Guide to Antibiotics in Urology

Truls E. Bjerklund Johansen
Tommaso Cai
Editors

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The editors dedicate this book to all patients suffering from urinary tract infections unleashed by risk factors due to standard of living, inheritance of host defense defects, or side effects of treatment of other diseases. It is our hope that they will receive antibiotic treatment that does not harm the delicate normal balance between host and microorganisms in their bodies and that effective antibiotic treatment will be available for the foreseeable future.

Preface

According to her death certificate, my great grandmother died of "nephritis chronica" in Norway in 1914. She was in her 40s. Seven childbirths and poor living conditions contributed to her infection risk. At that time, Norway had the highest death rate of tuberculosis in the world, and her nephritis might very well have been caused by tuberculosis. No urine cultures were taken, and there was no antibiotic treatment available for her.

Two generations later, my mother died of urosepsis in 2021 caused by multiresistant Pseudomonas aeruginosa. She was 97 years old and had risk factors related to bladder and intestinal dysfunction. The dysfunctions were caused by adjuvant irradiation of pelvic lymph nodes related to surgery for uterine cancer many years earlier. She received numerous courses of antibiotic treatment for recurrent UTI and had several episodes of urosepsis. Finally, there were no effective antibiotics available for her in our country. Fosfomycin, which would have been the preferred antibiotic, was not available due to national regulations introduced for the sake of antimicrobial stewardship.

In between the two deaths of my female ancestors, there has been an extraordinary development of modern medicine. At the time of my great grandmother's death, there were no medical specialties related to urinary tract infections such as microbiology, infectious diseases, or urology. There were very few doctors, no antibiotics and no intensive care units. As a child, I had to cross the old graveyard outside the old tuberculosis sanatorium to reach school. Every day, I was reminded of tuberculosis as a terrible cause of death. As the standard of living improved, the disease disappeared while we doctors were still treating patients with fresh air.

In the period between the two deaths, numerous antibiotics were developed and used with success to relieve patients of disabling symptoms and save lives. However, limited understanding of the delicate balance between humans and microorganisms, increased number of physicians, as well as marketing pressure from the pharmaceutic industry have brought us to a situation where this lucky period in our history might soon come to an end.

We use to think of ourselves as cohabitants in our own bodies with billions of microorganisms with whom we live in harmony most of the time. Infectious diseases occur when microorganisms enter body parts and cross tissue barriers like the urothelium. This invasion is made possible by virulence factors of the microorganism and is normally prevented by host-protective mechanisms. These mechanisms

are influenced by risk factors. Some of them might be eliminated while others remain challenges to antibiotic treatment.

The aims of this book are to provide the reader with understanding of the basic principles of diagnosis, prevention and treatment of urogenital tract infections, and to offer practical guidance on the use of antibiotics.

Stavern, Norway
July 2023

Truls E. Bjerklund Johansen

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Part I

Epidemiological and Microbiological Aspects of Urinary Tract Infections

Antimicrobial Resistance in Uropathogens

1

Gianpaolo Perletti and Vittorio Magri

1.1 Background

Urinary tract infections (UTIs) are among the most common infectious diseases in humans. Urinary antiseptics, naturally occurring antibiotics, and synthetic antibacterial agents (AAs) have been used for decades to treat infections like pyelonephritis and cystitis.

Today, about three generations after the introduction of antibiotics into the clinical practice, a return to the "pre-antibiotic era" due to the emergence of multidrug-resistant (MDR) pathogens is becoming "a disturbing possibility" [1]. In fact, we have reached a new crossroad whereby resistance to nearly all antimicrobial classes is increasing to the point that outbursts of infections carried by extremely drug-resistant or even pan-drug-resistant pathogens are happening around the world. In the frame of the Review on Antimicrobial Resistance commissioned by the prime minister of the United Kingdom, it has been foreseen that by year 2050 ten million premature deaths (one every 3 s) will be caused worldwide by pathogen resistance (cancer: about eight million), of which over three million will lose their lives to drug-resistant *E. coli* [2].

Bacterial resistance to antimicrobials is a very intricate subject, whose manifold aspects are determined by a large number of diverse elements. For example, it is known that antibacterial agents show different capacity in inducing resistance in pathogens, and that resistance patterns do not always reflect prescribing patterns [3], though in the urological field it was shown that individuals who have been

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prescribed antibiotics in primary care had bacteria in the urinary tract resistant to the same antibiotic for up to a year [4]. Moreover, the success of antibacterial therapy relies on specific clinical conditions. For example, the high urinary concentrations of antibacterials toward which a uropathogen shows resistance may be sufficient to treat UTIs but not infections detected in other districts of the body. Such and several other elements, together with the manifold resistance mechanisms that have been so far identified, have increased the complexity of the pathogen resistance scenario and have raised the public awareness about the pandemic threat it represents.

1.2 Principles of Bacterial Resistance to Antimicrobial Agents

When antibacterial agents were first introduced in clinical practice, resistance of exposed pathogens was immediately reported, also because certain resistance determinants were already expressed in the natural milieu where antibiotic-producing organisms were growing.

