at the "site of infection"
Antibiotic pharmacokinetic/pharmacodynamic characteristics
Appropriate antibiotic dosing and redosing
Obesity
Multidrug-resistant organisms
Local antibiotic resistance patterns
Allergies

SCIP, Surgical Care Improvement Project.

allergy is reported in up to 15% of the cases in some studies (38). However, up to 90% of patients who declared penicillin allergy could in fact receive penicillin after testing (39). This may be explained by misclassification (e.g., diarrhea), by a phenomena of desensitization over time, or even because penicillins used in therapy do not share the lateral chain causing the allergic reaction (40).

Antibiotic concentration at the "site of infection"

PAP is not intended to sterilize the tissues or prevent all possible contaminants, but rather provide protection against contamination with a high bacterial inoculum of dominant skin or site-specific flora (41,42). The risk of SSI has been shown to be markedly increased if the SS is contaminated with $>10^5$ microorganisms per gram of tissue (41,43). If foreign material is present, a ten-thousand-fold lower bacterial inoculum may result in infection (41,43). One unresolved critical variable is the minimal bacterial inoculum required to establish infection in different types of surgical procedures involving different tissues and procedural characteristics, as well as in individual patients according to comorbidities (44). Nevertheless, AP is used to reduce the number of viable bacteria resulting from intraoperative contamination to a level that cannot overwhelm host defenses (41). To accomplish this, antimicrobial agents must be administered with a correct timing so that a concentration of drug which is targeted to achieve a maximal antibacterial activity is established in serum and tissues by the time the skin is incised (41). These "therapeutic" concentrations of PAs should also be maintained in both serum and tissues at the SS throughout the operation and until, at most, a few hours after the incision is closed (41). The ability of an antimicrobial to reach the target tissues is clearly a key determinant of clinical outcome (45). Tissues at various SSs are not homogenous compartments, and the distribution of drug molecules in plasma and tissue depends on their physical-chemical properties (45). It is assumed that only the "free" unbound antibiotic at the target site is responsible for antimicrobial effects (45), and therefore the most relevant concentration for antibiotic efficacy may be the unbound concentration within the extracellular or interstitial space of target tissues where many SSIs occur. Traditionally only serum drug concentrations are monitored during clinical use or PK studies, leaving drug concentrations to be estimated at the tissue sites of interest (46). And for most antibiotics used for routine SP, with the possible exceptions of vancomycin and the aminoglycosides, drug concentrations are not routinely monitored.

Key physicochemical properties of antibiotics such as lipid solubility, protein binding (PB), molecular weight, and degree of ionization are known to influence antibiotic distribution (47,48). Hydrophilic agents have typically a smaller volume of distribution (Vd) and primarily distribute into the extracellular spaces with overall limited tissue distribution. An increased Vd has been demonstrated for hydrophilic antibiotics in many critically ill patients (47-49). Conversely, lipophilic agents (such as fluoroquinolones, macrolides, metronidazole, clindamycin) have a larger Vd because they partition intracellularly and into adipose tissue to a greater extent. Third-spacing of drugs due to pathophysiological changes may result in significantly increased Vd of hydrophilic antibiotics yet is comparatively insignificant for lipophilic agents (47-50). In addition, more extensive plasma PB of antibiotics may decrease their ability to penetrate into many tissues (45). Variations in PB may alter the PK of highly bound antibiotics, thus potentially compromising their efficacy in SP where achieving sufficient tissue concentrations of drug is considered key to success (51,52). Finally, the antibiotic dose, time since drug administration, types of tissue at the SS, and the patient's comorbid conditions may also affect antibiotic distribution (53).

Variability in antibiotic pharmacokinetic within individual surgical patients and specific surgical populations

Large inter- and intra-individual variability is observed in

the PK of intravenous antibiotics. A wide range of drug exposure is often observed when administering a fixed dose of drug to large numbers of patients within a target patient population (54-56). The variability in antibiotic PK within various surgical patients or populations remains to be adequately assessed. There is a lack of well-designed antibiotic PK studies within surgical populations, and population-PK models are almost non-existent. Their potential impact on appropriate drug dosing are therefore not well understood. Antibiotic PK/PD properties including the Vd, degree of PB, routes of drug metabolism, and rates of hepatic or renal drug clearance (CL) may be substantially altered by numerous patient-specific characteristics: underlying comorbidities such as obesity, renal or liver impairments; presence and degree of inflammation; need for cardiopulmonary bypass; complex and prolonged procedures such as liver transplant surgery; and critical illness resulting from trauma, sepsis, burn, or neurological insult (57). For example, both Vd and CL may be either increased or decreased in critically ill patients (58-60). Significant capillary leak syndromes, aggressive fluid resuscitation/loading, blood product transfusions, reduction in albumin serum concentration, advanced liver disease, presence of extra-corporal circuits, burns, trauma, surgical procedures, and positive pressure ventilation have all been shown to contribute to alterations in the PKs of many drugs (47,49,57). In addition, maldistribution of blood flow in the microcirculation may further decrease drug concentrations in certain tissues (49). The clinical importance of alterations in Vd and CL is particularly relevant for hydrophilic antimicrobials, such as β-lactams, vancomycin, linezolid, aminoglycosides or colistin (57). Although it is possible that some physiological alterations (e.g., renal impairment) may actually improve the PK/PD performance of perioperative antibiotics in some surgical patients, the potential for antibiotics to be adversely affected by such alterations with resultant increased risk of SSI is also highly likely and of greater concern. Furthermore, PK/PD alterations occurring within an individual patient may change according to the varying stages of illness, providing ample opportunity for significant intra-patient variability over time (57).

Again, the PK/PD properties of antibiotics in specific surgical populations or critically ill patients, and the corresponding clinical significance are not well characterized. The optimal dosing of antibiotics for surgical prophylaxis (SP) remains elusive. The duration of AP is generally limited to 24 hours postoperatively, and most antibiotics used prophylactically are generally well tolerated by patients. Therefore, the major concern with optimized dosing of perioperative antibiotics is related to insufficient dosing resulting in increased risk of SSI rather than excessive dosing resulting in drug accumulation and toxicity. Because significant and relatively unpredictable variability of PK parameters may exist within individual patients, the typical "one dose fits all" approach to AP which is currently used is likely flawed.

Antibiotic pharmacokinetic/pharmacodynamic PK/PD characteristics

Antibiotics are classified on the basis of their patterns of antibacterial activity as concentration dependent or time-dependent agents (*Table 3*) (3,6,55,61-67). The PK/PD indices which are thought to best represent the antibacterial activity of concentration-dependent antibiotics are the ratio of maximum serum antibiotic concentration (Cmax) to MIC (Cmax/MIC) and/or the ratio of the area under the concentration-time curve during a 24-hour dosing period ($AUC_{0–24}$) to MIC ($AUC_{0–24}$/MIC), whereas time-dependent antibiotics are best represented by the duration of time (expressed as a percentage of a given dosing interval or period) in which unbound antibiotic concentrations exceed the MIC (*f*T>MIC) (34,61).

