Review Article



# Resistance mechanisms

**Yasemin Cag[1], Hulya Caskurlu[1], Yanyan Fan[2], Bin Cao[3], Haluk Vahaboglu[1]**

[1]Enfeksiyon Hastaliklari ve Klinik Mikrobiyoloji Department, Istanbul Medeniyet Universitesi Goztepe Egitim Arastirma Hastanesi, Istanbul, Turkey; [2]Lab of Clinical Microbiology and Infectious Diseases, [3]Department of Respiratory and Critical Care Medicine, China-Japan Friendship Hospital, Beijing 100029, China

*Contributions:* (I) Conception and design: H Vahaboglu; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Y Cag, H Caskurlu, Y Fan; (V) Data analysis and interpretation: B Cao, H Vahaboglu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Haluk Vahaboglu. Istanbul Medeniyet Universitesi, Goztepe Egitim ve Araştırma Hastanesi, Dr. Erkin caddesi, Kadıköy, 34722 Istanbul, Turkey. Email: vahabo@hotmail.com.

**Abstract:** By definition, the terms sepsis and septic shock refer to a potentially fatal infectious state in which the early administration of an effective antibiotic is the most significant determinant of the outcome. Because of the global spread of resistant bacteria, the efficacy of antibiotics has been severely compromised. *S. pneumonia*, *Escherichia coli* (*E. coli*), *Klebsiella*, *Acinetobacter*, and *Pseudomonas* are the predominant pathogens of sepsis and septic shock. It is common for *E. coli*, *Klebsiella*, *Acinetobacter* and *Pseudomonas* to be resistant to multiple drugs. Multiple drug resistance is caused by the interplay of multiple resistance mechanisms those emerge via the acquisition of extraneous resistance determinants or spontaneous mutations. Extended-spectrum beta-lactamases (ESBLs), carbapenemases, aminoglycoside-modifying enzymes (AMEs) and quinolone resistance determinants are typically external and disseminate on mobile genetic elements, while porin-efflux mechanisms are activated by spontaneous modifications of inherited structures. Porin and efflux mechanisms are frequent companions of multiple drug resistance in *Acinetobacter* and *P. aeruginosa*, but only occasionally detected among *E. coli* and *Klebsiella*. Antibiotic resistance became a global health threat. This review examines the major resistance mechanisms of the leading microorganisms of sepsis.

**Keywords:** *Acinetobacter*; drug resistance, multiple; *Escherichia coli* (*E. coli*); *Klebsiella*; *Pseudomonas*; shock; septic; beta-lactamases; carbapenemase

Submitted Aug 02, 2016. Accepted for publication Sep 07, 2016.
doi: 10.21037/atm.2016.09.14
**View this article at:** http://dx.doi.org/10.21037/atm.2016.09.14

In general, bacteria resist to the inhibitory action of antibiotics through three primary mechanisms that often operate concurrently with each other. These are decreased uptake of the drug (1,2), target modification (3) and inactivation of the drug (4). Resistance develops among microorganisms by spontaneous mutations in existing genes or by the acquisition of extraneous genes. The survival and success of resistant mutants, on the other hand, is a matter of cost of fitness to the environment (5,6).

## Resistance mechanisms

### *Decreased uptake of antibiotics*

Bacteria may avoid accumulation of antibacterial molecules on their targets by reducing the absorption of these molecules or increasing the discharge of them, or by employing both mechanisms simultaneously.

In general, antibiotics must penetrate the outer membrane (OM) of bacteria to reach to their targets. The

OM of Gram-negative bacteria consists of a lipid bilayer and porins (7). In theory, hydrophobic antibiotics, such as quinolones and macrolides, pass through the lipid bilayer while hydrophilic antibiotics, such as beta-lactams, pass through porins (7,8). However, the OM of bacteria is a highly complex structure, and the permeation pathways of antibiotics are not fully understood (9). In some way, the OM of bacteria may be modified via the substitution of even one or two amino acids and transform to a permeability barrier for antibiotics.