In fact, throughout their evolution, bacteria have developed natural defense mechanisms against antibiotics produced by co-resident organisms. Such mechanisms are today defined as *intrinsic resistance* determinants. For example, Enterococci express low-affinity penicillin-binding proteins (PBPs) that bind very poorly to beta-lactams. As a result, minimum inhibitory concentrations (MICs) for these agents in *Enterococcus faecalis* and *Enterococcus faecium* are in general 2–8 mg/L and 8–16 mg/L, respectively [5].

However, clinicians and scientists are more frequently and more significantly confronted with the phenomenon of *acquired resistance*, occurring in pathogens which were at first susceptible to a given antibacterial agent. Acquired resistance occurs as the result of the rapid development of mutations at the chromosomal level, or through the horizontal exchange of genetic resistance determinants, occurring more commonly via bacterial conjugation, but also by transformation (i.e., by transfer of naked DNA), or by phage transduction.

Transferrable genetic resistance determinants are most commonly carried by *transposons* and *plasmids*, and incorporation of resistance gene cassettes into target chromosomes may be facilitated by *integrons*, which encode specific recombinases catalyzing the exchange of genetic material by site-specific recombination reactions. For example, co-trimoxazole resistance is transmitted by all these three mobile elements, which are commonly causing overexpression of dihydrofolate reductase and dihydropteroate synthase by the transferable *dhfr1* and *sul1(Tn21* transposon*)/sulI2(IncQ/pBP1* plasmids*)* genes, respectively.

Resistance to a specific antibacterial agent often results in resistance to other, often chemically unrelated agents, due to the co-expression of multiple resistance genes within the same operon.

The transition of chromosomal resistance determinants multidrug-resistant plasmid cassettes is a well-characterized phenomenon. For example, whereas in earlier years transmission of fluoroquinolone resistance was mainly chromosomal, more

recently genetic resistance determinants like the efflux pumps OqxAB and QepA and the modified aminoglycoside acetyltransferase AAC(6′)-Ib-cr now reside in plasmids, also containing elements conferring resistance to beta-lactams, tetracyclines, aminoglycosides, sulfonamides, trimethoprim, and rifampin.

Resistance mechanisms may be transmitted across species (as happens, e.g., between *Klebsiella* spp. and *Pseudomonas aeruginosa*), but appear to be species-specific in some cases. For example, whereas beta-lactamase expression occurs mainly in Gram-negative bacteria, resistance to beta-lactams in Gram-positive organisms occurs more frequently through mutational modification of PBPs.

Resistance of pathogens to antibacterial agents occurs in most cases by way of (1) increased efflux of the drug from the cell, (2) decreased cell wall permeability to the drug, (3) activity of enzymes modifying or disrupting the drug, (4) bypass of drug-induced metabolic blockades within bacterial cells, (5) protection, mutation, overexpression, or modification of the drug targets.

Explanatory examples of special interest to urologists and to specialists involved in UTI diagnosis and treatment will be briefly described in the following paragraphs.

1. A variety of mechanisms, showing different degrees of drug specificity, regulate the *efflux of antimicrobials* from bacterial cells. Various drugs, such as fluoroquinolones, beta-lactams, macrolides, and tetracyclines, are substrates of such mechanisms. Efflux pumps belong to five families: the major facilitator superfamily (MFS), the adenosine triphosphate (ATP)-binding cassette (ABC) family, the resistance-nodulation-division (RND) family, the small multidrug resistance (SMR) family, and the multidrug and toxic compound extrusion family [6]. For example, tetracyclines are extruded against protons by means of Tet efflux pumps belonging to the MFS, but are also extruded by other efflux mechanisms, as in *Enterobacteriaceae* and *P. aeruginosa* tetracyclines are extruded by means of RND efflux pumps like AcrAB-TolC and MexAB-OprM, respectively [7]. RND pumps also act as proton antiporters, are typically expressed in *E. coli*, and can extrude a variety of other drugs like fluoroquinolones, beta-lactams, chloramphenicol, and macrolides.
2. Porins are beta-barrel proteins allowing transmembrane exchange of solutes with various degrees of specificity. Alterations in structure or expression of porins are most commonly responsible for *decreased cell wall permeability* to antimicrobials. Typical porins conferring resistance to *P. aeruginosa* or *K. pneumoniae* are, for example, OprD and OmpK25/36, respectively. Notably, porin alteration concurs, together with other mechanisms, to carbapenem-resistant phenotypes [7].
3. A variety of enzymes can induce *modifications to drug molecules* or can disrupt their structure, mainly by hydrolysis. Enzymes belonging to the first category include aminoglycoside acetyltransferases (AAC(6′)-I) expressed by both Gram-negative and Gram-positive bacteria, adenylyltransferases, and phosphotransferases. Bifunctional enzymes (acetyl- and phosphotransferases) are also frequently found in resistant organisms [8]. The genes encoding such resistance determinants are carried in most case by mobile genetic elements, but, as happens in

Enterococcus faecium, they are also expressed chromosomally. *Enterobacteriaceae* express very frequently AAC(6′)-I, together with *P. aeruginosa* and *Acinetobacter*. A plasmid-harbored mutated version of AAC(6′)-I, encoded by *AAC(6′)-Ib-cr*, has evolved to acetylate certain fluoroquinolones at a specific site of their piperazine ring.

