Antimicrobial Resistance in Intra-abdominal Infections

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18.1 Introduction

Optimal management of abdominal sepsis relies upon several factors, the most important being prompt resuscitation, timely and efficient source control, provision of intensive care and administration of appropriate effective antimicrobials [1–3]. Antimicrobial resistance is a globally expanding threat, jeopardizing the therapeutic approach in diverse clinical settings [4–6]. Clinicians face the crucial dilemma between the administration of inadequate antimicrobial therapy entailing the risk of high failure rates and the unjustified use of broad-spectrum antibiotics promoting further selection of resistant pathogens. Understanding the underlying mechanisms of resistance development and the overall toll from antibiotic misuse is essential in order to effectively use antibiotics in intra-abdominal infections while limiting hazardous overprescribing behaviors [1].

The worldwide spread of antimicrobial resistance has been clearly associated with a significant increase of morbidity, mortality, and healthcare expenditures. As a general principle, resistance occurs as a natural microbial evolution phenomenon; antibiotics accelerate this process though selection pressure exerted on intestinal microbiota. Horizontal transfer of individual resistant bacteria to adjacent patients adds a dreadful dissemination potential [7]. Increased AMR prevalence in the community is becoming a major public health issue; community occurring multidrug-resistant (MDR) strains can be transferred across borders by displaced, otherwise healthy populations in their destination countries [8, 9]. Moreover, travels for professional reasons and medical tourism are other potential sources of importation of alarming MDR phenotypes from distant geographic regions; the introduction of

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M. Sartelli et al. (eds.), *Abdominal Sepsis*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-319-59704-1_18

NDM-1-producing bacteria into the UK has been linked to medical tourism and elective surgery performed in India and Pakistan. Worldwide dissemination of such resistant strains is possible, and prompt coordinated international surveillance is needed [10, 11]. A very recent, more worrisome event is the reports of imported plasmid-mediated resistance to colistin, a last resort drug, frequently used for carbapenemase-producing strains [12].

18.2 Mechanisms of Antibiotic Resistance

Antimicrobial resistance can be intrinsically expressed by a given species via chromosomal genes or acquired through two distinct but not mutually exclusive genetic events; mutations on existing genes (vertical evolution) or horizontal transfer of mobile genetic elements (MGEs) acquired from other species or strains (horizontal gene transfer). Vertical evolution is the increased expression of intrinsic resistance mechanisms resulting in production of antibiotic-inactivating enzymes or efflux pumps, alteration of membrane permeability, or modification of antimicrobial targets. Horizontal gene transfer is mediated through mobile genetic elements such as plasmids or transposons which often carry multiple resistance determinants, enabling the recipient strain to express multidrug resistance phenotypes. Horizontal dissemination of the conjugating plasmids or transposons among different bacterial species is fueled by the selection pressure of antimicrobial overuse [7].

18.2.1 *Enterobacteriaceae*

18.2.1.1 β-Lactam Resistance

β-Lactam resistance in *Enterobacteriaceae* is mainly mediated through the production of β-lactamases, enzymes that hydrolyze β-lactams and therefore prevent penicillin-binding protein inhibition. β-Lactams are classified either according to protein homology (Ambler classification, schematically presented in Fig. 18.1) or functional characteristics (Bush-Jacoby-Medeiros classification) [6, 7, 13]. Some *Enterobacteriaceae* species (e.g., *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*, and *Providencia* spp.) may exhibit strong induction of chromosome-encoded AmpC cephalosporinases in the presence of amoxicillin, clavulanic acid, cefoxitin, and first-generation cephalosporins (1GC), thereby potentially expressing an AmpC hyperproducing phenotype with intrinsic resistance to penicillins, aztreonam, third-generation cephalosporins (3GC), and ertapenem. Although cefepime is a poor inducer and substrate for AmpC β-lactamases, its effectiveness is questioned in the presence of high bacterial inoculum, and its use should be avoided in critically ill patients with suboptimal source control [14, 15]. Carbapenems are not vulnerable to AmpC-mediated hydrolysis, representing an optimal treatment option for severe cases.

Plasmid-borne extended-spectrum β-lactamases (ESBL) and carbapenemases carry the most important clinical impact on resistance among *Enterobacteriaceae*. Genes