Time-dependent antibiotics

β-lactams, the most commonly prescribed family of antibiotics for SP and ICU patients (12), are considered time-dependent antibiotics with *f*T>MIC being the best predictor of efficacy (34,54,61,66,68,69). However, extrapolations from neutropenic animal models describe differences among each β-lactam/organism combinations regarding the specific percentage of *f*T>MIC which is needed in order to achieve maximum efficacy (61). It has been proposed that bacteriostatic effects, rather than bactericidal, may be sufficient to achieve optimum antibacterial efficacy in non-neutropenic hosts (61); *f*T>MIC values required for bacteriostasis are approximately 29–34%, 35–55%, and 20–26% for penicillins, cephalosporins, and carbapenems, respectively (54,61,68). On the other hand, achievement of the maximal bactericidal effect requires *f*T>MIC of 50%, 60–70% and 40%, respectively for these β-lactam classes (54,61). *In vitro*, *in vivo*, and clinical studies have also suggested that larger drug exposures may be required in certain populations (70-75). In a febrile neutropenic population treated with

Table 3 *In vitro* PK/PD parameters correlating with antimicrobial efficacy

Bactericidal pattern activity *in vitro*	Antimicrobial agent	Physical properties	PK/PD index associated with bacterial killing	Drug concentration target	PK/PD optimization
Concentration-dependent	Aminoglycosides	Hydrophilic	Cmax/MIC	Cmax/MIC 8–10	30 min infusion and TDM
	Fluoroquinolones	Lipophilic	AUC_{0-24}/MIC or Cmax/MIC	AUC_{0-24}/MIC >125–250	
	Colistin	Hydrophilic	AUC_{0-24}/MIC	Unknown	
	Daptomycin	Hydrophilic	AUC_{0-24}/MIC	AUC_{0-24}/MIC >200–600	
Time-dependent	Penicillins	Hydrophilic	T>MIC	Cmin >MIC, *f*T >4–5, MIC 50–100%	Extending the %*f*T>MIC (LD & EI or CI, and TDM)
	Cephalosporins	Hydrophilic	T>MIC		
	Monobactams	Hydrophilic	T>MIC		
	Carbapenems	Hydrophilic	T>MIC		
	Vancomycin	Hydrophilic	AUC_{0-24}/MIC	AUC_{0-24}/MIC 400	LD and CI & TDM
	Linezolid	Lipophilic	AUC_{0-24}/MIC	*f*AUC_{0-24}/MIC ≥80–120, Cmin 2–8 mg/L	
	Clindamycin	Lipophilic	AUC_{0-24}/MIC	%T>MIC 85%	

PK/PD, pharmacokinetic/pharmacodynamic; MIC, minimum inhibitory concentration; Cmax/MIC, ratio of maximum serum antibiotic concentration to MIC; AUC_{0-24}/MIC, ratio of the area under the concentration-time curve during a 24-hour dosing period (AUC_{0-24}) to MIC; *f*T>MIC, duration of time (expressed as percentage of dosing interval or period) in which unbound antibiotic concentrations exceed the pathogen MIC; LD, loading dose; EI, extended infusion; CI, continuous infusion; TDM, therapeutic dosing monitoring; LD, loading dose.

meropenem, patients with a calculated median *f*T>MIC of 59% had a poor clinical response compared to those with *f*T>MIC >75% (76). This study also demonstrated a significant association between increasing %*f*T>MIC and increased probability of favorable clinical response (76). Other clinical data also suggest that higher and more prolonged exposure is associated with improved outcomes in critically ill patients (55,77-79). In an analysis of cefepime in gram-negative infections, clinical cure and microbiological eradication rates were improved when *f*T>MIC reached 100% (80). Similar associations of *f*T>MIC with drug efficacy for SP do not exist; however, based on consistency in other patient populations, it is reasonable to extrapolate that *f*T>MIC may also be applicable to surgical populations in the setting of PAP.

For the treatment of established infections in humans, the optimal %*f*T>MIC remains controversial and definitive values have yet to be established in specific patient populations. Moreover, whether time-dependent bactericidal action of β-lactams is achieved at any concentration above the MIC or whether some dose dependency is still operative is unclear (70,75,80). Data suggest that maximum bactericidal activity of β-lactams occurs at concentrations approximately ≥4–5 times the MIC for the entire dosing interval. Also, an association between AUC_{0-24}/MIC and outcomes has been described for the cephalosporins (78,81-86), further suggesting an element of concentration dependency in the activity of these drugs since AUC_{0-24} reflects both the magnitude and duration of drug exposure. Moreover, there is a clear relationship between the AUC_{0-24}/MIC parameter and the risk of development of bacterial resistance (86). This concentration-dependent effect may be observed with different pathogens, more resistant organisms or large inoculum sizes (69,87,88).

Based on available data from a variety of studies, it follows that not all β-lactams necessarily exhibit the same pharmacodynamic behavior in all organisms (77,78,80,87-90), or in patients with severe/life-threatening bacterial infections and/or infections caused by multidrug-resistant organisms (MDRO) (49). Evidence is lacking to clearly and definitively show that PD targets and response rates with β-lactams should be the same for different therapeutic endpoints, for different populations, among different pathogens, or even among strains of the same pathogen species with different antibiotic susceptibilities.

Given the previous discussion, optimal PD targets for PAP are even more unclear since all currently established PD targets concern treatment of infection rather than prevention of infection (established tissue infection rather

than tissue contamination). Whether currently established PD targets for treatment of infection are applicable in determining the antibiotic dosages for SP has not been adequately studied (52,53,91,92). According to current guidelines, the goal of PAP is to achieve adequate free serum and tissue drug concentrations that exceed the MICs for pathogens most likely to contaminate the SS across the period of potential contamination (12,22,23). The importance of adequate antibiotic concentrations at closure in the prevention of SSI has been previously shown (22,93,94), and the SCIP project also recommends dosing to ensure adequate antimicrobial concentrations until wound closure (12,22,23). Because intra-operative contamination may occur at any time during the procedure, a β-lactam PD target of *f*T>MIC of 100% over the full duration of the surgical procedure is a reasonable goal for optimization of β-lactam prophylactic therapy (51-53), especially considering the many uncertainties of β-lactam PK/PD in various surgical populations and the lack of literature to the contrary. Nevertheless, it cannot be ruled out that Cmax/MIC and/or AUC_{0-24}/MIC may also perhaps play a role in predicting optimal β-lactam activity in prophylactic therapy. Clearly, the optimal PK/PD parameters for β-lactams in SP remain to be established.

Concentration-dependent antibiotics

While the focus of this discussion has been on the β-lactams, similar uncertainties regarding optimal PK/PD targets for concentration-dependent antibiotics also exist. While Cmax/MIC and AUC_{0-24}/MIC are the PK/PD parameters associated with concentration-dependent antibiotics, maintaining adequate concentrations at surgical wound closure have also been shown to be associated with reduced SSI during prophylactic aminoglycoside use (93). The optimal PD targets for concentration-dependent antibiotics in prophylaxis become equally uncertain when considering variables such as inoculum size and the potential timing of bacterial contamination (51,52). Unless the antibiotic has unusually high penetration and long persistence in tissues, achieving a high Cmax/MIC ratio prior to surgical incision should have no benefit if a high-inoculum bacterial contamination occurs near the end of a prolonged surgical procedure.