Beta-lactamases can hydrolyze the cyclic amide bond of the four-membered lactam ring of beta-lactam agents, thus disrupting their inhibitory activity on the final phase of bacterial cell wall peptidoglycan biosynthesis. The activity of beta-lactamases has been characterized as early as 1940 [9], and from that moment on, discovery of new beta-lactams was invariably followed by the development of hundreds of chromosomal or transferable bacterial genes (*bla*) encoding more and more potent beta-lactamases [10]. Today, extended-spectrum beta-lactamases and carmapenemases are top worldwide medical emergencies. These resistance determinants will be described in greater detail in Sect. 1.3.1.

4. A typical example of resistance achieved through *bypass of the metabolic target of antimicrobial agents* is the resistance to sulfonamides. It is known that bacteria rely on their own enzymatic machinery for folate synthesis, and that sulfonamides act as competitive inhibitors of a major component of this machinery, the enzyme dihydropteroate synthase (DHPS). Thus, resistant pathogens can bypass this metabolic blockade by overexpressing DHPS through mutations in the promoter region of the DNA encoding such enzyme. Overproduction of dihydropteroic acid can overcome the ability of sulfa drugs to block folate production. An alternative "bypass" to such blockade is the acquisition of the ability to incorporate tetrahydrofolic and folinic acids from the environment, typically shown by Enterococci [11].
5. Resistance to antibacterial agents can be achieved by *protection, mutation, or modification of drug targets*. Glycopeptides (vancomycin, teicoplanin) bind the D-Ala–D-Ala portion of the pentapeptides of the peptidoglycan precursor and block the formation of peptide cross-links and bacterial wall synthesis. Vancomycin resistance in Enterococci involves the acquisition of a "cluster" of genes (located in most cases on Tn-3 transposons harbored within conjugative plasmids) encoding an enzymatic machinery that modifies the synthesis of peptidoglycans. The destruction of the normal D-Ala–D-Ala portion to prevent vancomycin binding to the cell wall precursors is one of the manifold mechanisms whereby such machinery can induce resistance to glycopeptides [12]. Bacterial resistance to fluoroquinolones occurs frequently via *protection or mutation of the target* of this class of agents, i.e., DNA gyrase and topoisomerase IV. The *qnr* gene product, expressed in the form of variant alleles (qnr A, B, C, D, S, VC, with comparable mechanism of action), is a pentapeptide repeat protein acting as a DNA homologue, able to bind to the DNA-binding sites of DNA gyrase and topoisomerase IV [13]. Well-characterized gyrase or topoisomerase-IV mutants conferring resistance to fluoroquinolones are, for example, *gyrA*, *gyrB*, *parC*, and *parE* [14].

The next section of this chapter will expand on some of the most worrisome resistance mechanisms among the ones described above, based on the type of pathogen expressing such determinants.

1.3 Emerging Resistance Threats

Antimicrobial resistance has been defined by the World Health Organization as "one among of the biggest threats to human health." Resistant Gram-negative pathogens like *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter* spp., involved in bacteremia, urinary tract infections, pneumonia, and intra-abdominal infections, but also multi-resistant Gram-positive Enterococci and Staphylococci are today the main driving force of such threat. Information and awareness thereof are thus of great significance to urologists and infectious disease specialists.

1.3.1 Gram-Negative Pathogens

1.3.1.1 Extended-Spectrum Beta-Lactamases (ESBLs), Carbapenemases

The most worrisome threats in the field of antibacterial therapy are represented by the worldwide surge of ESBL-producing multidrug-resistant (MDR) and carbapenemase-producing extensively drug-resistant *Enterobacteriaceae*.

ESBLs can be defined in different ways. Basically, ESBLs are a group of plasmid-transmissible enzymes, originated in the 1980s from a single-nucleotide mutation in the *blaSHV* gene, resulting in an altered structure of the catalytic serine site conferring a broader substrate spectrum and enabling these enzymes to hydrolyze antibiotics belonging to the penicillin, monobactam, and extended-spectrum cephalosporin groups.

The currently most common class variants of ESBLs are the CTX-M-type, TEM, sulfhydryl variable (SHV), and oxacillin (OXA) beta-lactamases, showing hundreds of genetic variants. The former is the most prevalent ESBL types globally, and has been found in association with insertion sequences (IS*Ecp1*) and transposable elements like Tn-*402* transposons, and can be included in a broad panel of phage-like and conjugative plasmids (reviewed in: [7]). ESBLs can be inhibited to various extents by beta-lactamase inhibitors like clavulanic acid, tazobactam, or sulbactam.

The therapy of choice for infections caused by ESBL-producing members of the *Enterobacteriaceae*—mainly *E. coli* and *K. pneumoniae*—is a carbapenem. However, the raise of worldwide carbapenem resistance in *Enterobacteriaceae* showing a multidrug-resistant phenotype is dramatically decreasing the therapeutic possibilities against such pathogens, both in adult and pediatric populations [15].