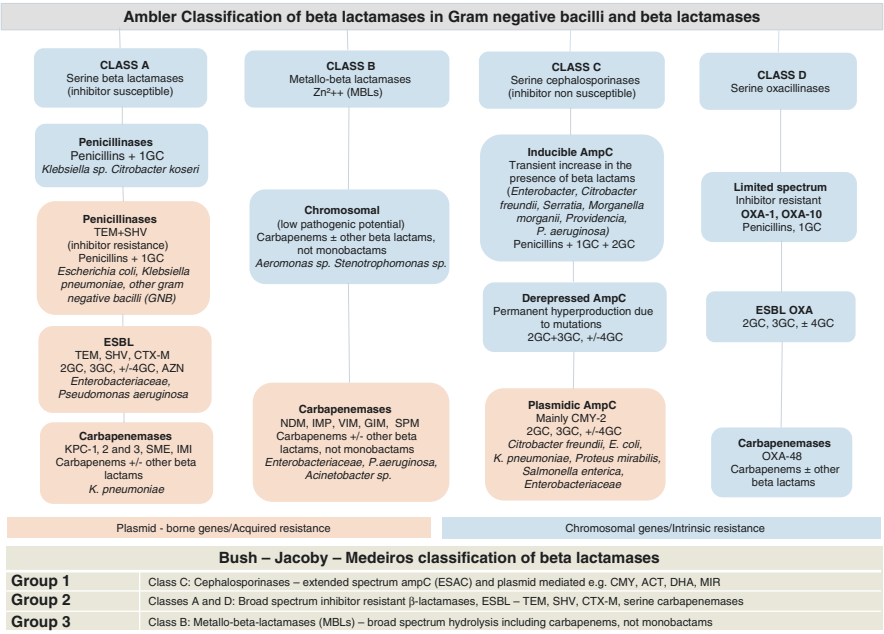

Fig. 18.1 Classification of beta-lactamases in Gram-negative bacilli according to two major systems [6, 7, 13]. *1GC* first-generation cephalosporins, *2GC* second-generation cephalosporins, *3GC* third-generation cephalosporins, *4GC* fourth-generation cephalosporins, *ESBL* extended-spectrum beta-lactamases

encoding for the majority of ESBL enzymes (TEM-, SHV-, and CTX-M) are located on plasmids that usually harbor additional resistance mechanisms to other agents such as aminoglycosides and fluoroquinolones. These enzymes (most frequent being CTX-M) are capable of inactivating most β-lactams including 3GC. Although carbapenems remain active, carbapenems-sparing schemes are narrowed by co-resistance to other agents described above [15, 16]. Recent literature on the use of β-lactam/β-lactam inhibitor combinations (BLBLI) in the treatment of infections caused by ESBL producers has been conflicting, depending on the infectious source, inoculum, and patient's clinical condition [17, 18]. Currently EUCAST has recommended and set a threshold for BLBLI use against ESBL-producing *Enterobacteriaceae*, that is, a MIC ≤ 8 mg/L (or ≤4 mg/L according to most recent publications) [19]. In critically ill septic, bacteremic patients with uncontrolled intra-abdominal septic foci, the inoculum effect should be taken into account; therefore, only patients with less serious infections originating from the urinary tract or well-controlled intra-abdominal foci (i.e., biliary tract) could be administered a high dose of BLBLI [17, 20]. Dissemination of ESBLs, within the community represents a challenging scenario in Southeast Asia and the eastern Mediterranean countries, with rates of intestinal carriage among otherwise healthy individuals reported to be as high as 60%. This community based reservoir provides a continuous inflow of resistant strains within hospital settings, hampering appropriateness of empirical therapy for community-acquired intra-abdominal infections [21].

Carbapenemases confer the largest spectrum of antibiotic resistance since they hydrolyze not only carbapenems but practically all β-lactams. *Klebsiella pneumoniae* carbapenemases (KPC) are the most important enzymes of class A serine carbapenemases [7, 16]. The initial reservoirs of KPC were *K. pneumoniae* in the USA, Israel, Greece, and Italy, those of NDM were *K. pneumoniae* and *E. coli* in the Indian subcontinent, and those of OXA-48 were *K. pneumoniae* and *E. coli* in North Africa and Turkey; notably, NDM and OXA-48 producers may present as either nosocomial- or community-acquired pathogens [22]. Their rapid worldwide dissemination has emerged as a global medical threat. Currently, among European countries, Greece, Italy, Montenegro, Spain, and Serbia reported the highest incidence rates of carbapenems non-susceptible *K. pneumoniae* and *E. coli* [23]. DNA fingerprinting analysis of carbapenemase-producing *Klebsiella pneumoniae* isolates, have elucidated as more prevalent the *K. pneumoniae* ST258 lineage producing the KPC-2 enzyme in most countries, whereas the ST512 lineage related to KPC-3 production predominates in Italy [23–25]. Increased use of colistin, which is frequently the only available treatment option in the aforementioned clinical scenarios, has led to the emergence of colistin-resistant KPC-producing strains [26]. Although initial reports were about chromosomal mechanisms of resistance, recent emergence and dissemination of plasmid-borne colistin resistance (discussed below in detail) represents one of the most alarming threats in infectious diseases [27, 28]. Class B carbapenemases are metallo-β-lactamases (MBLs) conferring resistance to all beta-lactams except monobactams. Chromosomally encoded MBLs are primarily found in *Aeromonas* and *Stenotrophomonas* spp., *P. aeruginosa*, and *A. baumannii*, and *Enterobacteriaceae* harbor MBLs transmitted by mobile gene elements (VIM, IMP, NDM, SPM, GIM), which are frequently co-transmitted with additional resistance genes inactivating aztreonam as well [7, 16]. Finally, class D oxacillinases (OXA-β-lactamases) possess a variable hydrolyzing spectrum of activity. Among them, OXA-23 and OXA-48 are able to inactivate carbapenems; dissemination of OXA-48 among *Enterobacteriaceae* is currently an important cause of resistance particularly in the Mediterranean [7, 16, 23, 29]. In a recent initiative directed by the European Centre for Disease Prevention and Control (ECDC), 455 sentinel European hospitals from 36 countries collected contemporary carbapenem-resistant *K. pneumoniae* and *E. coli* isolates between 2013 and 2014, illustrating a significant problem centered around the Mediterranean and Balkan area. Worrisomely, colistin resistance among reported isolates heralds the loss of the last frontier, with resistance ranging from 8% in the UK to 70.5% in Romania [23].