Most published antimicrobial PK/PD indices are based on antibiotic concentrations in the blood rather than in tissues. Tissue concentration of antibiotic at the wound site at the time of potential bacterial contamination is a critical factor in determining the efficacy of prophylaxis, but data related to tissue penetration of antibiotics are limited and highly variable among various studies (53). In heterogeneous patient populations, extrapolating optimal PK/PD indices to an outcome (SSI) which may be relatively infrequent in many types of procedures becomes somewhat problematic from the perspective of conducting meaningful clinical studies. Finally, as already underlined, the activity of the same antibiotic may be variably influenced by specific factors at the site of contamination (34,51).

Issues related to appropriate antibiotic dosing and redosing

Selection and dosing of antimicrobials based on PK/PD principles has become common in order to optimize therapeutic outcomes in the treatment of infections and to prevent the emergence of resistance. As discussed, use of these same PK/PD principles for evaluating antibiotics for SP is largely unsupported by clinical evidence and remains controversial (51,53,62). The actual guideline-recommended drugs and dosing regimens have been relatively unchanged over the past 20 years (12,23). Limited published data exist regarding appropriate antimicrobial selection and dosing for prophylaxis. To compound the problem, the antibiotic susceptibilities of clinically isolated pathogens have substantially changed over the past two decades while recommended drug doses have remained mostly unchanged (53). Thus, it is questionable whether appropriate doses and dosing frequencies of PAs are currently being used (53).

For example, standard dosing of ertapenem (1 g) was demonstrated to be more effective than cefotetan (2 g) in the prevention of SSI in patients undergoing elective CRSs (32). Whilst selection of a specific antimicrobial agent is only one of many considerations in reducing SSI rates, the primary reason for cefotetan failure in this study was most likely inferior achievement of optimal PK/PD targets against key organisms compared with ertapenem (33,53,95). Applying currently accepted PK/PD principles of antibiotic dosing and prediction models (i.e., Monte Carlo Simulation), cefotetan was shown to have extremely poor predicted PK/PD performance against *Escherichia coli*, *Bacteroides fragilis* and *Staphylococcus aureus* over the first 3–4 hours post-infusion (53). Cefotetan failed to meet any specified PK/PD target (e.g., *f*T>MIC of 100%) at any dose (1 and 2 g doses) or at any time point after dosing against any of the three targeted organisms, suggesting a cefotetan 2 g dose is entirely inadequate for routine use as a prophylactic agent in CRS (53). In comparison, ertapenem

1 g had virtually 100% probability of achieving 100% *f*T>MIC across the entire 4-hour period post-infusion and against all three organisms (53).

The optimal strategy for intraoperative redosing of PAs is still debated. According to published guidelines, redosing of a drug is needed to ensure adequate serum and tissue concentrations of the antibiotic if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss (12,23). Increased duration of surgery is a well-known significant risk factor for SSIs (32,96,97). The relative risk of SSI significantly increases after roughly 2 hours in the operating room and increases further with every extra hour of operative time thereafter (97). However, there are no convincing data demonstrating significantly lower SSI rates with multiple-dose regimens versus single doses (12,91,92). It can be argued that additional dosing may increase the risk of resistant organisms and *Clostridium difficile* colitis (91). Nonetheless, it is recommended that additional intraoperative doses may be needed to optimize the potential effectiveness of the prophylaxis depending on the length of surgery, antibiotic PK/PD characteristics, and individual patient characteristics (51-53). Administration of β-lactams via extended or continuous infusions after an initial loading dose may optimize β-lactam PK/PD characteristics without increasing toxicity or cost (22). In addition, administering higher doses by extended infusion may also allow for more optimal drug exposures against strains of less-susceptible organisms with relatively high MICs (61). These alternative administration methods have already been suggested to optimize the PD profile of β-lactams for both therapeutic treatment of infection and SP (98,99).

In adults, the dosing of many antimicrobials is not typically based on body weight as is common in children (12,100). Administration of a "standard" dose instead of a weight-based dose may be insufficient to achieve adequate antibiotic concentrations in blood and tissues in many adults, particularly in patients with high body weight, increased body mass or abnormal mass composition (100). It was shown that up to 80% of patients undergoing elective total joint and spine surgery who receive vancomycin are under-dosed when given a standard 1-g dose preoperatively rather than 15 mg/kg (101). In that study, a 1 g dose would have been appropriate only for patients weighing <67 kg (101). Although weight-based dosing appears to offer clear PK/PD advantages in certain patient populations, data to support such recommendations are scarce and weight-based dosing is recommended for only three drugs in current prophylaxis guidelines (10,12).

Obesity

Differences in proportion of adipose tissue, lean muscle tissue and fluid status in obese patients can greatly affect antibiotic PK through alterations in drug distribution, metabolism and excretion (102-104). The Vd may be dramatically different compared to normal-weight patients (105). Beyond a greater percentage of adipose tissue compared to non-obese individuals, physiological changes such as tissue blood flow and changes in cardiac output may also alter drug distribution of both hydrophilic and lipophilic drugs in obesity (105). In addition, physiological changes in the liver and kidneys can alter metabolism and excretion (105). However, as already discussed, the dosing of many prophylactic antimicrobials in adults is not based on body weight or composition despite the known physiological differences and PK alterations known to occur in obese patients (12,100,105). Even if comprehensive reviews on antibacterial use in obese patients are available in the literature (65,106,107), limited published data exist regarding appropriate dosing of antimicrobials for prophylaxis in this population (56). Evidence-based antibiotic dose adjustments for obesity are lacking for many drugs, including antimicrobials for which optimal dosing in this population continues to present significant challenges (105,107,108). Again, the standardized "one dose fits all" approach to antibiotic dosing for prophylaxis cannot be assumed adequate for obese patients (107). In the study comparing ertapenem and cefotetan in CRS, nearly 30% of the enrolled patients were obese [body mass index (BMI) >30 kg/m^2], yet no dose adjustments were made for either drug (32,102). Rates of SSI were significantly higher in patients with a BMI ≥30 kg/m^2 compared to those with BMI <30 kg/m^2 regardless of the antibiotic administered, perhaps because drug doses were inadequate for obesity (102). It is generally stated in published recommendations that PAs should be given in doses which are adequate based on patient weight, adjusted dosing weight, or BMI (12,23); however, specific doses for individuals with various BMI are not often provided. The 2005 National Surgical Infection Prevention project made weight-based dose recommendations for adults, but these doses were primarily derived from published pediatric recommendations (12,23). In 2013, although AP dosing was discussed in the context of obesity, weight-based dosing recommendations for adults were not addressed due to a lack of clinical data (12). If some authors argue that increasing the dose of hydrophilic antibiotic such as cephalosporins may be unable to increase

tissue concentration, recent observational data suggest that higher dose of cefazolin would be more effective (109,110). Appropriate drug dosing for SP in obese patients is clearly an area in which well-designed clinical studies and evidence-based recommendations are sorely needed.