Upregulated efflux molecules may work concurrently with porin modifications which dramatically augment the discharge of antibiotics, thereby avoiding accumulation on target (2). Efflux-mediated resistance to tetracycline was first detected among *Escherichia coli* (*E. coli*) isolates during the 1970s (10,11). Since then, various structures operating as efflux pumps have been discovered. The substrate specificity of efflux pumps varies widely, and some of them have an extraordinarily broad spectrum (12). Efflux pumps are accepted as one of the primary mechanisms of multi-drug resistance (MDR) among bacteria, particularly among gram-negative bacteria (12,13).

### *Target modification*

Bacteria replace or modify target molecules to avoid the harmful effects of antibiotics (14). Methicillin resistance among *Staphylococcus aureus* (*S. aureus*) was first noticed in the 1960s which emerge through the replacement of the target molecule (15). Beta-lactam antibiotics inactivate PBPs, particularly PBP 2 of *S. aureus*, initiate dysregulation of peptidoglycan synthesis and trigger a chain of events that eventually lead to the death of the bacteria (16). Methicillin-resistant *S. aureus* produces PBP 2a, a homolog enzyme with a low affinity to beta-lactam antibiotics, which is fully active and able to restore the vital functions of inactivated PBPs. PBP 2a is encoded on the *mec* locus, a gene package that is extraneous, likely evolved and spread from another Staphylococcus species to *S. aureus* (17).

There are several modes of target modification. Resistance to linezolid occurs by the alteration of 50S subunit of rRNA (3). Another form of target modification occurs through the methylation of ribosomal genes. Methylation protects the target molecule from the inhibitory effect of antibiotics. Macrolide resistance is mostly caused by this type (18).

Plasmid-mediated quinolone resistance (PMDR) is a notable example of target protection. Some proteins are capable of protecting gyrase from the inhibition of quinolones (19). These unique proteins are encoded on naturally occurring alleles, which are now referred to as "*qnr*" and primarily spread on multi-resistance plasmids, mostly along with extended-spectrum beta-lactamases (ESBLs) (19,20).

Bacteria, specifically *Acinetobacter spp*., resist to polymyxin antibiotics by modifying the lipid A component of the OM through spontaneous mutations (21,22). It was, however, surprising to discover that plasmidic colistin resistance conferred by lipid A modifying enzymes are insidiously spreading around the members of Enterobacteriaceae (23,24).

### *Enzymatic inactivation of antibiotics*

Resistance to aminoglycosides emerged among various species of bacteria, particularly among Gram-negatives, Gram-positives, and *Mycobacterium*, due to the dissemination of aminoglycoside-modifying enzymes (AMEs) on mobile genetic elements (25). AMEs mimics the rRNA targets of aminoglycosides ,and so can pair with aminoglycosides in the replacement of the target molecule and inactivate them (26).

Beta-lactamase-mediated resistance accounts for the most significant negative impact on human health care. Beta-lactam antibiotics attack PBPs and interfere with cell wall synthesis. Three-dimensional configuration of beta-lactamases imitates PBPs. Therefore, beta-lactamases can bind to and inactivate beta-lactam antibiotics as a substitute of PBPs (27).

Beta-lactam antibiotics are natural products of some microorganisms. Therefore, in nature, even before the human history, microorganisms produced beta-lactamases and survived against antibiotic producers (28). These enzymes remained rare before the mass-production and consumption of beta-lactam antibiotics. Extensive selective pressure caused by the widespread use of antibiotics enabled the evolution and dissemination of beta-lactamases, especially among gram-negative microorganisms. This scenario repeated after the introduction of every new beta-lactam antibiotic to the market, irrespective of how expanded the spectrum of the new antibiotic was. Now, gram-negative microorganisms produce various beta-lactamases simultaneously and confer resistance to multiple classes of beta-lactam antibiotics.

Ambler classified beta-lactamases under four molecular classes, Class A through Class D (29). Enzymes from molecular Class A, Class C and Class D are typically

 

serine beta-lactamases, while enzymes from Class B are metalloenzymes (MBLs) those require zinc ion for activation.

The distinctive feature of Class A beta-lactamases is that these enzymes are highly susceptible to inhibitor beta-lactams clavulanate, sulbactam, and tazobactam (30). Most Class A enzymes exhibit extended-spectrum activity towards third-generation cephalosporins. These enzymes are also referred to as ESBLs and evolved from a TEM, SHV or CTX-M narrow-spectrum precursor by one or more amino-acid substitutions. TEM and CTX-M type Class A ESBLs are primarily encoded on a mobile element and have a tendency to spread among the members of Enterobacteriaceae, whereas VEB and PER type Class A ESBLs have a tendency to spread among *Acinetobacter* and *Pseudomonas* (31,32). KPC type enzymes are Class A carbapenemases, classically found among *Klebsiella* species (33).