18.2.1.2 Resistance to Fluoroquinolones, Aminoglycosides, and Colistin

Chromosomal mutations in DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) are the main resistance mechanism, conferring high-level resistance against quinolones and fluoroquinolones. First-step mutants may exhibit in vitro susceptibility to fluoroquinolones, but in vivo, and in the presence of high inoculum, they develop rapidly full resistance. Other mechanisms are mediated through chromosomal overexpression of efflux pumps or decreased permeability. Recently described

qnr-encoded proteins confer low-level resistance through plasmid-mediated mechanism. These genes are usually linked to other antibiotic resistance determinants (most frequently ESBL), resulting in MDR phenotypes [7, 16, 30].

Aminoglycoside-modifying enzymes (AMEs) are the major mediators of aminoglycoside resistance in *Enterobacteriaceae* (chromosomal in *Serratia marcescens* and *Providencia stuartii*). Plasmid-borne AME genes are often co-transmitted with ESBLs being associated with resistance rates as high as 60% for gentamicin and 20% for amikacin among nosocomial isolates of *Enterobacteriaceae*. Plasmid-mediated methylation of 16S rRNA subunit is now recognized as a major mechanism of resistance to all parenteral aminoglycosides with global dissemination particularly in NDM-producing strains. At least seven genes have been associated with methylase production (*armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rmtE*, and *npmA*) [31].

18.2.2 Non-fermenting Gram-Negative Bacteria

18.2.2.1 *Pseudomonas aeruginosa*

Agents with activity against *P. aeruginosa* include ticarcillin (+/− clavulanate); piperacillin (+/− tazobactam); ceftazidime; cefepime; imipenem, meropenem, and doripenem; and (variably) aztreonam. Ticarcillin-clavulanate is less active compared to piperacillin-tazobactam owing to the strong induction of AmpC by clavulanate. AmpC hyperproducing variants remain susceptible to carbapenems. The most common mechanisms of carbapenems resistance in *P. aeruginosa* resulting in MDR phenotypes is overexpression of efflux pumps (most commonly the MexAB-OprM system involving multiple antibiotics) and mutations of the OprD porin, hijacking antimicrobial passage through the outer membrane (affecting mainly imipenem) [7, 16]. Acquisition of various MGEs may result in resistance to a wide range of β-lactams and aminoglycosides [32]. Resistance mechanisms for *P. aeruginosa* are schematically presented in Table 18.1.

18.2.2.2 *Acinetobacter baumannii*

Natural expression of AmpC cephalosporinase and OXA-51-like carbapenemase by *A. baumannii* confers intrinsic resistance to aminopenicillins, first- and second-generation cephalosporins, and aztreonam. In the context of AmpC hyperproduction, acquired resistance broadens and includes carboxypenicillins, ureidopenicillins, and third-generation cephalosporins [7, 16]. Dissemination of carbapenem-resistant (CR) strains is of major clinical importance since their prevalence continues to increase especially in Southern European countries [33]. CR may result from acquisition of carbapenemases (e.g., OXA-23-like, IMP, VIM, and more recently NDM-1) or through overexpression of OXA-51-like oxacillinases (Table 18.1).

Acquired resistance to other agents such as fluoroquinolones or aminoglycosides often accompanies ESBL-producing and CR-*A. baumannii* strains, narrowing significantly therapeutic choices which in the majority of cases reside on the use of colistin [33]. Extended use of colistin in hospital settings with high prevalence of CR has resulted in colistin-resistant isolates through reduction of the negative

Table 18.1 Resistance mechanisms for non-fermenting gram negative causing cIAIs [19–23]

Gram-negative non-fermenting	Resistance phenotype	Resistance mechanism
Pseudomonas aeruginosa	β-Lactams	Enzyme inhibition (AmpC, ESBL, MBLs), active efflux (MexAB), decreased permeability (loss of OprD)
	Aminoglycosides	Enzyme inhibition (AMEs), efflux (MexxYY), target modification (ribosomal methylation)
	Fluoroquinolones	Efflux (MexAB, CD, EF, XY, GH, VW), target modification (gyrA)
	MDR	Overexpression of active efflux pumps (MexA, MexB, OprM)
	Polymyxins	LPS modifications
Acinetobacter baumannii	β-Lactams	Enzyme inhibition (AmpC, plasmid-borne TEM-, SHV-, CTX-M, MBLs, OXA-type carbapenemases), target modification (PBPs), efflux pumps, reduced permeability
	Aminoglycosides	AMEs, target modification (16S rRNA methylases)
	Fluoroquinolones	Efflux pumps, target modification (DNA gyrase
	Tigecycline	Efflux pumps
	Polymyxins	LPS modifications—mcr-1
Stenotrophomonas maltophilia	β-Lactams	Inducible MBLs, impermeable outer membrane
	TMP–SMX	Target modification (plasmid-borne sul1, sul2)
	Fluoroquinolones	Target modification, efflux pumps
	MDR	MDR efflux pump