Multidrug resistant organisms (MDROs)

Emerging new pathogens and changing patterns of antibiotic resistance are potential factors further contributing to SSIs during use of traditional prophylactic drugs. *Enterococcus* species, methicillin-susceptible (MSSA) and methicillin-resistant *S. aureus* (MRSA) are playing an increasingly important role in SSIs (32,103,104,111,112). Approximately 50% of SSI complicating knee and hip primary arthroplasty are attributable to *S. aureus* and 40% of these infections are caused by MRSA (108). More challenging gram-negative bacteria such as extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (ESBL-PE), inducible AmpC-cephalosporinase-producing *Enterobacteriaceae*, and multidrug-resistant *P. aeruginosa* are also more commonly found in SSIs (32,103,104,111,113-115). The prevalence of carriage of resistant GNB among patients about to undergo surgery in which endogenous GNB are the main cause of SSI varies from 1% to 46% and varies by geography and over time (116). The increasing proportions of SSIs caused by organisms intrinsically resistant to accepted β-lactams may seriously confound the optimal choice of antibiotic for SP (112,116). Patients colonized with ESBL prior to CRS have an increased risk of SSI from ESBL (113). The data establishing the efficacy of these accepted β-lactams for SP were generated before the appearance of these MRDOs (14). Exemplifying this point, the study comparing ertapenem and cefotetan for CRS found cefotetan resistance in 67% and 46% of isolated SSI pathogens in the cefotetan and ertapenem arms, respectively (32). Additionally, 16% of isolated pathogens in both treatment groups were also resistant to ertapenem (102). In a multicenter prospective nonrandomized, nonblinded, interventional study, presurgical screening for ESBL-PE carriage before CRS and personalizing prophylaxis for carriers is efficacious in reducing SSIs (117). In intention-to-treat analysis, any type of SSI rates [45/209 (21.5%) in the baseline phase as compared to 47/269 (17.5%) in the intervention phase] did not reach statistical difference, nor deep SSI rates (117). Thus the authors did not prove the effectiveness of the intervention (117). The as-treated analysis showed that ertapenem prophylaxis for ESBL-PE carriers significantly decreased the risk of SSI (a 33% reduction) and the risk of SSI caused by ESBL-PE (a 86% reduction), supporting the efficacy of the personalized prophylaxis strategy (117).

In the US, standard AP regimens (cefazolin or cefuroxime) used in coronary artery bypass graft and hip/knee arthroplasty procedures had inadequate activity against more than 50% of reported SSI pathogens (118). When vancomycin and/or an aminoglycoside were combined with cefazolin or cefuroxime, 14% to 19% of SSI pathogens were still resistant to these regimens (104). Of interest, the organism most commonly associated with antimicrobial failure in this study was MSSA, a pathogen which was susceptible *in vitro* to all administered regimens (104). This finding further highlights that the problem of SSI is not only one of appropriate drug selection, but also likely involves a constellation of aforementioned host-specific, pathogen-specific, PK/PD-related, and procedure-specific variables.

There is scant evidence to suggest that broad-spectrum antimicrobial agents result in lower rates of postoperative SSI compared with "older" antimicrobial agents with a narrower spectrum of activity, with notable exceptions being ertapenem in CRS, or prophylactic use of therapeutic antibiotics based on the results of preoperative bile cultures in hepato-pancreatico-biliary (HPB) surgery or broad-spectrum antibiotics in pancreatoduodenectomy (12,32,112,119). Some data have even demonstrated an association between development of SSI due to MSSA and use of vancomycin as a sole agent for AP (120), and that the addition of anti-MRSA agents (including vancomycin) does not reduce the incidence of MRSA infections (121). Likewise, there is little evidence and no consensus regarding AP in a patient with past infection/colonization with MDROs, nor in patients with risk factors for MDROs (12,116). The frequent use of broad-spectrum antimicrobials for prophylaxis may further contribute to the selection of drug-resistant pathogens, thereby decreasing prophylaxis efficacy and future options (104,111). Whether past infection or colonization with MDROs, or potential risk factors for MDRO, led to significant differences in effectiveness of AP and therefore require more broad-spectrum "customized patient-specific" regimens rather than the more traditional, narrow-spectrum "standardized population-based" regimens for PAP is still unclear. This topic was not addressed in recent guidelines for SSI prevention issued by the US Centers for Disease Control (10) and the World Health Organization (11). For other professional groups, the decision to alter PAP in

known carriers of MDROs must take into consideration the pathogen, its susceptibility profile, the host, the procedure, and the distance between the carriage site and the operative site (12,116).

For cardiac and orthopedic procedures in patients known to be at high risk for MRSA infection or in hospitals with high rates of MRSA related SSIs, glycopeptides are recommended as part of the perioperative antimicrobial regimens (12,23). However, patients may still develop gram-positive and/or MRSA infections despite the use of glycopeptides as recommended (52,118,121,122). A previous study compared cefazolin to vancomycin for prophylaxis in patients undergoing cardiac surgery in an institution with a high prevalence of MRSA (123). Although not statistically different, patients who developed an SSI following cefazolin prophylaxis were more likely to be infected with MRSA, whereas those who received vancomycin were more likely to be infected with MSSA (123). Furthermore, while the choice of antimicrobial agent used for prophylaxis may have influenced the infecting organisms, it did not apparently alter the observed infection rates (118,122). These findings are consistent with those reported in the orthopedic literature (124) and have been confirmed by three systematic reviews (52,125-127).

Exceptions to the above findings regarding the tailoring of PAs to known risk factors for MDROs may include transplant recipients with history of colonization or infection with resistant pathogens, assuming that these pathogens are relevant to SSIs in the planned procedure (12,128). However, targeted or individualized perioperative antimicrobial regimens have not been clearly shown to result in reduction in SSI rates in such circumstances (103,129). No rigorous studies have formally addressed optimal prophylaxis for these patients (129). Some data provides evidence for screening for MDRO carriage before elective orthopedic, cardiac and colorectal surgeries and personalized AP for patients who screen positive (117).

Antibiotic-associated harm

Antibiotics-associated harm are more and more highlighted, such as drug toxicity, mitochondrial dysfunction, allergic reaction, microbiota alteration and *C. difficile* colitis that has been shown to be as frequent after AP than after antibiotic treatment (130,131). Moreover, PAs side effects are poorly reported (132). To ensure PA effectiveness and limit the risk of side effects, PAP must follow recommendations published by major organizations (10-12,23). Each institution should develop protocols for the proper surgical prophylaxis to standardize practices.