AmpC enzyme of Enterobacter cloacae is the most studied chromosomally-encoded Class C enzyme (34). Typically, this is an ESBL, encoded on the chromosome downstream to some regulatory genes and, hence, inducible. Clinical significance of being inducible is that exposure to a substrate, such as cefotaxime and ceftazidime, causes overexpression of the enzyme which increases the MICs and leads to treatment failures.

Class D enzymes (oxacillinases) are weak-to-moderate substrates of beta-lactamase inhibitors (30). Genes encoding oxacillinases are mostly joined to an insertion sequence or located in an integron as a gene cassette (35). OXA-carbapenemases have variable substrate specificity. However, they are usually weak carbapenemases and confer high-level resistance to carbapenems with the simultaneous involvement of other resistance mechanisms (35,36).

MBLs, belonging to Ambler Class B, have high hydrolytic capability over carbapenem antibiotics and spread on virulent or resistant plasmids. The dissemination of MBLs herald the emergence of pan-resistant bugs and an approaching health-care crises worldwide (37).

## Evolution of resistance and mobile genetic elements

Spontaneous mutation is one of the key mechanism bacteria use to survive stress conditions. Mutation frequencies of bacterial species are limited but may change in stress conditions (38). Environmental stress factors, such as antibiotic pressure, may select bacterial subsets with deficient DNA mismatch repair mechanisms. These bacterial subsets with less DNA replication fidelity are termed as mutators. A mutator may have 100 to 1,000 times the mutation rate of the wild-type bacteria. Therefore, mutators readily accumulate compound mutations to develop complex resistance mechanisms and gain a short term fitness advantage (39).

Mobile genetic elements, jumping genes (40), are the principal means of the spread and accumulation of resistance genes. From the simplest to most complex; insertion sequence, integron, transposon, and plasmid are currently explored mobile elements.

An insertion sequence (IS) is a short transposable DNA element composed of one or two genes encoding a transposase, a protein with recombinase activity, along with flanking inverted repeat sequences of various lengths on both sites (41). Based on a site-specific recognition, ISs wrap and carry a resistance gene, for example, a beta-lactamase gene, and its promoter sequence during transposition (42). A site-specific recombination means that ISs and associated resistant genes spread selectively among bacteria. A transposon is a more composite form of IS, bracketed by inverted ISs on both extremes and therefore capable of carrying more than one genetic determinant. Transposons may cause complex DNA rearrangements and may accumulate various resistance genes to confer an MDR phenotype (43). Integron is another mobile structure, composed of an integrase gene and a promoter sequence for its cargo. Gene cassette is a gene associated with a 59-base element which enables the gene to integrate to an integron. Integrons may carry multiple resistance determinants simultaneously (44,45).

The structures as mentioned earlier may unintentionally accumulate over a plasmid during the evolution, thereby conferring resistance to virtually all antibiotics (43). These plasmids with MDR islands spread among compatible microorganisms.

## Leading microorganisms and major resistance mechanisms: a global perspective

Studies reporting gram-positive bacteria as the predominant etiology of sepsis and septic shock are rare (46). Most studies found gram-negative bacteria as the leading cause (47-49). Predominant pathogens identified in severe sepsis and septic shock, however, may vary among studies depending on the setting, study time and the country in which the study conducted. A prospective observational study carried out in multiple ICUs in China found pneumonia as the most common underlying disease associated with sepsis

 

and septic shock (86.6%). In this study, *Acinetobacter* was the predominant microorganism (14.1%), followed by *Pseudomonas* spp. and *Klebsiella* spp. (48). A study conducted in 12 ICUs in France between 1996 and 2009, reported *S. pneumoniae* as the most common etiology of community-acquired sepsis followed by *E. coli*, whereas non-fermenters such as *Acinetobacter*, *Pseudomonas*, and *Stenotrophomonas* were the most common etiologies among nosocomial sepsis cases (50).