ESBL extended-spectrum β-lactamases, *MBL* metallo-beta-lactamases, *MDR* multidrug resistant, *AME* aminoglycoside-modifying enzymes, *PBPs* penicillin-binding proteins

charge of lipopolysaccharide, therefore lowering the affinity for the positively charged colistin [27]. Until now colistin resistance occurred through chromosomal mutations which imposed significant fitness cost upon the bacterium. Recent reports on the emergence of transmissible, plasmid-mediated colistin resistance in the form of MCR-1 gene are of major global significance and concern. The gene has been repeatedly isolated from the environment thus indicating possible transmission to *Enterobacteriaceae* regardless of selection pressure, rendering extensively drug-resistant pathogens, pandrug resistant [27, 28]. In this challenging scenario, data regarding optimal treatment are lacking. Rifampin has demonstrated in vitro synergy with colistin; however, clinical data of the combination including a randomized-controlled trial have shown only a marginal beneficial effect on microbiologic eradication without effect on mortality [34]. In vitro synergy has been demonstrated between colistin and glycopeptides; clinical data mostly from retrospective studies

were encouraging. Therefore, the addition of a glycopeptide to colistin might represent an option for salvage treatment [35, 36]. Sulbactam has variable in vitro activity against *A. baumannii*; clinical data are still scarce. Tigecycline exhibits an acceptable in vitro susceptibility profile without established breakpoints of resistance; its clinical use off-label in *A. baumannii* infections is jeopardized by the lack of solid clinical data and particular risks for superinfections and breakthrough infections. Monotherapy is discouraged and double dose is advisable with careful follow-up of liver function [36].

18.2.3 Enterococci and *Bacteroides fragilis*

Overexpression of low-affinity PBPs by enterococci, or less often acquisition of beta-lactamases, results in increased resistance against penicillins. Intrinsic low-level resistance of enterococci against aminoglycosides precludes their use as monotherapy, and high-level resistance is being disseminated with acquisition of MGEs carrying AMEs. Of major clinical importance however is the development of glycopeptide-resistant enterococci, which have emerged as a major cause of nosocomial infections. Strains of *E. faecium* and *E. faecalis* with high-level resistance to vancomycin and teicoplanin harbor the *vanA* gene, resulting in reduced affinity of the bacterial peptidoglycan with the glycopeptide. Strains harboring the *vanB* gene display variable MICs against vancomycin (from 1024 to 4 μg/ml) and in vitro susceptibility to teicoplanin without direct association with clinical efficiency. *E. gallinarum*, *E. casseliflavus*, and *E. flavescens* are characterized by chromosomal expression of the *vanC* gene complex, resulting in low-level resistance to vancomycin and susceptibility to teicoplanin [37] (Table 18.2).

Resistance against beta-lactams for *B. fragilis* isolates is mediated through production of β-lactamases, most commonly cephalosporinases, which may be inhibited in the presence of lactamase inhibitors. High-level carbapenem resistance in *B. fragilis* is rare, being usually associated with overexpression of the *cfiA* gene which encodes for a metallo-β-lactamase. Resistance against metronidazole still remains at low prevalence. The most common mechanism described is through expression of 5-nitroimidazole nitroreductases that are located both on chromosomal genes or MGEs [38] (Table 18.2).

18.3 Epidemiology of Resistance in Intra-abdominal Infections

Resistance trend in IAIs follows the data presented in the section of mechanisms of resistance. Due to geographic and epidemiologic variations, it is important that each country collects and analyzes its own data, in order to issue treatment guidelines. Compiled data from international registries and studies focused on IAIs are presented below.

Table 18.2 Resistance mechanisms of Gram-positive and anaerobes causing cIAIs [27, 28]

Microorganism	Resistance phenotype	Resistance mechanism
Staphylococcus aureus	β-Lactams—penicillin	Enzyme inhibition (penicillinase)
	β-Lactams—methicillin, oxacillin, nafcillin, cephalosporins (MRSA)	Target modification (PBP2a–mecA)
	Glycopeptides—GISA	Thickened cell wall-drug prevention from binding
	Glycopeptides—GRSA	Alteration of cell wall precursor targets—plasmid-borne transfer of VanA genes from VRE
Enterococci	β-Lactams (ampicillin)	Target modification (PBP5—*E. faecium*), enzyme inhibition (penicillinase—*E. faecalis*)
	Aminoglycosides	Enzyme inhibition (high-level resistance AMEs), target modification
	Vancomycin	Alteration of cell wall precursor target (Van A,B,D—high-level resistance, Van C,E,G—low-level resistance)
	Linezolid	Target modification (23S rRNA mutations)
Bacteroides spp.	β-Lactams	Enzyme inhibition (CepA cephalosporinases, MBLs—cfiA), efflux, target modification (PBPs)
	Macrolides, lincosamides, streptogramin B	Target modification (ribosomal)
	Metronidazole	Efflux, overexpression of DNA repair protein (RecA), expression of 5-nitroimidazole nitroreductases (nimA-G)
	Quinolones	Target modification (DNA gyrase—gyrA), efflux

MRSA methicillin-resistant *S. aureus*, *GISA* glycopeptide-intermediate *S. aureus*, *GRSA* glycopeptide-resistant *S. aureus*, *VRE* vancomycin-resistant *Enterococci, MBL* metallo-beta-lactamases, *AME* aminoglycoside-modifying enzymes, *PBPs* penicillin-binding proteins

18.3.1 ESBL and Carbapenem-Resistant *Enterobacteriaceae*

The SMART study (The Study for Monitoring Antimicrobial Resistance Trends) recording in vitro susceptibility patterns of Gram-negative isolates from IAIs, since 2002 reported a notable worldwide dissemination of ESBL-producing *Enterobacteriaceae*, both within hospital settings and within the community [39]. From 2002 to 2008, ESBL-producing *E. coli* isolates from IAIs in European centers rose from 4.3% to 11.8%, whereas the prevalence of *K. pneumoniae* ESBL-producing strains remained relatively stable (from 16.4% to 17.9%). As expected, among ESBL producers hospital-associated isolates predominated [40]. An increasing prevalence has been documented also in Asia and North America [41, 42]. Data from the CIAOW Study (Complicated Intra-Abdominal infections Worldwide

Observational study), reported that among intraoperative isolates collected worldwide from October 2012 to March 2013, ESBL producers represented 13.7% of all *E. coli* isolates and 18.6% of all *K. pneumoniae* isolates [43]. A particularly high percentage of ESBL producers (42.8%) was recorded among hospital-acquired *K. pneumoniae* isolates.