Antibiotics in critical care

Septic shock and sepsis are medical emergencies and, treatment and resuscitation should begin immediately (3). Early administration of appropriate antibiotics is one of the most effective interventions to decrease mortality in patients with sepsis (3). On a given day in ICU, 48% to 70% of the patients are receiving empirical or definite antimicrobial treatments (6,133). International guidelines for management of sepsis and septic shock are published, and periodically updated (3). Antimicrobial therapy recommendations are summarized in *Table 4*.

The clinical diagnosis of sepsis (suspected or documented infection complicated with life-threatening organ dysfunction) is challenging and largely over-estimated in ICU (6,137). Up to 43% of patients treated for suspected sepsis are unlikely to have an infection (137). Aggressive empirical antibiotic use—antibiotics started as soon as infection is suspected before microbiological evidence of infection—might be harmful in ICU patients (138). Patients managed under an aggressive antibiotic therapy had a more rapid start of treatment, a lower chance of receiving initially appropriate treatment, a prolonged duration of antimicrobial treatment, and significantly lower survival (138). In the last Surviving Sepsis Campaign recommendations, "for adults with possible sepsis without shock, it is suggested a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized" (3). "For adults with a low likelihood of infection without shock, it is even suggested to defer antimicrobials while continuing to closely monitor the patient" (3). Molecular diagnostics (PCR-based systems targeting selected pathogens and resistance markers), performed alongside conventional cultures, may accelerate the diagnosis process, identifying pathogens and their susceptibilities faster than conventional methods (6). Nevertheless, further studies are warranted to fully appraise their impact on patient outcome (6).

If the appropriateness of the initial empiric antibiotic treatment is directly correlated to the mortality (6,139-141), the dosing selection of the appropriate antibiotic treatment is challenging (*Table 6*) (6,55,142-145). Roberts and colleagues have shown large variability of β-lactam antibiotic plasma concentrations in critically ill patients and,

Table 4 Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic shock in adult patients—antimicrobial administration recommendations (3)

Main considerations	Recommandation
Indications	• Septic shock and sepsis
	• "For possible sepsis without shock, rapid assessment of the likelihood of infectious versus noninfectious causes of acute illness"
Optimal timing	• Possible septic shock, or a high likelihood for sepsis: administer antimicrobials immediately, ideally within 1 h of recognition
	• Possible sepsis without shock; it is suggested a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognized
	• Low likelihood of infection and without sepsis and/or shock: defer antimicrobials while continuing to closely monitor the patient
Optimal selection	• The empiric antimicrobial regimen includes at least one effective agent active against the most common causative organisms. The optimal choice depends on the source of infection, potential causative agents, local/regional prevalence of resistant organisms, local antibiogram, patient characteristics and risk factors for resistant organisms[†], and the severity of illness
	• According to the risk of MDR organisms[†]:
	o High risk: it is suggested using two GNB agents
	o Low risk: it is suggested a single GNB agent for empiric treatment
	• According to the risk of MRSA[‡] (sepsis or septic shock):
	o High risk: empiric GNB broad-spectrum therapy with MRSA coverage
	o Low risk: it is suggested against using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage
	• According to the risk of fungal infection[§] (sepsis or septic shock):
	o High risk: it is suggested using empiric antifungal therapy over no antifungal therapy
	o Low risk: it is suggested against empiric use of antifungal therapy
Antimicrobial combination	• According to the risk of MDR organisms[†]:
	o High risk: it is suggested using double GNB coverage for empiric treatment over one gram-negative agent
	o Low risk: it is suggested against using two gram-negative agents for empiric treatment, compared with one gram-negative agent
Route	• Intravenous administration
Dosing and delivery of antibiotics	• For sepsis or septic shock, it is
	o Suggested using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion
	o Recommended optimizing dosing strategies of antimicrobials based on accepted PK/PD principles and specific drug properties
De-escalation	• For sepsis or septic shock,
	o Daily assessment for de-escalation of antibiotics over using fixed durations of therapy without daily reassessment for de-escalation
	o It is suggested against using double gram-negative coverage once the causative pathogen(s) and the susceptibilities are known
	o Once both the pathogen(s) and susceptibilities are known, it is encouraged stopping an antimicrobial that is no longer necessary or changing an antimicrobial to narrow the spectrum

Table 4 *(continued)*

Table 4 *(continued)*

Main considerations	Recommandation
Discontinuation-duration	• "For suspected sepsis or septic shock but unconfirmed infection, it is recommended continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected"
	• For an initial diagnosis of sepsis or septic shock and adequate source control:
	o We suggest using shorter over longer duration of antimicrobial therapy (*Table 5*)
	o Where optimal duration of therapy is unclear, we suggest using procalcitonin and clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone

†, risk factors for MDR pathogens (3,6): proven infection or colonization with antibiotic-resistant organisms within the preceding year (3), local prevalence of antibiotic-resistant organisms (3), hospital-acquired/healthcare-associated infection (*vs.* community-acquired infection) (3), broad-spectrum antibiotic use within the preceding 90 days (3), concurrent use selective digestive decontamination (3), travel to a highly endemic country within the preceding 90 days and hospitalization abroad within the preceding 90 days (3), advanced poor hygiene practices in hospital, co-morbid illnesses (6), immunosuppression (6), recent hospital stay (or ICU stay) (6), prior antifungals (6), broad-spectrum antibiotics or with potent activity against intestinal anaerobes are also risk factors for MDR pathogens (6). ‡, MRSA risk factors (3): prior history of MRSA infection or colonization, recurrent skin infections or chronic wounds, recent IV antibiotics, presence of invasive devices, hemodialysis, recent hospitalization and severity of illness. §, risk factors for fungal infection (3): Candida colonization at multiple sites, neutropenia, surrogate markers such as serum beta-D-glucan, immunosuppression, severity of illness, longer ICU length of stay; central venous catheters, persons who inject drugs, total parenteral nutrition, broad spectrum antibiotics, gastrointestinal tract perforations and anastomotic leaks, emergency gastrointestinal or hepatobiliary surgery, acute renal failure and hemodialysis, severe thermal injury, prior surgery. MDR, multidrug resistant; GNB, gram-negative bacteria; MRSA, meticillin-resistant *S. aureus*; PK/PD, pharmacokinetic/pharmacodynamic; ICU, intensive care unit; IV, intravenous.

Table 5 Duration of antimicrobial therapy in ICU—shorter versus longer therapy according to clinical syndrome (3,134-136)

Diseases	Short course therapy (days)	Long course therapy (days)
Community-acquired pneumonia	3–5	7–10
Nosocomial pneumonia (including ventilator-associated pneumonia)	7–8	10–15
Bacteremia	5–7	10–14
Intra-abdominal infection	4–8	10–15
Skin infections (cellulitis, major abscesses, wound infections)	5–6	10
Urinary tract infections	5	10

ICU, intensive care unit.

thus, <50% of patients achieved PK/PD targets (defined as 50% $fT>4\times MIC$) (55). Underdosing of antibiotics is thus frequent in ICU patients, and these patients are less likely to have positive clinical outcome (6,55). Variability in antibiotic pharmacokinetics within individual surgical or ICU patients is already developed above. Therefore, initial higher doses and routine therapeutic drug monitoring (TDM) appears necessary to avoid underdosing (maximizing drug efficacy through optimized PK), as well as overdosing (drug-related toxicity) (6). To properly achieve PK/PD targets and allow for a personalized antibiotic dosing, both the drug serum concentrations and the actual MICs of the causative pathogens need to be measured to treat sepsis and septic shock (55). Moreover, to increase the likelihood for PK/PD attainments and potential therapeutic success, maintaining exposure via continuous or extended infusion of β-lactams (which display a time-dependent mechanism of action) may be of great clinical benefits for critically-ill patients with sepsis and septic shock, particularly with higher MIC pathogens (146-148).