Comparison between the worldwide map of carbapenem resistance published by Nordmann et al. in the year 2014 [16] and a previous map released by the same authors in the year 2009 [17] gives a tangible impression of the dramatic surge of resistance to carbapenem antibiotics. Briefly, whereas in 2009 the spread of the

Klebsiella pneumoniae carbapenemase (KPC) in the USA was defined as *sporadic* in half of the federal states and *less than sporadic* in the rest of the states, in 2014 the whole of the USA has become affected by *endemic* isolation of KPC. The concern caused by such emerging resistance trend is due to the fact that carbapenemases are lactamases able to breakdown almost all beta-lactam antibiotics including in first place carbapenems that are today last-resource weapons in the struggle against Gram-negative complicated and life-threatening infections. Resistance to carbapenemases is in most cases mediated by horizontally transferable genetic elements (e.g., plasmidic or chromosomal integrons, transposons), also containing a multiplicity of resistance determinants, often conferring a multidrug- or extensively drug-resistant phenotype to carrier pathogens. Urinary catheters, mechanical ventilation, and previous exposure to broad-spectrum antibacterial agents and surgical procedures like transplantations are known risk factors for infection with carbapenem-resistant *Enterobacteriaceae* (CREB).

The 2016 report of the by the European Centre for Disease Prevention and Control reported that *K. pneumoniae* (KP) is the most prominent pathogen among carbapenemase-producing pathogens [18]. High mortality rates have been attributed to carbapenemase-resistant KP. A meta-analysis has shown that the mortality rate was as high as 42.1% in patients infected with carbapenemase-resistant KP, versus 21.2% in those infected with carbapenem-susceptible KP [19]. Moreover, the mortality of patients with UTIs was 13.5%, raising to 43.1% in intensive care unit cases. When the severity of infection was classified according to the resistance determinants, the mortality was 47.66% in patients infected with KPC-producing KP and 46.71% in those infected with VIM-producing KP. As far as the geographic distribution is concerned, the mortality reported in studies from North America, South America, Europe, and Asia was 33.2%, 46.7%, 50%, and 44.8%, respectively [19]. Concerning the specific mortality related to UTIs, a careful study by Hauck et al. reported that a *net excess hospital mortality* was not observed in hospitalized patients with UTI, compared to control populations [20].

Several groups of carbapenemases have emerged in the last decade, showing different efficiency in their hydrolytic activity as well as distinct catalytic site structures, which direct their assignment to different classes.

Class A enzymes include among others (SME, IMI, GES-5) the plasmid-encoded *K. pneumoniae* carbapenemase (KPC), which has an active serine in its catalytic site, and which is only weakly inhibited by clavulanate and tazobactam. Class A carbapenemases can hydrolyze virtually all beta-lactam agents, including carbapenems, penicillins, broad-spectrum cephalosporins, and monobactams. However, cefamycins and ceftazidime are only weakly hydrolyzed by these enzymes [17]. KPC genes are frequently located within the IncFIIK2, IncF1A, IncI2 plasmids and Tn4401 transposon and are at the moment the most common transmissible class A genes in *Enterobacteriaceae* worldwide [21]. Notably, strains of KP harboring the bla_{KPC} gene, which is present in plasmids showing various structures and dimensions, are very often co-resistant to co-trimoxazole, fluoroquinolones, and aminoglycosides [22]. Many variants of KPC have been isolated worldwide in various settings, including acute care facilities, intensive care units, and tertiary care

hospitals, but are also increasingly found in community-acquired infections. In Europe, their diffusion is endemic in Greece, Italy, and Poland [17]. KPC are classified on the basis of their variant amino acid sequences, KPC-2 and-3 variants having been isolated worldwide. Importantly, KPC-producing uropathogens are often difficult to identify, as routine disc-diffusion tests report them as carbapenem-susceptible or borderline-intermediate. Indeed, it is known that the resistant phenotype in these cases is fully expressed when other resistance determinants, for example, outer membrane permeability defects or efflux pumps, are compresent.

The most representative family of genes encoding for *class C beta-lactamases* is AmpC, a penicillinase/cephalosporinase harbored in chromosomes of *Enterobacter* spp. Class C enzymes do not include carbapenemases, are not inhibited by clavulanic acid, and show poor activity against monobactams.

The *D class* includes over 400 serine oxacillinase-type OXA beta-lactamases, divided into several subgroups and often found within the IncL/M, Tn1999, and IS1999 mobile genetic elements. OXA-48 and its derivative variants are commonly identified in *K. pneumoniae*, *E. coli*, and *E. cloacae*, and are today disseminated throughout Europe, Mediterranean countries, and the world [23]. OXA enzymes can breakdown penicillins at high rate, carbapenems at a low level, and expanded-spectrum cephalosporins to a limited extent. Despite such weak carbapenemase activity, carbapenem resistance may result from the combined action of an OXA-type carbapenemase with other mechanisms such as mutated porins or overexpressed efflux pumps [24].