The increasing prevalence of *K. pneumoniae* carbapenemases (KPCs) worldwide is becoming one of the major challenges in hospital settings [23]. An analysis in the context of the SMART study reported that 6.5% of *K. pneumoniae* worldwide isolates from intra-abdominal infections were ertapenem resistant based on the 2010 CLSI breakpoints (MIC ≥ 1 μg/ml) [44]. Among ertapenem-resistant strains, a wide variety of carbapenemase genes was found, in addition to numerous ESBL and/or AmpC beta-lactamases backgrounds. These strains were clonally related, and when a separate analysis was performed, carbapenem-resistant isolates from the Asia-Pacific region were almost exclusively collected from India and expressed NDM-1 carbapenemases [45, 46].

18.3.2 *Pseudomonas aeruginosa*

Based on the results from the SMART study, *P. aeruginosa* was the third most common isolated pathogen from IAIs [39]. In North America, resistance against fluoroquinolones has significantly risen over the years from approximately 22% in 2005 to 33% in 2010, compared to the relatively unchanged imipenem resistance (approximately 20%). Relatively unchanged during the same study period remained also the resistance rates against piperacillin-tazobactam, cefepime, and ceftazidime, ranging from 23% to 26% [47]. It should be highlighted however that various geographic variations of antimicrobial resistance exist and should be taken into account accordingly [39].

18.3.3 Enterococci

Enterococci have emerged as a significant pathogen of hospital-acquired infections, associated with significant mortality [48, 49]. Results from the EBIIA study (Etude épidémiologique Bactério-clinique des Infections Intra-Abdominales) reported significantly higher prevalence of enterococcal infections in hospitalized patients compared to community-acquired infections (33% for hospital-acquired infections compared to 19% for community-acquired infections) without isolation of VRE strains, indicating the sustained suitability of vancomycin or teicoplanin use in both types of infections [50]. The preponderance of enterococci isolation for hospital-acquired IAIs compared to community-acquired infections was also demonstrated by the CIAOW study (22.3% vs. 13.9%), with *E. faecalis* and *E. faecium* being the most prevalent Gram-positive aerobic isolates accounting for 15.9% of total pathogens cultured from intraoperative samples [43].

18.3.4 *Bacteroides fragilis*

The exact prevalence of MDR *B. fragilis* is not easy to be determined due to technical difficulties related to transfer and processing of clinical specimens for culturing in anaerobic conditions. Therapy is always started empirically since the majority of *B. fragilis* strains remain susceptible to metronidazole, β-lactam/β-lactamase inhibitor combinations, and carbapenems. However individual isolate testing should be considered for highly virulent microorganisms, such as *Bacteroides*, *Prevotella*, and *Fusobacterium* spp. [51]. Data from a national United States survey on the antimicrobial resistance in *Bacteroides* spp. strains from 1997 to 2007 reported resistance rates ranging from 0.9% to 2.3% against carbapenems and piperacillin-tazobactam. Antimicrobial resistance was greater among *non-fragilis Bacteroides* species, than among *B. fragilis*, with very high resistance rates against moxifloxacin (especially for *B. vulgatus*) and clindamycin [52]. The importance of geographic variations is highlighted by a study from Asia, where higher non-susceptibility rates of *B. fragilis* of 7%, 12%, and 90% for imipenem, meropenem, and moxifloxacin, respectively, were reported [53].

18.4 Risk Factors for Acquiring Resistant Strains and Unusual Pathogens as Guide to the Selection of Empirical Regimen

Peritonitis, the most common type of IAI is classified as primary, secondary, and tertiary. Primary peritonitis is a rare usually monomicrobial IAI generated by hematogenous spread of bacteria or translocation from the gut, particularly in hosts with a predisposing condition [54, 55]. Secondary peritonitis, accounting for 80–90% of IAIs is most often due to gastrointestinal perforation or invasion by adjacent infected viscera. It is further classified as community acquired (70%) and postoperative (30%), the latter being most frequently attributed to anastomotic dehiscence. Community-acquired peritonitis is a mixed infection caused by bacteria of the patient's gastrointestinal flora, mainly *E. coli*, streptococci, and anaerobes with *B. fragilis* as the predominant species. In postoperative peritonitis, however, after patient's exposure to the hospital environment and antibiotics, causative pathogens tend to display MDR phenotypes (i.e., ESBL or AmpC or CR Gram-negatives, or MRSA [55]); *E. coli* and streptococci are less frequent compared to community infections [50]. Enterococci including *E. faecalis* and VRE as well as *Candida* species may also participate. Empirical treatment decisions should be based on local antimicrobial resistance data and patient's personal risk factors. After pathogen's identification, treatment can be adapted [56, 57]. Tertiary peritonitis develops when secondary peritonitis persists after failure of source control procedures. Fueled by prolonged hospital stay and antibiotic use, causative pathogens resemble those of postoperative peritonitis, including enterococci (and VRE), staphylococci (and *methicillin-resistant Staphylococcus aureus*/MRSA), *Enterobacteriaceae* with

multiple MDR phenotypes, difficult-to-treat non-fermenters (*P. aeruginosa*, *A. baumannii*), anaerobes, and *Candida* species. No surgical intervention is usually required [58].