Also already underlined, emerging new pathogens, changing patterns of antibiotic resistance and continued development of new types of resistance are contributing to increased morbidity, mortality, length of stay in ICU and

Table 6 Recommended doses of initial empirical antibiotics in ICU patients with sepsis and septic shock (6,142-145)

Antibiotics	Timsit *et al.* 2019	IDSA guidelines (Kalil *et al.* 2016, Tamma *et al.* 2022)
Ceftaroline	600 mg q12h	–
Ceftazidime/avibactam	2.5 g q8h	2.5 g q8h, EI 3 h
Ceftolozane/tazobactam	1.5 g q8h; or 3 g q8h (VAP)	3 g q8 h, EI 3 h
ATM/AVI	6,500 mg ATM/2,167 mg AVI q24h on day 1 followed by 6,000 mg ATM/2,000 mg AVI q24h	CAZ-AVI 2.5 g q8h EI 3 h + Aztreonam: 2 g q8h EI 3 h, infused during CAZ-AVI infusion
Meropenem/vaborbactam	2 g/2 g q8h	4 g q8h, EI 3 h
Cefiderocol	2 g q8h	2 g q8h, EI 3 h
Imipenem/relebactam	500 mg/250–125 mg q6h	1.25 g q6h, EI 30 min
Eravacycline	1 mg/kg q12h	1 mg/kg q12h
Plazomicin†	15 mg/kg q24h	15 mg/kg × 1 dose
Tedizolid	200 mg q24h (IV or oral)	–
Piperacillin/tazobactam	4.5 g q6h CI	4.5 g q6h§
Ceftazidime	6 g q24h CI	2 g q8h§
Cefepime	2 g q8h or CI	2 g q8h, EI 3 h
Aztreonam	1 g (2 g) q8h	2 g q8h
Imipenem/cilastatin	500 mg (1 g) q6h	500 mg q6h§
		ESBL/AmpC: EI 30 min
		CRE & CRAB: EI 3 h
Meropenem	1 g (2 g) q8h or CI	ESBL/AmpC: 1–2 g q8h EI 30 min
		CRE & CRAB: 2 g q8h EI 3 h
Ertapenem	–	1 g q24h, EI 30 min
Tigecycline	100–200 mg loading dose, then 50–100 mg q12h	200 mg loading dose, then 100 mg q12h
Gentamicin†	7 mg/kg/day q24h	7 mg/kg/day q24 h
Amikacin†	25–30 mg/kg/day q24h	20 mg/kg q24h
Colistin†	9 MU loading dose, then 4.5 MU q8–12 h	5 mg/kg IV loading dose, then 2.5 mg × (1.5 × CrCl + 30) daily, divided q12h¶
Polymixin B	–	2.5–3.0 mg/kg/d divided in 2 daily IV doses
Vancomycin†	15–30 mg/kg LD, 30–60 mg/kg every 12 h, 6 h or CI	15 mg/kg IV q8–12h, consider a LD of 25–30 mg/kg × 1 for severe illness‡
Linezolid	600 mg q12h	600 mg q12h
Ciprofloxacin	–	400 mg q8h–12h
Levofloxacin	–	750 mg q24h
Trimethoprim-sulfamethoxazole	–	8–12 mg/kg/day trimethoprim IV/PO divided q8–12h (max 960 mg trimethoprim q24h)

†, drug levels and adjustment of doses and/or intervals required (142,143). ‡, vancomycin target trough level: 15–20 mg/L. §, extended infusions may be appropriate (143). ¶, dosing is based on colistin-base activity CBA: one million IU of colistin is equivalent to about 30 mg of CBA which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10,000 units) (142-145). ICU, intensive care unit; IDSA, Infectious Diseases Society of America; EI, extended infusion; VAP, ventilator-associated pneumonia; ATM, aztreonam; AVI, avibactam; CAZ, ceftazidime; CI, continuous infusion; AmpC, ampicillin chromosomal cephalosporinase; CRE, carbapenem-resistant *Enterobacteriaceae*; CRAB, carbapenem-resistant A baumannii; IV, intravenous; LD, loading dose.

Table 7 Ambler classification and main concerning β-lactamases. Mechanisms of resistance among pathogens (GNB) with extended-drug resistance

β-lactamases	Enzymes	Species	Effective inhibitors	Susceptibility pattern
Class A serine β-lactamases/ Penicillinases	ESBL: SHV, TEM, CTX-M	*Enterobacteriaceae*	Clavulanate, tazobactam, sulbactam	R: AMX, TZP, CTX, CAZ, ATM I/R: ETP S/I/R: IMP MER Partially inhibited by Clav-A and TZB
Class A serine β-lactamases/ Carbapenemases	KPC, IMI, SME, GES, SHV	*Enterobacteriaceae, Pseudomonas spp, Acinetobacter spp*	Avibactam, relebactam, vaborbactam	R: AMX, TZP, CTX, CAZ ATM I/R: ETP S/I/R: IMP MER Partially inhibited by Clav-A "S": AVI, RE, VAB
Class B metallo-β-lactamases	NDM, VIM, IMP, GIM, SPM, DIM, SIM	*Enterobacteriaceae, Pseudomonas spp, A. baumannii, S. maltophilia, Bacteroides fragilis*	–	R: AMX, AMC, CTX, I/R: TZP, CAZ, ETP S/I/R: IMP, MER S: ATM
Class C serine β-lactamases	AmpC, ACT, CMY, DHA, FOX, ADC	*Enterobacteriaceae*[†], *Pseudomonas spp, A. baumannii*	Avibactam, relebactam, vaborbactam	R: AMX, AMC, CTX, TZP, CAZ
Class D serine β-lactamases-Oxacillinase OXA	OXA-48, OXA-23, OXA-51, OXA-58, OXA-24/40, OXA-58…	*Enterobacteriaceae, A. baumannii*	Avibactam, relebactam (variable inhibition)	R: AMX, AMC S/I: CTX, IMP, ETP, MER S: CAZ, ATM, CFP