Unlike class A and D serine enzymes, class B metallo beta-lactamases (MBL) require zinc for their catalytic nucleophilic reaction directed toward the beta-lactam ring. These enzymes, expressed in *Enterobacteriaceae* (including *Klebsiella oxytoca*) and in *P. aeruginosa*, can hydrolyze a broad range of beta-lactams (with the exception of aztreonam, but not in all strains) and are known to be resistant to all beta-lactamase inhibitors so far produced [17]. Transferable MBL genes include the New Delhi MBL (NDM, found in IncA/C, ISAba125, and other mobile genetic elements), the Verona Integron-encoded MBL (VIM, found in IncN, IncI1, and other mobile genetic elements), the IMP beta-lactamase (found in IncL/M, IncA/C, and other mobile genetic elements), and the German imipenemase (GIM-I) MBL, detected in Germany in *E. cloacae*, *K. oxytoca*, and *E. coli* isolates [22, 25, 26]. The NDM enzymes share little amino acid identity with other MBLs, and hydrolyze carbapenems to various extents, with the NDM-4, NDM-5, and NDM-7 variants showing increased breakdown activity. NDMs are often co-expressed with other carbapenemases (OXA-48, VIM, and KPC), and are almost always associated with various resistance determinants, such as plasmid-borne AmpC cephalosporinases, clavulanic acid-inhibited ESBLs, and determinants conferring resistance to aminoglycosides (e.g., 16S RNA methylases), quinolones (e.g., Qnr), macrolides (esterases), rifampicin, chloramphenicol, and co-trimoxazole [22]. Thus, basically most NDM-expressing pathogens show residual susceptibility only to colistin or fosfomycin, which represents a very limited choice among last-resource agents.

1.3.1.2 Polymyxin Resistance Determinants

The mobilized colistin resistance *mcr-1* gene encodes a phosphatidylethanolamine transferase, which modifies cell membrane lipid A to decrease its affinity to colistin. The *mcr-1* gene has been detected in *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. [27]. The increasing diffusion of this plasmid-borne, cross-species transferable resistance gene, likely facilitated by the usage of colistin as cattle fattening agent in Asia and elsewhere, will soon compromise the efficacy of this last-resort antibiotic for treatment of carbapenem-resistant *Enterobacteriaceae*.

1.3.1.3 Plasmid-Mediated Fluoroquinolone Resistance

Plasmid-mediated fluoroquinolone (FQ) resistance (PMQR) in *Enterobacteriaceae* is dramatically increasing worldwide, and in many countries quinolones are no longer recommended as drugs of choice for treatment of UTIs and other uro-genital infections like prostatitis. International guidelines from the Infectious Diseases Society of America, the European Society for Microbiology and Infectious Diseases and other agencies no longer recommend empirical administration of fluoroquinolones in areas showing resistance rates higher than 10% (raised to 20% in the Asia-Pacific region) [28, 29].

As mentioned in the previous section, FQs interfere with the activity of bacterial gyrase (main target in Gram-negative pathogens) and topoisomerase IV (main target in Gram-positive organisms), which are essential for DNA replication and cell duplication. Mutations (e.g., *gyr*A, *gyr*B, *par*C, *par*E) occurring on the *quinolone resistance determining regions* of genes encoding these type II topoisomerases are the most common chromosomal determinants of FQ resistance [14]. Determinants of PMQR also include (1) the *qnr* genes, whose *pentapeptide-repeat* product protects DNA gyrase from the interaction with FQs, (2) the variant aminoglycoside acetyl-transferase *aac (6′)-Ib-cr*, which acetylates and inactivates the piperazine ring of certain FQs, (3) the *qep*A-encoded efflux pumps, sharing sequence homology with MFS 14-transmembrane transporters, and (4) the *oqxAB*-encoded efflux pumps, very common in *K. pneumoniae* and *E. coli*-borne plasmids, but also on bacterial chromosomes [30–33].

Determinants of PMQR are commonly associated with genes encoding ESBLs, AMP-C beta-lactamases, and other genetic elements conferring resistance to various antibacterial agents. *qnrA1, A3, A6, B2, B4, B6*, and *B10* are associated with the mobilizing element insertion sequence ISCR, whereas *qnrB1* and *B20* are associated with IS26 and Orf1005. The *aac (6′)-Ib-cr* enzyme-encoding gene is often found in association with *qnr*B and *blaCTX* in a cassette within an IS26 transposon. *qep*A and the OqxAB-encoding genes are also often mobilized by IS26 transposons.

In Europe, the areas most affected by increasing resistance trends are the Mediterranean countries, together with Mediterranean North African regions. A comprehensive systematic review by Yanat and coworkers included a map describing the geographic distribution of high-rate PMQR, extending to the entire Mediterranean area, including Spain, Tunisia, Italy, France, Algeria, Egypt Morocco, Greece, Slovenia, Croatia, and Turkey [34].

1.3.1.4 *Pseudomonas aeruginosa*

Multidrug-resistant (MDR) *P. aeruginosa* (PA) is steadily expanding worldwide. Isolates of MDR PA show resistance to third-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones, whose determinants are expressed within transposons, plasmids, and integrons. It has been reported that ESBL typically found in *Enterobacteriaceae* (e.g., PER-1, VEB, GES, and BEL-1) are gradually spreading to PA [35]. Similarly, the KPC carbapenemase, previously found exclusively in *Enterobacteriaceae*, as well as several metallo-beta lactamases (IMP, VIM, SPM) are increasingly found in PA [35, 36]. In this context, Nordmann and coworkers foresee that pan-drug resistance in ICU-acquired PA will be increasingly reported worldwide [35].