General factors predisposing to poor patient outcomes in IAIs include severe disease, severe comorbidities, inadequate source control, non-appendicular origin, healthcare-acquired infection, and inadequate empiric antimicrobial regimen [59, 60]. Minimum turnover time of 48–72 h is required from specimen to susceptibility testing with conventional microbiological methods; therefore, initial antimicrobial therapy is usually empirical. Empirical treatment decisions must target the presumed pathogens, taking into account the infectious source, risk factors for resistance, and patient's severity of illness [55]. Studies in critically ill patients have clearly demonstrated the importance of early recognition of risk factors for resistant pathogens since adequate and timely treatment has been associated with reduced mortality [61]. In this sense, the distinction between community-acquired or healthcare-associated IAI is an important element. Classification of IAIs as "complicated" and "uncomplicated" seems to be less relevant to the implication or not of difficult-to-treat bacteria [62].

As mentioned above, community-acquired infections are likely caused by bacteria of the patient's gastrointestinal flora. As an exception to this rule, ESBL producers can be the cause of community infections, either without risk factors or associated with prior use of antibiotics (particularly the class of third-generation cephalosporins). It is therefore important to recognize patients exposed to antibiotics, especially those who were pretreated with prolonged or multiple antibiotic courses due to comorbidities [63–66]. Another important factor jeopardizing the distinction between community and nosocomial IAIs is an increasing volume of patients who reside in the community but are in close contact with the healthcare system. This group comprises nursing home residents, people receiving intravenous therapy at home, and people undergoing hemodialysis, chemotherapy, or irradiation as outpatients. These hosts tend to develop infections by pathogens that resemble to the nosocomial patterns of resistance, the so-called healthcare-associated infections (HCAIs) [67–69]. In a study of 2049 healthcare-associated IAIs, MDR pathogens accounted for 79% of those recovered [70]. HCAIs portend substantial morbidity and mortality; nevertheless, early and adequate empirical treatment proved to reduce complications and mortality [71].

Box 18.1 summarizes the most important risk factors for the acquisition of resistant strains in IAIs. Evidently, the most in-risk clinical settings are that of tertiary and postoperative peritonitis, with several factors predisposing to infections by MDR *Enterobacteriaceae*, *Pseudomonas* spp., *Acinetobacter* spp., enterococcal infections including VRE, MRSA, and *Candida* spp. It is important to consider also moving patients/populations as potential carriers of MDR bacteria harboring sometimes alarming resistance determinants [8–12]. In Southeast Asia, NDM-1 has been detected from sewage waters; in China, *Enterobacteriaceae* harboring mcr-1 gene carrying plasmid-mediated resistance to colistin were isolated from the food chain; KPC-producers and XDR

A. baumannii colonize/infect frequently inpatients in the Mediterranean region; ESBL may unexpectedly colonize healthy subjects from Mediterranean and Asian countries [22–24]. MRSA is not a frequent pathogen in IAIs and should be considered in hospital-acquired (particularly wound) infections and in patients with known previous colonization. Other pathogen-specific predisposing factors in IAIs are detailed in Table 18.3 [11, 58, 62, 65, 66, 69, 70, 72–76].

Box 18.1 Risk factors and clinical scenarios with increased likelihood of multidrug-resistant (MDR) pathogens in intra-abdominal infections [65–70]

Risk factors for recovery of multidrug-resistant bacteria in patients with intra-abdominal infections
Healthcare-associated infection (outpatient intravenous treatment, wound treatment, antineoplastic therapies, hemodialysis, nursing home residents)
Recent exposure to broad-spectrum antibiotics (<3 months)
Length of hospitalization >5 days
Prior or current admission in intensive care unit
Liver disease
Pulmonary disease
Diabetic foot infection with antibiotic use
Organ transplantation
Corticosteroid use
Patient receiving immunosuppressive agents
Patient with recent exposure in areas with MDR prevalence in the community or in environmental sources
Patient hospitalized in areas with MDR prevalence
Postoperative peritonitis Long time between first and second surgery
Tertiary peritonitis
Recurrent interventions in the biliary tract
Pretreated necrotizing pancreatitis

In general, broad-spectrum regimens are recommended in critically ill patients. Although coverage of enterococci and MDR bacteria is not recommended in patients with community-acquired peritonitis, enterococci should be considered in patients with septic shock, immunosuppression, and recurrent IAIs among other predisposing conditions listed in Table 18.3. Local epidemiology is a crucial factor to consider when selecting antimicrobial therapy. Surveillance strategies are important to guide selection of empirical treatment, particularly for severely ill patients [1, 2, 72]. Box 18.2 provides some useful pearls integrating microbiology into clinical practice that might assist clinicians in the selection of the correct antibiotic.