[†], *Serratia*, *Providencia*, "indole-positive" *Proteus* species, *Citrobacter*, and *Enterobacter* species. GNB, gram-negative bacteria; SHV, sulfhydryl variant of the TEM enzyme; TEM, Temoneira class A extended-spectrum β-lactamase; CTX-M, cefotaxime-hydrolyzing β-lactamase-Munich; AMX, amoxicillin; TZP, piperacillin-tazobactam; CTX, cefotaxime; CAZ, ceftazidime; ATM, aztreonam; ETP, ertapenem; IMP, imipenemase metallo-β-lactamase; MER, meropenem; TZB, tazobactam; KPC, *Klebsiella pneumoniae* carbapenemase; IMI, imipenem hydrolyzing β-lactamase; SME, *Serratia marcescens* enzyme; GES, Guiana extended-spectrum β-lactamase; SHV, sulfhydryl variant of the TEM enzyme; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; GIM, German imipenemase; SPM, Sao Paulo metallo β-lactamase; DIM, Deutch imipinemase; SIM, Seoul imipenemase; AMC, amoxicillin-clavulanic acid; AmpC, ampicillin chromosomal cephalosporinase; ACT, AmpC type β-lactamase; CMY, cephamycin-hydrolyzing β-lactamase; FOX, plasmid-mediated class C β-lactamase; OXA, oxacillin carbapenemase/oxacillinase; CFP, cefoperazone.

hospital, and costs (4,149,150). Recently, CDC reported that: "More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. In addition, 223,900 people required hospital care for *C. difficile* and at least 12,800 people died in 2017" (4). *Candida auris*, *Enterococcus faecium* [vancomycin-resistant *Enterococcus* (VRE)], methicillin-resistant *S. aureus* (MRSA), ESBL-producing *Enterobacteriaceae* (essentially *K. pneumoniae* and *E. coli*), inducible AmpC-cephalosporinase-producing *Enterobacteriaceae* (Enterobacter species), and multidrug-resistant *P. aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* are the most frequent antimicrobial-resistant germs playing an increasingly important role in healthcare-associated nosocomial infections and community-acquired infections, and represent a global threat to human health (4,149-152).

Concerning GNB, the most important emerging β-lactamases correspond to the production of ESBL, AmpC cephalosporinases, and carbapenem-hydrolizing β-lactamases, the latest conferring resistance to almost all β-lactams (*Table 7*) (5,151-159). The worldwide spread of these β-lactamase-producing GNBs is an important source of concern since these β-lactamase resistance mechanisms are frequently combined with other β-lactam-resistance

mechanisms [drug uptake limitations (porin loss, biofilm), drug target alterations, and/or drug efflux pump] and non-β-lactam resistance mechanisms, therefore leading to multi-drug resistant (MDR/XDR) isolates (5,151,152). Infection rates due to MDROs are increasing steadily throughout the world and antimicrobial agents active against MDROs, especially carbapenem resistant (CR) GNBs, remain limited and are associated with high rates of mortality (6,149,151,160,161).

Therefore, antimicrobial stewardship programs and carbapenems-sparing strategies must be implemented to preserve the effectiveness of carbapenem antibiotics and new β-lactams/β-lactamase-inhibitors (BLI) (3,134-136,142,149,153-155,162-177) (*Tables 7,8*). Early identification of colonized patients, appropriate and strict antibiotic control policies, care staff education and training, and contact/isolation precaution measures are of paramount importance to prevent transmission and spread of these CR and MDR/XDR-GNB (149).

Microbiota

Gut dysbiosis—reduction in the gastrointestinal tract in microbiota diversity and replacement of normal commensal microbial organisms ["health-promoting" colonizing commensal microbe population, such as Bacteroidetes (mainly *Bacteroides spp*, *Prevotella spp*) and Firmicutes (mainly *Lactobacillus spp*, *Clostridium spp*, but also small quantity of *Enterococcus spp* and *Staphylococcus spp*)] with pathogenic and virulent organisms (such as Proteobacteria, called "pathobionts", mainly Enterobacterales and small quantity of *P. aeruginosa*)—is considered to play a major role in the pathogenesis for many acute or chronic diseases, and is associated in ICU patients with poor outcomes (associated with increased susceptibility to nosocomial infections, sepsis, and organ failures) (178-181). Therefore, even if the gut microbiota is unique to each individual and the "healthy microbiota" is not defined, the majority of the normal gut microbiota consists of obligate anaerobic bacteria, which inhibit the growth of pathogenic bacteria (essentially aerobic or facultative anaerobic bacteria such as *E. coli* and other *Enterobacteriaceae*) (179,182). Gut dysbiosis and secondary alteration of microbiota-derived metabolites interact with intestinal receptors, induce adverse local and systemic effects and affect different organ systems (178,179,182,183). During hospitalization, many factors, such as food, parenteral nutrition, discontinuation of the normal diet, general anesthesia, antibiotics, medications (antipsychotics, proton pump inhibitors, opioids, non-steroidal anti-inflammatory drugs, hypoglycemic agents, beta-blockers, amines, chemotherapeutic agents), surgery (stress, injury, hemorrhage and blood transfusion), critical illness, mechanical ventilation, sepsis, splanchnic hypoperfusion, inflammation, electrolytes disturbances, and/or decreased intestinal motility directly, reduce the diversity (qualitative alteration) and alter proportion of the bacterial species (quantitative alteration) in the gut microbiota within 1 or 2 days (178-185). Therefore, significant gut microbiome alterations occur in critically ill patients and are associated with disease severity and clinical outcome (182,186,187). Similarly, gut microbiome alterations occur also in the processes leading to endogenous SSIs and post-surgical complications (188-190).

Antibiotics, frequently used in ICUs, are probably the most common cause of dysbiosis (gut and upper respiratory tract microbiome dysregulation) (180,191). If antibiotic therapies target pathogenic bacteria, they are also targeting the commensal "health-promoting" bacteria making our microbiota (181,182,192). The use of antibiotics highly active against anaerobic strains increases the risk of MDROs compared with other antibiotic regimen (193,194). The microbiota is rapidly and sustainably affected by antibiotics, and is then the main reservoir for MDROs, which will be involved in further infections (182,188-204). The effects of antibiotics on microbiota are multifactorial and depend on the class of antibiotic used, the spectrum of activity, the activity against anaerobic bacteria and potential impact on the intestinal microbiota, the administration route, the pharmacokinetic and pharmacodynamics properties, the route of elimination, the bowel bioavailability and the comorbidities of the patient (179,182,205-207). Emergence of MDROs may occur from the very first day (202,203,208). A single day of imipenem therapy may increase the incidence of imipenem-resistant bacteria colonization in the ICU population (202). Even a single dose of surgical AP alters the bacterial epidemiology of early ventilator-associated pneumonia in brain-injured patients (208). It has been shown that a single dose of third generation cephalosporin is likely to modify the digestive and vaginal flora (209,210). Moreover, the impacts on the microbiota is specific of each antibiotic with different effects between antibiotics of the same class [ertapenem versus imipenem (211,212) or ceftriaxone versus cefotaxime (213)].

Gut microbiota disruption contributes to hospital-acquired infections, sepsis and influences the outcome of sepsis leading to multiple organ failures (180,190,192,214-216).