Briefly, *S. pneumonia*, *E. coli*, *Klebsiella*, *Acinetobacter*, and *Pseudomonas* are the predominant pathogens of sepsis and septic shock. Except *S. pneumoniae*, the MDR phenotype is common among these pathogens.

Therefore, main resistance mechanisms contributing to the MDR phenotype among these species worth mentioning.

### *E. coli* & *Klebsiella*

Resistance is almost always plasmidic among *E. coli* and *Klebsiella*; the contribution of porin and efflux-mediated mechanisms are negligible. The hallmark of the MDR phenotype among *E. coli* and *Klebsiella* is the co-transfer of genes encoding an AME, a quinolone resistance determinant, and an ESBL on the same resistance plasmid (51,52).

ESBLs belonging to the CTX-M family are widespread among *E. coli* and *Klebsiella* (53-55). The recent spread of Class B carbapenemases among the members of Enterobacteriaceae is the herald of pan-resistant pathogens. VIM, IMP, and NDM-type Class B carbapenemases are increasingly more reported among *E. coli* and *Klebsiella* (43,51,56-59). The OXA-48 family is the primary OXA-type carbapenemase found among Enterobacteriaceae. The OXA-48 family enzymes were first reported from Turkey. These enzymes are weak carbapenemases. However, mutants of OXA-48 with various hydrolytic capabilities have also been identified (60). The OXA-48 family enzymes are mostly susceptible to expanded-spectrum cephalosporins like ceftazidime and cefepime (61).

It is noteworthy to mention that KPC-type Class A carbapenemases is the most prevalent carbapenemase among *Klebsiella* (62).

Porin/efflux-mediated resistance is not a major determinant among *E. coli* and *Klebsiella*.

### *Acinetobacter* & *pseudomonas*

Porin/efflux-mediated resistance is mostly a major component of the MDR phenotype among *Acinetobacter* and *P. aeruginosa* (63). Since porin/efflux mechanisms are activated by spontaneous mutations, emergence of resistance during treatment is a significant concern for *Acinetobacter* and *P. aeruginosa* infections.

PER, VEB & GES type enzymes are the most common Class A ESBLs among *Acinetobacter* (64). PER-1 is the first ESBL identified in *P. aeruginosa* (65). It was later found to be widespread among *Acinetobacter* and *P. aeruginosa* in Turkey (32).

OXA-type carbapenemase, such as OXA-23, OXA-51, and others are suggested to occur naturally in *Acinetobacter* (66). Also, multiple OXA-type carbapenemases may co-exist in *Acinetobacter* and contribute to high-level carbapenem resistance (67).

## The epidemiology of antibiotic resistance

### *S. aureus*

*S. aureus* is a leading cause of bloodstream infections (BSIs), and is also the main reason regarding BSIs-associated death, especially MRSA. In Europe, according to the latest report from ECDC in 2013, Romania has the highest rates of MRSA (>50%) isolated from cerebrospinal fluid (CSF) or blood. In another five regions (Cyprus, Greece, Hungary, Italy and Spain), the isolate rate of MRSA ranged from 25% to 50% (68). In the USA, 50% of *S. aureus* associated the central line-associated bloodstream infections (CLABSIs) was MRSA, data from the CDC's National Healthcare Safety Network (NHSN) (69). In mainland China, data from the Ministry of Health National Antimicrobial Resistance Investigation Net (Mohnarin) showed the rate of MRSA BSIs was 51.3% in 2011 (70). Over the last decade, the rates of nosocomial MRSA bacteremia remained stable or decreased in many geographic regions of the world (71).

### *Enterococci*

VRE was first identified in the late 1980s in Europe, and then in the United States, caused epidemiological controversy (72,73). In the USA, VRE was a much bigger problem than elsewhere, according to the data from NHSN, the proportion of VRE isolated from CLABSIs remained stable from 2011 to 2014, the approximate rates of resistant isolates were 82% in *E. faecium* and 10% for *E. faecalis* (69). In Europe, Ireland has the highest rate of vancomycin-resistant *E. faecium* isolated from blood of

 

nosocomial patients, which increased from 33% in 2007 to 45% in 2012 (74). In China, the incidences of vancomycin-resistant *E. faecalis* and *E. faecium* were 1.8% and 6.9% in 2011, respectively, according to Mohnarin (70).