1.3.2 Gram-Positive Cocci

Enterococci, the third most frequently isolated pathogens in the hospital setting, are among the most common etiological determinants of urinary tract infections. In these species, expression of penicillinase resistance determinants is infrequent, though Enterococci are intrinsically resistant to cephalosporins via expression of penicillin-binding proteins (PBP) showing low affinity for these antibiotics (MIC range: 2–16 mg/L for Enterococci). Resistance to ampicillin and similar agents is mainly present in *E. faecium*, also due to the presence of low-affinity PBP. Enterococci may also acquire beta-lactamases via horizontal transfer of *bla* genes or similar.

The ability of Enterococci to uptake folic acid from the surrounding milieu makes them naturally resistant to co-trimoxazole. *E. faecalis* is also intrinsically resistant to lincosamides, though this characteristic is probably of lesser importance in the management of UTIs, as agents like clindamycin are mainly excreted through the biliary system.

Enterococci are intrinsically non-susceptible to aminoglycosides due to inability of these to enter coccal cells in the absence of a cell wall synthesis inhibitor. Hence, co-administration of a penicillin confers a synergic and rapidly bactericidal action to this antibiotic combination. Nevertheless, as described in the previous section, Enterococci can become resistant to aminoglycosides mainly by acquisition of modifying enzymes like phosphotransferases and nucleotidyltransferases. Importantly, acetyltransferases (AAC) like AAC(6′)-Ii are ubiquitous among *E. faecium*. As mentioned above, high-level aminoglycoside resistance occurs through acquisition of a bifunctional resistance determinant encoding a phosphotransferase and an acetyltransferase, *aph(2″)-Ia-aac(6′)-Ie* [37].

Conjugation in Enterococci is made easy by pheromone-stimulated production of *aggregation substance*, which facilitates cell–cell contact by interacting with the *enterococcal binding substance*, thus resulting in horizontal exchange of resistance determinants [5].

Three types of transposons facilitate gene exchange in Enterococci: Tn3, composite, and conjugative transposons. An example of the former is the common Tn917, conferring resistance to macrolides, lincosamides, and dalfopristin.

Acquired resistance to glycopeptide antibiotics is given by five determinants (clusters): VanA, VanB, VanD, VanE, and VanG, responsible for the expression of peptidoglycan pentapeptide precursors (PPP) showing decreased binding affinity for vancomycin and other glycopeptides. In particular, VanA-type Enterococci are also resistant to dalbavancin, a last-generation glycopeptide, but retain susceptibility to oritavancin, possibly due to the dual mechanism of action—including transglycosidase inhibition—shown by this second-generation agent [38]. Horizontal transfer of Van genes may occur via Tn-1546 transposons, which are found in conjugative and non-conjugative plasmids [5].

In Gram-positive cocci including Enterococci, resistance to fluoroquinolones is given by mutations occurring in the gyrase and topoisonerase-IV *GyrA* and *ParC* genes, with higher MICs achieved by cumulative mutations in both genes [39].

The synergistic bactericidal activity of the streptogramin combination quinupristin/dalfopristin (QD) is due to the binding of the two agents to different domains of the 50S ribosomal subunit of vancomycin-susceptible or -resistant *E. faecium. E. faecalis* is resistant to these streptogramins in most cases, due to the activity of the Lsa efflux pump, which is probably expressed constitutively by this species. Streptogramin resistance is also mediated by drug-modifying enzymes. Quinupristin resistance in Enterococci is given by acetyltransferases encoded by plasmid-mediated *vatD and vatE* genes, whereas dalfopristin resistance is mediated by lyases encoded by *vgb(A)* and *vgb(B)* genes [38].

Resistance to the oxazolidinone linezolid is acquired via mutations in the target genes encoding the 23S ribosomal RNA. In particular, the G2576T point-mutation has been detected in Enterococci in several countries [40, 41], whereas the transferable *cfr* gene, identified in *E. faecalis,* encodes a rRNA methyltransferase which prevents the binding of linezolid through modification of the linezolid binding region of the 23S rRNA.

1.4 Recommendations and Future Perspectives

- Detailed diagnostic guidelines, treatment algorithms, and expert recommendations are regularly published and upgraded worldwide (e.g., [42, 43]). Strict adherence to such guidelines and recommendations is encouraged by national and international health organizations, by academic institutions, and by scientific/medical societies.
- Strict stewardship strategies, aimed at selecting types, optimal dosages, and combinations of antibacterial agents aimed at minimizing the emergence and spread of chemoresistance should be applied worldwide, and modifiable practice patterns should be implemented in those countries where bad prescription practices, negligent dispensation attitudes, and incorrect patient compliance are highly prevalent.
- To date, available options for treatment of CREB infections are limited to polymyxins and aminoglycosides, but toxicity and adverse effects of these agent classes often hinder the implementation of effective therapeutic protocols.