Table 8 Newer intravenous antimicrobial agent with activity against MDR/XDR GNB (3,142,149,153-155,162-177)

Drugs	*Enterobacteriaceae*				Non-fermenting carbapenem-resistant GNB			
	Class A ESBL	Class C AmpC[†]	Class A Carbapenemase KPC	Class B Carbapenemase NDM, IMP, VIM	Class D Carbapenemase OXA type	*P. aeruginosa* (MDR/XDR)	*A. baumannii* (MDR/XDR)	*S. maltophilia*
Ceftolozane-tazobactam	Yes[‡]	Yes/no	No	No	No	Yes[§]	No	No
Ceftazidime-avibactam	Yes	Yes	Yes	No	Yes	Yes	No	No[¶]
Aztreonam-avibactam	Yes	Yes	Yes	Yes	Yes	Variable*	No	Yes
Ceftaroline-avibactam[¥]	Yes	Yes	Yes	No	Yes	No	No	No
Cefepime-enmetazobactam	Yes	Yes	No	No	No	No	No	No
Cefepime-zidebactam	Yes	Yes	Yes	Yes	Yes	Yes	Limited	Yes
Cefepime-taniborbactam	Yes	Yes	Yes	Yes[&]	Yes	Yes	No	Yes
Meropenem-vaborbactam	Yes	Yes	Yes	No	No	No[Ω]	No	No
Meropenem-nacubactam	Yes	Yes	Yes	Yes	Yes[£]	No[δ]	No[δ]	No
Imipenem-cilastatin-relebactam	Yes	Yes	Yes	No	No	Yes	No	No
Sulbactam-durlobactam	No	No	No	No	No	No	Yes	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plazomicin	Yes	Yes	Yes	No	Yes	Variable[#]	Variable[#]	No
Eravacycline[$]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Omadacycline[$]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

[†], *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii* are at moderate to high risk (8% to 40% of infections caused by these pathogens) for clinically significant AmpC production (142). In contrast, *Serratia marcescens*, *Morganella morganii* and *Providencia spp* are unlikely (<5%) to overexpress AmpC (142). There is no significant investigation on Hafnia alvei, *Citrobacter youngae* and *Yersinia enterolitica* (142). [‡], the role of ceftolozane-tazobactam in invasive infections due to ESBL-producing *Enterobacteriaceae* needs to be clarified (175). Carbapenems still remain the preferred treatment for any ESBL-producing *Enterobacteriaceae* infections (175). [§], treatment option for mainly carbapenem-resistant non-carbapenemase producing *P. aeruginosa* (172). [¶], the combination of ceftazidime-avibactam and aztreonam is suggested for moderate to severe *S. maltophilia* infections when neither TMP-SMX nor minocycline are considered viable treatment options (142). *, the combination of aztreonam and ceftazidime-avibactam may be a viable treatment option against serine-β-lactamase- and metallo-β-lactamase producing *Enterobacteriaceae* and *P. aeruginosa* (166). [¥], ceftaroline: "Novel" fifth generation cephalosporin with bactericidal against MRSA (and vancomycin-intermediate, heteroresistant vancomycin-intermediate, and vancomycin-resistant *S. aureus*) and MDR *Streptococcus pneumoniae*. [&], not efficient against IMP class B metallo-β-lactamase (carbapenemase)—incompletely efficient (70–80%) against NDM (class B metallo-β-lactamase (carbapenemase) (167). [Ù], similar activity as meropenem against *P. aeruginosa* (172). [£], class D: only active against OXA-48/181 like (149). [δ], similar activity to meropenem for *Pseudomonas* and *Acinetobacter spp* (172). [#], Not superior to other aminoglycosides (amikacin, gentamicin, tobramycin) against *P. aeruginosa* and *A. baumannii* (169,172). [$], inactive against *Proteus spp*, *Providencia spp* and *P. aeruginosa*. GNB, gram-negative bacteria; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; IMP, imipenemase metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; OXA, oxacillin carbapenemase/oxacillinase; MDR, multidrug resistant; XDR, extensively drug-resistant.

Microbiota-targeted therapeutics or "dysbiosis therapy" aimed at restoring the balance between commensal "health-promoting" and pathogenic organisms may improve post-surgical patient and/or critically ill patient outcomes (180,190-192,217,218). Unaltered or restored microbiota is a key element for local mucosal gut and systemic immunities, and in the fight against MDROs (colonization, infection, and spread) (182,191). Probiotic/prebiotic/symbiotic nutrition or fecal microbiota transplantation strategies to modulate or modify the microbiome are potential interventions to prevent or cure infections (180,184,190,219-222). These different strategies may then contribute to reduce the use of antibiotics and multidrug resistance (222).

Antibiotic potential alternatives for GNB infections

Novel treatment approaches such as bacteriophage therapy (phagotherapy) targeting MDR/XDR strains of GNB (*A. baumannii*, *P. aeruginosa* or *K. pneumonia*), or lysins (bacteriophage-derived enzymes with bacteriolytic activity against *Staphylococcus spp*), lectin inhibitors (*P. aeruginosa*), antimicrobial peptides, quorum sensing inhibitors (*P. aeruginosa*), immunotherapy (therapeutic antibodies targeting *S. aureus* virulence factors, *Acinetobacter baumannii* capsule, *P. aeruginosa* lipopolysaccharides or other virulence factors, or antibiotic resistance mechanisms, and acting concomitantly or synergistically with antibiotics) and GNB vaccines are developed to decrease the pathogen virulence (antivirulence therapy), enhance the therapeutic arsenal against MDROs, and prevent MDRO infections (146,163,164,223-232). Unfortunately, their potential is yet to be explored to demonstrate consistent clinical efficacy in combination with antibiotic therapy.

Conclusions

Community-acquired and hospital-acquired infections caused by MDR bacteria are an ongoing therapeutic challenge. With the emergence and continuous spreading of ESBL- and carbapenemase-producing GNB, therapeutic options for clinicians are more and more limited. Despite the development of new antibiotics, most being combinations of a β-lactam and a β-lactamase inhibitor, MDROs cause difficult-to-treat infections with increased morbidity and mortality, and increased health care costs. Unnecessary antibiotic therapy—i.e., treatment duration longer than necessary, inappropriateness of treatment of noninfectious or nonbacterial syndromes, or inappropriateness of treatment of colonization/contamination—further contributes to the development of resistance and its dissemination, as well as to antibiotic-related harms to patients. In addition, most antibiotics cause collateral damage on commensal bacteria and gut microbiota. Antibiotic stewardship programs are critical to significantly decrease antibiotic inappropriate use, consumption and duration, and promote optimal use of newer antibiotics. Parallel provider education is also mandatory. Antimicrobial effectiveness is a precious and limited resource and should be preserved.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Tobias Eckle and Benjamin Scott) for the series "Highlights in Anesthesia and Critical Care Medicine" published in *Annals of Translational Medicine*. The article has undergone external peer review.

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5585/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5585/coif). The series "Highlights in Anesthesia and Critical Care Medicine" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Premachandra A, Moine P. Antibiotics in anesthesia and critical care. Ann Transl Med 2024;12(1):6. doi: 10.21037/atm-22-5585