### *Enterobacteriaceae*

#### ESBL

Production of ESBLs was the main mechanism conferring antibiotic resistance in gram-negative pathogens. *E. coli* was one of the most frequently isolated pathogens in BSIs. CTX-M-15 ESBL producing-*E. coli* has spread worldwide (75). In the USA, the rates of ESBL-producing *E. coli* isolates were varied between 8.1% to 13.7% (76,77). According to Chinese antimicrobial resistance surveillance of nosocomial infections (CARES), ESBL producing in *E. coli* caused BSIs was 63.4% (78).

#### Carbapenem resistance

*K. pneumonia* was the most common Enterobacteriaceae specie exhibiting carbapenem resistance. In the USA, data from NHSN in 2014 showed that the all CRE rate in CLABSI was 7.1%, carbapenem-resistant *K. pneumonia or K. oxytoca* was 10.9%, carbapenem-resistant *Enterobacter spp.* was 6.6% and carbapenem-resistant *E. coli* was 1.9 (69). Few studied have known their CRE epidemiology in children, a recently study reported that the frequency of CRE increased from 0.0% in 1999–2000 to 5.2%, 4.5%, and 3.2%, respectively, in 2011–2012 , among children in the USA (79). In Europe, the top three regions with highest rates of carbapenem resistant *K. pneumonia* were Greece (59.4%), Italy (34.3%) and Romania (20.5%) (68). There was rare report about carbapenem resistant *E. coli* and the highest prevalence were found in Bulgaria and Turkey, with 2.6% and 4.0% of frequency, respectively (68,80). A comprehensive study from China reported the overall prevalence of carbapenem-resistant *E. coli* and *K. pneumoniae* was 1.0% and 5.5%, respectively (81).

### *Non-fermenting Gram-negative bacteria*

The most common non-fermenting Gram-negative bacteria caused BSIs are *Acinetobacter spp. and P. aeruginosa*, always exhibiting multidrug-resistant (called MDR-A and MDR-PA). The prevalence of MDR-A and MDR-PA isolated from CLABSIs were 43.7% and 17.9%, which decreased than 2011 (60.9% and 21.7%) (69). One study from China, the overall prevalence of extensively drug-resistant strains of Pseudomonas aeruginosa (XDRPA) and Acinetobacter baumannii (XDRAB) isolated from BSIs were 13.7% and 4.2%, respectively (81).

## Acknowledgements

None.

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

## References

1. Pagès JM, James CE, Winterhalter M. The porin and the permeating antibiotic: a selective diffusion barrier in Gram-negative bacteria. Nat Rev Microbiol 2008;6:893-903.
2. Poole K. Efflux-mediated antimicrobial resistance. J Antimicrob Chemother 2005;56:20-51.
3. Sander P, Belova L, Kidan YG, et al. Ribosomal and non-ribosomal resistance to oxazolidinones: Species-specific idiosyncrasy of ribosomal alterations. Mol Microbiol 2002;46:1295-304.
4. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: A clinical update. Clin Microbiol Rev 2005;18:657-86.
5. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol 2010;8:260-71.
6. Blázquez J, Oliver A, Gómez-Gómez JM. Mutation and evolution of antibiotic resistance: antibiotics as promoters of antibiotic resistance? Curr Drug Targets 2002;3:345-9.
7. Delcour AH. Outer membrane permeability and antibiotic resistance. Biochim Biophys Acta-Proteins Proteomics 2009;1794:808-16.
8. Chapman JS, Georgopapdakou NH. Routes of quinolone permeation in Escherichia coli. Antimicrob Agents Chemother 1988;32:438-42.
9. Cohen SP, McMurry LM, Hooper DC, et al. Cross-resistance to fluoroquinolones in multiple-antibiotic-resistant (Mar) Escherichia coli selected by tetracycline or chloramphenicol: Decreased drug accumulation associated with membrane changes in addition to OmpF reduction. Antimicrob Agents Chemother 1989;33:1318-25.
10. Levy SB, McMurry L. Detection of an inducible membrane protein associated with R-factor-mediated tetracycline resistance. Biochem Biophys Res Commun

 