Box 18.2 Clinical pears integrating microbiology into clinical practice of intra-abdominal insections

- Identify patient's risk factors for resistant pathogens
- Get familiar with local epidemiology
- Third-generation cephalosporins should be avoided for treating wild-type inducible AmpC-producing *Enterobacteriaceae*—piperacillin and ticarcillin should be preferred
- ESBL[b]-producing *Enterobacteriaceae* are often resistant to other antimicrobial classes besides β-lactams (e.g., aminoglycosides or quinolones)
- BLBLI[c] should preferably be avoided unless MIC[d] ≤ 4 mg/L; bacteremic patients with inadequate source control have an increased risk to fail such treatment
- If susceptibility is confirmed, cefepime can be considered as a suitable carbapenem-sparing option for AmpC hyperproducing mutants, only if adequate source control is feasible because of the [a]inoculum effect
- Carbapenems remain active against AmpC hyperproducing and a potent agent against ESBL[b]-producing *Enterobacteriaceae*
- KPC[e] enzymes inactivate all β-lactams; ceftazidime/avibactam represents a new option
- Colistin remains currently the milestone for combination treatment of KPC[e] producing strains
- Selection of [f]colistin-resistant KPC-producing strains is an emerging global threat, mandating judicious colistin use
- Agents potentially effective against *Pseudomonas aeruginosa* are ticarcillin (±clavulanate); piperacillin (±tazobactam); ceftazidime; cefepime; meropenem, imipenem, and doripenem; ceftolozane/tazobactam; and ceftazidime/avibactam. Susceptibility against aztreonam varies
- Clavulanate is a strong inducer of AmpC production in *P. aeruginosa*
- Enterococci exhibit intrinsic resistance to some penicillin, all cephalosporins, and low-level resistance to aminoglycosides. Quinolones should not be considered adequate coverage
- Glycopeptide-resistant enterococci (GRE) are a significant cause of nosocomial infections with the majority of infections attributed to *E. faecium*
- *Bacteroides fragilis* is the most frequently isolated anaerobe from cIAIs[g]; it displays low resistance rates against metronidazole

a: In vitro studies showed that when a higher inoculum was used, the MIC for cefepime was significantly increased, b: ESBL; extended-spectrum β-lactamases c: BLBLI; β-lactam/β-lactamase inhibitor d: MIC; Minimum inhibitory concentration e:KPC; *Klebsiella pneumoniae* carbapenemase f: Colistin exposure is a risk factor for colistin resistance emergence in carbapenem-resistant Gram-negative bacilli g: cIAIs; complicated intra-abdominal infections

18.5 Prevention of Resistance

18.5.1 Antibiotic Stewardship and Implication of Surgeons

Currently published guidelines for the management of IAIs prioritize patients' safety and optimization of outcomes [2, 77, 78]. Antimicrobial stewardship is a novel approach intended to optimize antibiotic selection while minimizing

Table 18.3 Characteristics and predisposing factors for specific resistant phenotypes among pathogens recovered from intra-abdominal infections and guide for empirical coverage [11, 58, 62, 65, 66, 69, 70, 72–76]

	Bacteria with MDR phenotype or unusual bacteria in intra-abdominal infections				
	Enterobacteriaceae with resistant phenotype (ESBL or AmpC- or CR-producing *Escherichia coli, Enterobacter* spp., *Klebsiella* spp., *Serratia* spp., *Proteus* spp. etc.)	Non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*, etc.)	*Enterococcus faecium E. faecalis* including vancomycin-resistant *E. faecium*	*Staphylococcus aureus*	*Candida* spp.
Predisposing conditions	Healthcare-associated infection; local epidemiology considered	Healthcare-associated infection; local epidemiology considered	Recent antibiotic exposure (particularly prolonged cephalosporin treatment)	Abdomen left-open (compartment syndrome)	Postoperative peritonitis
	Patients with a history of recent travel (tourism and trade) in regions with high prevalence (Egypt, Thailand, India)	Length of hospital stay >5 days	Postoperative peritonitis	Postoperative infections	Prolonged antibiotic exposure
	Medical tourism or medical emergencies with hospital procedures in geographic areas with prevalent MDR and XDR *Enterobacteriaceae*	Recent antibiotic exposure	Tertiary peritonitis	Wound infections	Tertiary peritonitis following failure of source control
	Otherwise healthy migrants and refugees from countries with prevalent MDR and XDR *Enterobacteriaceae*	Chronic underlying conditions leading to antibiotic exposure (diabetic foot, chronic ulcers, chronic pulmonary conditions)	Septic shock and failure of early surgical source control	Patients receiving immunosuppressive agents	Upper GI tract perforation
	Patient with known colonization with resistant bacteria	Recent ICU admission	Immunosuppression and liver transplantation	Posttransplantation	Prior administration of fluconazole predisposes for fluconazole resistance

	Pretreated necrotizing pancreatitis	Immunocompromised status (*P. aeruginosa, S. maltophilia*) and corticosteroid use (*P. aeruginosa*)	Prosthetic heart valves	Previously colonized	Immunodeficiency
	Recurrent operations of biliary tract with obstruction	Pretreated necrotizing pancreatitis	Recurrent intra-abdominal infections		

ESBL extended-spectrum β-lactamases, *MDR* multidrug resistant, *XDR* extensively drug resistant, *GI* gastrointestinal

unnecessary antibiotic use along with its undesirable effects on further promotion of resistance [1]. Basic components of an antimicrobial stewardship program (ASP) are surveillance of resistance, implementation of infection control practices, and rational antibiotic use. The latter relies upon repetitive educational approaches to improve prescribers' ability to understand and conform to antimicrobial treatment principles. Optimal use of perioperative prophylaxis is a pillar of every ASP, mandating administration of narrow spectrum antibiotics for the shortest possible duration to prevent postoperative infections. Timing and possible repeat dosing of antibiotics as prophylaxis should follow national or local protocols and take into consideration duration of surgical procedures and antibiotic pharmacokinetics [1, 79, 80].