- Many *in vitro* studies have shown that combination therapy with various classes of antibacterial agents shows enhanced cure rates of infections caused by CREB. These protocols may include aminoglycosides, aztreonam, colistin, rifampicin, tigecycline, or fosfomycin (e.g., [44]). Several studies seem to univocally show that combination therapy with two or more *in vitro*-active agents are associated with lower mortality than treatment with a single *in vitro*-active agent. Presentation of various possible combination regimens is beyond the scope of this chapter.
- Research focusing on suppressive drug combinations, a seemingly paradoxical phenomenon showing that selection of resistant mutants can be inverted by administration of hyper-antagonistic combinations of antibacterial agents, produced interesting preliminary results and should be further investigated, though it is still early to imagine how such findings will be implemented in the clinics [45, 46].

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Bacterial Resistance: What Is the Epidemiological Scenario?

2

David M. Livermore

2.1 Introduction: the Nature of Resistance

Antibiotics kill susceptible bacteria while leaving resistant ones to survive and to accumulate. The initial emergence of resistance is random, contingent of chance genetic events. Its subsequent accumulation reflects the extent of selection pressure, meaning the weight of antibiotic use, the strength or weakness of infection control, and the fitness of the strains that have acquired resistance.

At a genetic level, resistance can arise via mutations—DNA copying errors—that engender resistance in a previously-susceptible strain or species, or by transfer of mobile DNA, in the form of transposons or plasmids carrying resistance genes. Plasmids existed in the pre-antibiotic era but have since become major vectors of resistance, recruiting and spreading genes from organisms which, of themselves, have little or no clinical relevance [1]. For example, (1) many of the genes that encode aminoglycoside-modifying enzymes were mobilized to plasmids from aminoglycoside-producing streptomycetes [1, 2]; (2) the genes encoding the (now predominant) CTX-M extended-spectrum β-lactamases (ESBLs), responsible for cephalosporin resistance originated in environmental *Kluyvera* spp. [2], and (3) those encoding OXA-48 carbapenemases were recruited from free-living *Shewanella* spp. [3].

Over time, the accumulation of mutations and or resistance plasmids can lead to historically susceptible species becoming broadly resistant, with the drug "lost," as with *Escherichia coli* in the case of ampicillin or *Staphylococcus aureus* and penicillin [4].

Resistance can also accumulate because inherently resistant species became more important at the expense of more susceptible ones. This is important in the case of opportunistic gram-negative infections in vulnerable hospitalized patients,

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where *Enterobacter*, *Klebsiella*, and *Pseudomonas* spp. have gained importance over time, but is less so in the case of UTIs, where *Escherichia coli* has remained the principal pathogen since before the antibiotic era [5].

2.2 Resistance and the Pathogens of UTI

E. coli accounts for around 65–90% of UTIs, regardless of whether these are complicated or uncomplicated, affect the lower or upper urinary tract, and are community- or hospital-acquired [5].

As a species, *E. coli* has little inherent resistance except to antibiotics that cannot penetrate gram-negative bacteria in general or which are very rapidly effluxed (e.g., macrolides, clindamycin, oxazolidinones, glycopeptides, rifampin, and fusidic acid) [6]. Rather, most resistance to UTI-relevant β-lactams, aminoglycosides, and antifolates arises from plasmid acquisition; most resistance to fosfomycin and fluoroquinolones arises via mutation (Table 2.1; Refs. [7–20]).

Among other important gram-negative uropathogens, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa* all have greater inherent resistance than *E. coli* owing to (1) the production of more potent chromosomally encoded β-lactamases and (2) slower uptake, reflecting a less favorable (from the clinician's standpoint) balance of uptake and efflux, with efflux particularly important in the case of *P. aeruginosa* (Table 2.2) [6, 7, 21]. *Proteus mirabilis*, another frequent gram-negative uropathogen, is inherently more susceptible than *E. coli* to many β-lactams and fluoroquinolones, but is inherently resistant to colistin, tetracyclines, and nitrofurantoin (Table 2.2) [22–24].

Non-*E. coli* Enterobacteriaceae, including *Klebsiella*, *Enterobacter*, and *Proteus* spp., as well as rarer uropathogens such as *Serratia*, *Morganella*, and *Providencia* spp. commonly acquire the same plasmid-mediated resistances as *E. coli*; plasmid-mediated resistance is rarer in *P. aeruginosa*, with mutational mechanisms—notably, upregulation of efflux and hyperproduction of chromosomal AmpC β-lactamase—much more important (Table 2.2) [24].

Among frequent gram-positive uropathogens, *Enterococcus faecalis* remains almost universally susceptible to ampicillin, but with universal inherent resistance to cephalosporins and mecillinam owing to target insensitivity [23]; *Staphylococcus saprophyticus* is often resistant to unprotected ampicillin but typically remains susceptible to amoxicillin/clavulanate.