1974;56:1060-8.
11. McMurry L, Petrucci RE, Levy SB. Active efflux of tetracycline encoded by four genetically different tetracycline resistance determinants in Escherichia coli. Proc Natl Acad Sci U S A 1980;77:3974-7.
12. Nikaido H, Pagès JM. Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. FEMS Microbiol Rev 2012;36:340-63.
13. Li XZ, Nikaido H. Efflux-Mediated Drug Resistance in Bacteria An Update. Drugs 2009;69:1555-623.
14. Wright GD. Molecular mechanisms of antibiotic resistance. Chem Commun (Camb) 2011;47:4055-61.
15. Chambers HF. Methicillin-resistant staphylococci. Clin Microbiol Rev 1988;1:173-86.
16. Chambers HF. Methicillin resistance in staphylococci: molecular and biochemical basis and clinical implications. Clin Microbiol Rev 1997;10:781-91.
17. Wu S, Piscitelli C, de Lencastre H, et al. Tracking the evolutionary origin of the methicillin resistance gene: cloning and sequencing of a homologue of mecA from a methicillin susceptible strain of Staphylococcus sciuri. Microb Drug Resist 1996;2:435-41.
18. Long KS, Poehlsgaard J, Kehrenberg C, et al. The Cfr rRNA methyltransferase confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A antibiotics. Antimicrob Agents Chemother 2006;50:2500-5.
19. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. Lancet 1998;351:797-9.
20. Strahilevitz J, Jacoby GA, Hooper DC, et al. Plasmid-mediated quinolone resistance: A multifaceted threat. Clin Microbiol Rev 2009;22:664-89.
21. Hejnar P, Kolár M, Hájek V. Characteristics of Acinetobacter strains (phenotype classification, antibiotic susceptibility and production of beta-lactamases) isolated from haemocultures from patients at the Teaching Hospital in Olomouc. Acta Univ Palacki Olomuc Fac Med 1999;142:73-7.
22. Li J, Rayner CR, Nation RL, et al. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2006;50:2946-50.
23. Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. Lancet Infect Dis 2016;16:161-8.
24. McGann P, Snesrud E, Maybank R, et al. Escherichia coli Harboring mcr-1 and blaCTX-M on a Novel IncF Plasmid: First Report of mcr-1 in the United States. Antimicrob Agents Chemother 2016;60:4420-1.
25. Bush K, Miller GH. Bacterial enzymatic resistance: beta-lactamases and aminoglycoside-modifying enzymes. Curr Opin Microbiol 1998;1:509-15.
26. Romanowska J, Reuter N, Trylska J. Comparing aminoglycoside binding sites in bacterial ribosomal RNA and aminoglycoside modifying enzymes. Proteins 2013;81:63-80.
27. Davies C, White SW, Nicholas RA. Crystal structure of a deacylation-defective mutant of penicillin-binding protein 5 at 2.3-A resolution. J Biol Chem 2001;276:616-23.
28. Bhullar K, Waglechner N, Pawlowski A, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. PLoS One 2012;7:e34953.
29. Ambler RP. The structure of beta-lactamases. Philos Trans R Soc Lond B Biol Sci 1980;289:321-31.
30. Biondi S, Long S, Panunzio M, et al. Current Trends in beta-Lactam Based beta-Lactamases Inhibitors. Curr Med Chem 2011;18:4223-36.
31. Poirel L, Menuteau O, Agoli N, et al. Outbreak of extended-spectrum β-lactamase VEB-1-producing isolates of Acinetobacter baumannii in a French hospital. J Clin Microbiol 2003;41:3542-7.
32. Vahaboglu H, Öztürk R, Aygün G, et al. Widespread detection of per-1-type extended-spectrum β-lactamases among nosocomial Acinetobacter and Pseudomonas aeruginosa isolates in Turkey: A nationwide multicenter study. Antimicrob Agents Chemother 1997;41:2265-9.
33. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob Agents Chemother 2001;45:1151-61.
34. Pfaller MA, Jones RN, Marshall SA, et al. Inducible Amp C β-lactamase producing gram-negative bacilli from blood stream infections: Frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE). Diagn Microbiol Infect Dis 1997;28:211-9.
35. Walther-Rasmussen J, Høiby N. OXA-type carbapenemases. J Antimicrob Chemother 2006;57:373-83.
36. Poirel L, Nordmann P. Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology. Clin Microbiol Infect 2006;12:826-36.
37. Maltezou HC. Metallo-beta-lactamases in Gram-negative bacteria: introducing the era of pan-resistance? Int J Antimicrob Agents 2009;33:405.e1-7.