Although highly referenced, ASPs have not yet reached a universally accepted structure; therefore they are mainly based to local capacities and practices. Interventions may include antibiotic restriction, mixing, cycling, clinical guidelines, and practice algorithms. De-escalation is an important strategy to limit unnecessary use of broad-spectrum antibiotics after receipt of susceptibility results. Treatment duration is well established in IAIs and rarely should exceed 7 days, in complicated infections [1, 2, 79, 80]. Despite diversity of ASPs, observational studies have demonstrated a beneficial effect on antimicrobial resistance after implementation of ASP in surgical and trauma intensive care unit, which decreased in parallel with broad-spectrum antibiotic orders [81].

The Infectious Diseases Society of America has identified two types of approaches in the implementation of ASPs [1]. First, a persuasive-proactive approach requiring restriction formulary or pre-approval for select antibiotics or both. Second, a restrictive approach consisting of prospective audit with intervention with subsequent feedback of the prescribers. Both types of interventions have been associated with reduction of restricted antibiotics along with cost [1, 81, 82]. A Cochrane meta-analysis of 89 studies encompassing ASPs showed that the restrictive approach had more immediate results compared to the proactive one and was associated with reduction of antimicrobial resistance; on the other hand, persuasive approach was associated with better patients' outcomes. Nevertheless, after 6 months, no difference could be demonstrated. Despite the rapid results obtained with restrictive measures, after a short period of a few months, physicians were able to bypass obstacles to deliberate prescription of antibiotics [79].

Acceptance of ASPs is not straightforward; surgeons are frequently reluctant to share responsibility of their patient and "obey to restrictions." The success of every ASP relies on the building of confidence and the strong participation of all stakeholders in joint efforts. Adherence to surveillance practices and infection control measures may pose an additional obstacle in "conformation with restrictions." Both are important elements for containment of antimicrobial resistance. As far as infection control measures are concerned, surgeons may represent the most relevant specialties to understand the rationale and the procedure, since they are familiar with surgical procedures under aseptic conditions. Baseline educational activities may be decisive as well as the strong implication of a surgeon with well-appreciated knowledge and skills in both communication and management of surgical infections.

Equally important is the provision of continuous feedback to the surgeons with the results of strategies taken in order to improve antibiotic prescription and tackle antimicrobial resistance in their setting [83–85].

18.5.2 The Value of Targeted Therapy

It is very important to guide treatment decisions by appropriate cultures taken before empirical treatment initiation. There is discordance between published guidelines by the IDSA and the WSES [2, 62, 78] regarding the necessity of intraoperative cultures in uncomplicated IAI from the community. The issue has been very clearly addressed in the AGORA position paper [3]. In terms of clinical benefit on a patient basis, microbiologic confirmation might not affect clinical outcome in mild community IAIs [3, 86, 87]. However, it helps understanding microbiological trends in the community and survey antimicrobial resistance, given the fact that many resistance mechanisms in *Enterobacteriaceae*, namely, ESBLs and NDM-1, are now recovered from otherwise healthy persons without healthcare-associated risk factors [8–12]. Furthermore, microbiological documentation will enable de-escalation decisions, in order to curtail unnecessary use of broad-spectrum antibiotics selected as part of the empirical regimen. On the other hand, in case of a pathogen with unexpected pattern of resistance, antibiotic testing will enable prompt adaptation of treatment. Blood cultures are very rarely positive in IAI; nevertheless, in critically ill patients and particularly those with previous ICU admission and having implanted devices and central lines, a set of two blood cultures before initiation of treatment is highly advisable [3].

Perioperative tissue and pus specimens are also advisable in every patient with community-acquired IAI. Notably, perioperative and pus specimens are considered standard of care in hospital-acquired IAI or complications of previous surgery, recurrent bile duct surgeries, and necrotizing pancreatitis [2, 62, 78]. In view of escalating resistance and in patients not responding to the administered regimens, properly obtained and transported samples for anaerobic cultures should be ordered in select cases. It is also important to seek advice from infectious diseases physicians, clinical microbiologists, and possibly clinical pharmacologists in order to customize treatment in difficult-to-treat MDR pathogens. Finally, after almost two decades of dry pipeline, launching of a handful of new antibiotics with activity against some of the most cumbersome MDR/XDR pathogens mandates a prudent use of them by the clinicians. For these new antibiotics empirical use should be kept to a minimum, and their use as targeted treatment should be clinicians' priority.

Conclusion

Antimicrobial resistance is a worldwide expanding phenomenon with unprecedented consequences in morbidity, mortality, and healthcare expenditures. Evidently, surgical departments follow the global alarming trends with less than a handful antibiotics active against bacteria with pandrug-resistant phenotypes. Surgeons are by definition in the frontline of emergencies; now, they have to

confront the obstacle of antimicrobial resistance. Enhancing surgeons' knowledge on antibiotics and resistance will help the acceptance of ASP and all other measures targeting the containment of the problem. Antibiotic stewardship is not just a restriction for prescribers; it is an integrating model to lead hospitals in preservation of antibiotics while maximizing clinical efficacy. Frontline physicians are (by definition) part of the solutions.

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