Table 2.1 Major mechanisms of resistance among *E. coli* isolates to UTI-relevant antibiotics

Drug class affected	Major plasmid-mediated mechanisms	Major mutational mechanisms
Ampicillin [7]	TEM, SHV, OXA β-lactamases	Upregulation of chromosomal AmpC β-lactamase, by loss of terminator codons
Mecillinam [8]	ESBLs (variable, with type SHV-5 strongly active, CTX-M-15 moderately active, and CTX-M-9/14 minimally active)	Multiple mutations affecting the stringent response and thereby compensating for inhibition of penicillin-bring protein-2 by mecillinam
Cephalosporins (first generation) [7, 9]	TEM, SHV β-lactamases (marginal) ESBLs (mostly CTX-M types)	Upregulation of chromosomal AmpC β-lactamase, by loss of terminator codons
Cephalosporins (3/4 generation) [7, 9]	ESBLs (mostly CTX-M types); plasmid-mediated AmpC β-lactamases	Upregulation of chromosomal AmpC β-lactamase, by loss of terminator codons; compromises third-generation analogs only
Amoxicillin/clavulanate and piperacillin/tazobactam [10, 11]	Hyperproduction of TEM β-lactamases; OXA-1 or plasmid-mediated AmpC β-lactamases; mutant TEM β-lactamases with reduced inhibitor binding	Upregulation of chromosomal AmpC β-lactamase, by loss of terminator codons
Carbapenems [9, 12, 13]	Metallo-carbapenemases (NDM, VIM, IMP)[a], also KPC[a], and OXA-48-like[b] serine β-lactamases	Porin loss together with plasmid-mediated ESBLs or AmpC enzymes or upregulation of chromosomal AmpC β-lactamase, by loss of terminator codons
Trimethoprim [14, 15]	Multiple trimethoprim-resistant dihydrofolate reductases, compensating for inhibition of corresponding chromosomal enzymes	
Sulfonamide [15]	Sul1/2 sulfonamide-resistant dihydropteroate synthases, compensating for inhibition of corresponding chromosomal enzymes	Mutations affecting chromosomal dihydropteroate synthase
Fluoroquinolones [16]	Qnr efflux pumps and mutant AAC(6′)-1b-cr, augmenting resistance, though unable to cause resistance as sole mechanism	Mutations affecting both DNA gyrase and topoisomerase IV
Aminoglycosides [17, 18]	Enzymes modifying aminoglycosides by acetylation, nucleotidylation, or phosphorylation. Amikacin is compromised by fewer such enzymes than gentamicin or tobramycin Methyltransferase enzymes modifying rRNA to block binding of all relevant aminoglycosides	Rare
Fosfomycin [8, 19]	FosA enzymes, adding glutathione to fosfomycin and thereby inactivating the drug	Loss of hexose and triose sugar transporters ordinarily exploited by fosfomycin for uptake across the cytoplasmic membrane
Nitrofurantoin [8, 20]		Mutations to nitroreductase-encoding *nfsA* and *nfsB* genes

[a]Also confer resistance to penicillins, penicillin/β-lactamase-inhibitor combinations, and cephalosporins
[b]Also confer resistance to penicillins, penicillin/β-lactamase-inhibitor combinations, not cephalosporins

Table 2.2 Inherent and acquired resistance in important uropathogens besides *E. coli*

Species or genus	Inherent resistances, present in all/almost all isolates [22, 23]	Acquired resistances
Klebsiella spp., except *K. aerogenes*	Ampicillin, owing to chromosomal SHV-like β-lactamases; nitrofurantoin; fosfomycin at doses used for oral therapy	As *E. coli*, Table 2.1
Enterobacter spp., also *K. aerogenes* and *Citrobacter freundii*	Ampicillin, amoxicillin/clavulanate, and first-generation cephalosporins owing to chromosomal AmpC β-lactamases; nitrofurantoin; fosfomycin at doses used for oral therapy	As *E. coli*, Table 2.1; heightened risk of mutational hyperproduction of chromosomal AmpC β-lactamases leading to cephalosporin resistance
Proteus mirabilis	Nitrofurantoin (high level); tetracyclines; colistin	As *E. coli*, Table 2.1
Serratia, Morganella, and *Providencia* spp.	Ampicillin, amoxicillin/clavulanate, and first-generation cephalosporins owing to chromosomal AmpC β-lactamases; nitrofurantoin (high level); fosfomycin at doses used for oral therapy; colistin	As *E. coli*, Table 2.1; heightened risk of mutational hyperproduction of AmpC β-lactamases leading to cephalosporin resistance *Serratia* only, heightened risk of hyperproduction of chromosomal AAC(6′)-Ic conferring aminoglycoside resistance
Pseudomonas aeruginosa	All *except* piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, aminoglycosides, and colistin	Mostly via mutation: hyperproduction of chromosomal AmpC compromises piperacillin/tazobactam and ceftazidime; upregulation of various efflux pumps compromise all agents except imipenem and colistin; loss of porin OprD compromises imipenem and meropenem; reduced cytoplasmic membrane transport compromises aminoglycosides; mutations to DNA gyrase and topoisomerase IV compromise fluoroquinolones [6, 24]

2.3 Prevalence of Resistance

The likelihood of resistance in a clinical isolate depends on time, place, and risk factors pertinent to the specific patient. Owing to the great limitations of resistance surveillance for UTIs, described in the next section, it is not helpful to provide long catalogues of reported resistance rates by country or region. Rather, it is better to stress general principles, and to encourage development of better local surveillance to guide empirical therapy and international comparisons. What these systems need to deliver, and how to achieve this, is outlined at the end of this chapter.

There is no doubt that resistance to relevant antibiotics has accumulated substantially in relevant uropathogens. At introduction, ampicillin (1963),