 

38. Kenna DT, Doherty CJ, Foweraker J, et al. Hypermutability in environmental Pseudomonas aeruginosa and in populations causing pulmonary infection in individuals with cystic fibrosis. Microbiology 2007;153:1852-9.
39. Jayaraman R. Mutators and hypermutability in bacteria: the Escherichia coli paradigm. J Genet 2009;88:379-91.
40. McCLINTOCK B. The origin and behavior of mutable loci in maize. Proc Natl Acad Sci U S A 1950;36:344-55.
41. Nevers P, Saedler H. Transposable genetic elements as agents of gene instability and chromosomal rearrangements. Nature 1977;268:109-15.
42. Mugnier PD, Poirel L, Nordmann P. Functional analysis of insertion sequence ISAba1, responsible for genomic plasticity of acinetobacter baumannii. J Bacteriol 2009;191:2414-8.
43. Feng J, Qiu Y, Yin Z, et al. Coexistence of a novel KPC-2-encoding MDR plasmid and an NDM-1-encoding pNDM-HN380-like plasmid in a clinical isolate of Citrobacter freundii. J Antimicrob Chemother 2015;70:2987-91.
44. Hall RM, Collis CM. Mobile gene cassettes and integrons: capture and spread of genes by site-specific recombination. Mol Microbiol 1995;15:593-600.
45. Poirel L, Carrër A, Pitout JD, et al. Integron mobilization unit as a source of mobility of antibiotic resistance genes. Antimicrob Agents Chemother 2009;53:2492-8.
46. Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med 2007;33:606-18.
47. Beale R, Reinhart K, Brunkhorst FM, et al. Promoting global research excellence in severe sepsis (PROGRESS): Lessons from an international sepsis registry. Infection 2009;37:222-32.
48. Zhou J, Qian C, Zhao M, et al. Epidemiology and outcome of severe sepsis and septic shock in intensive care units in mainland China. PLoS One 2014;9:e107181.
49. Chen XC, Yang YF, Wang R, et al. Epidemiology and microbiology of sepsis in mainland China in the first decade of the 21st century. Int J Infect Dis 2015;31:9-14.
50. Zahar JR, Timsit JF, Garrouste-Orgeas M, et al. Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality. Crit Care Med 2011;39:1886-95.
51. Ode T, Saito R, Kumita W, et al. Analysis of plasmid-mediated multidrug resistance in Escherichia coli and Klebsiella oxytoca isolates from clinical specimens in Japan. Int J Antimicrob Agents 2009;34:347-50.
52. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. Lancet Infect Dis 2006;6:629-40.
53. Lewis JS 2nd, Herrera M, Wickes B, et al. First report of the emergence of CTX-M-type extended-spectrum beta-lactamases (ESBLs) as the predominant ESBL isolated in a U.S. health care system. Antimicrob Agents Chemother 2007;51:4015-21.
54. Paterson DL, Hujer KM, Hujer AM, et al. Extended-spectrum beta-lactamases in Klebsiella pneumoniae bloodstream isolates from seven countries: dominance and widespread prevalence of SHV- and CTX-M-type beta-lactamases. Antimicrob Agents Chemother 2003;47:3554-60.
55. Livermore DM, Canton R, Gniadkowski M, et al. CTX-M: changing the face of ESBLs in Europe. J Antimicrob Chemother 2007;59:165-74.
56. Scoulica EV, Neonakis IK, Gikas AI, et al. Spread of blaVIM-1-producing E. coli in a university hospital in Greece. Genetic analysis of the integron carrying the blaVIM-1 metallo-beta-lactamase gene. Diagn Microbiol Infect Dis 2004;48:167-72.
57. Miriagou V, Tzelepi E, Gianneli D, et al. Escherichia coli with a self-transferable, multiresistant plasmid coding for metallo-beta-lactamase VIM-1. Antimicrob Agents Chemother 2003;47:395-7.
58. Nordmann P, Boulanger AE, Poirel L. NDM-4 metallo-β-lactamase with increased carbapenemase activity from escherichia coli. Antimicrob Agents Chemother 2012;56:2184-6.
59. Hornsey M, Phee L, Wareham DW. A novel variant, NDM-5, of the New Delhi metallo-beta-lactamase in a multidrug-resistant Escherichia coli ST648 isolate recovered from a patient in the United Kingdom. Antimicrob Agents Chemother 2011;55:5952-4.
60. Poirel L, Héritier C, Tolün V, et al. Emergence of oxacillinase-mediated resistance to imipenem in Klebsiella pneumoniae. Antimicrob Agents Chemother 2004;48:15-22.
61. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: The phantom menace. J Antimicrob Chemother 2012;67:1597-606.
62. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis 2009;9:228-36.
63. Rumbo C, Gato E, Lopez M, et al. Contribution of efflux pumps, porins, and ??-lactamases to multidrug resistance in clinical isolates of Acinetobacter baumannii. Antimicrob Agents Chemother 2013;57:5247-57.


 

64. Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in Pseudomonas aeruginosa and Acinetobacter baumannii: Mechanisms and epidemiology. Int J Antimicrob Agents 2015;45:568-85.
65. Nordmann P, Ronco E, Naas T, et al. Characterization of a novel extended-spectrum beta-lactamase from Pseudomonas aeruginosa. Antimicrob Agents Chemother 1993;37:962-9.
66. Héritier C, Poirel L, Fournier PE, et al. Characterization of the naturally occurring oxacillinase of Acinetobacter baumannii. Antimicrob Agents Chemother 2005;49:4174-9.
67. Vahaboglu H, Budak F, Kasap M, et al. High prevalence of OXA-51-type class D beta-lactamases among ceftazidime-resistant clinical isolates of Acinetobacter spp.: Co-existence with OXA-58 in multiple centres. J Antimicrob Chemother 2006;58:537-42.
68. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance interactive database (EARS-Net), 2015.
69. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 2016:1-14. [Epub ahead of print].
70. Ma XZ, Lv Y, Zheng B. Ministry of Health National Antimicrobial Resistance Investigation Net annual report of 2011: bacterial distribution and resistance in bloodstream infection. Chinese J Clin Pharmacol 2012;28:927-32.
71. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. Virulence 2016;7:252-66.
72. Leclercq R, Dutka-Malen S, Brisson-Noel A, et al. Resistance of enterococci to aminoglycosides and glycopeptides. Clin Infect Dis 1992;15:495-501.
73. Frieden TR, Munsiff SS, Low DE, et al. Emergence of vancomycin-resistant enterococci in New York City. Lancet 1993;342:76-9.
74. Ryan L, O'Mahony E, Wrenn C, et al. Epidemiology and molecular typing of VRE bloodstream isolates in an Irish tertiary care hospital. J Antimicrob Chemother 2015;70:2718-24.
75. Cantón R, Coque TM. The CTX-M beta-lactamase pandemic. Curr Opin Microbiol 2006;9:466-75.
76. Sader HS, Farrell DJ, Flamm RK, et al. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). Diagn Microbiol Infect Dis 2014;78:443-8.
77. Sader HS, Flamm RK, Jones RN. Frequency of occurrence and antimicrobial susceptibility of Gram-negative bacteremia isolates in patients with urinary tract infection: results from United States and European hospitals (2009-2011). J Chemother 2014;26:133-8.
78. Chen HB, Zhao CJ, Wang H, et al. An analysis of resistance of nosocomial infection pathogens isolated from 13 teaching hospitals in 2011. Zhonghua Nei Ke Za Zhi 2013;52:203-12.
79. Logan LK, Renschler JP, Gandra S, et al. Carbapenem-Resistant Enterobacteriaceae in Children, United States, 1999-2012. Emerg Infect Dis 2015;21:2014-21.
80. WHO. WHO Regional Office for Europe. Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR). CAESAR Annual report 2014.
81. Xu A, Zheng B, Xu YC, et al. National epidemiology of carbapenem-resistant and extensively drug-resistant Gram-negative bacteria isolated from blood samples in China in 2013. Clin Microbiol Infect 2016;22 Suppl 1:S1-8.

**Cite this article as:** Cag Y, Caskurlu H, Fan Y, Cao B, Vahaboglu H. Resistance mechanisms. Ann Transl Med 2016;4(17):326. doi: 10.21037/atm.2016.09.14

 