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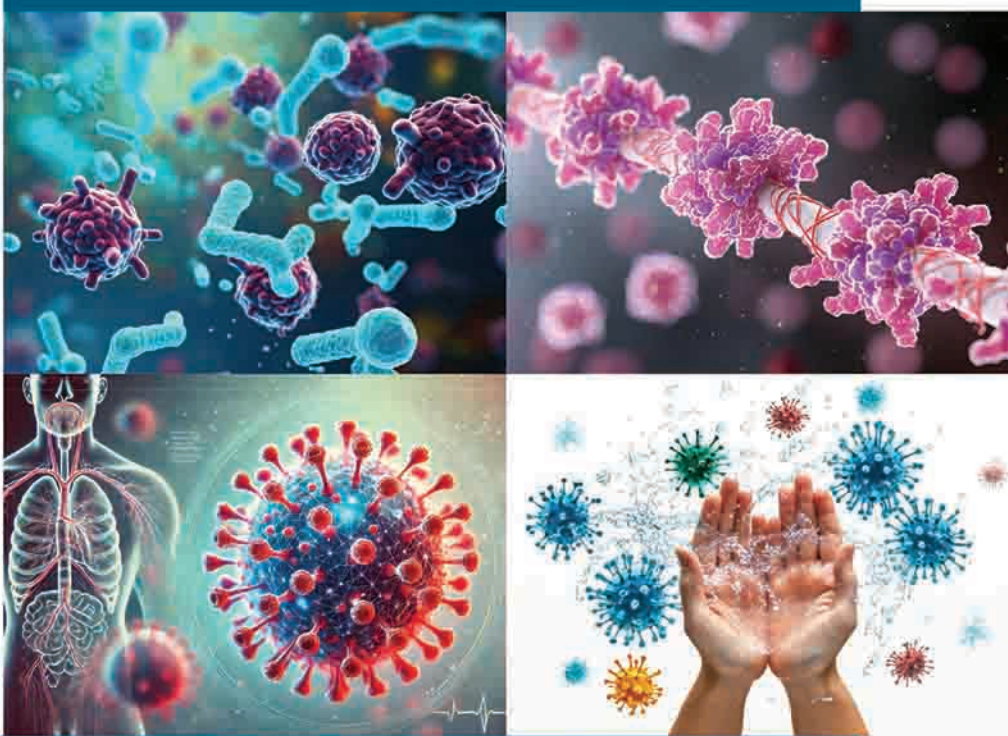

Safeguarding
The Critically Ill

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CHAPTER

Multidrug-resistant Organisms

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LEARNING OBJECTIVES

- Understand the growing prevalence of infections caused by multidrug-resistant organisms (MDROs).
- Comprehend the ways in which organisms develop resistance mechanisms.
- Understand management of infections with MDROs.
- Discuss the role of isolation and cohorting to prevent the spread of infections due to MDROs.

INTRODUCTION

Antimicrobials are medicines used to treat infectious diseases caused by bacteria, viruses, fungi, and parasites. Resistance to antimicrobials emerged very soon after the discovery and therapeutic use of antimicrobials. Since the discovery of penicillin, numerous classes of antibiotics have been discovered; however, microbes have kept up with the progress in the pharmaceutical industry, and resistance has also grown across classes of antibiotics. Resistance is not only something restricted to bacteria, but viruses, parasites, and fungi all have the propensity to develop resistance. Antimicrobial resistance (AMR) refers to this situation wherein bacteria, viruses, fungi, and parasites do not respond to treatment with antimicrobials. AMR is almost a natural phenomenon as microbes slowly develop genetic changes to the new challenge in their environment. Adaptation is the key to survival, and the fittest organism passes its genes to its progeny. And microorganisms follow this Darwinian principle to the hilt. The culmination of the process of acquiring resistance by microbes is to be pan-drug resistant (PDR). Multidrug-resistance (MDR) is an important intermediary in this evolution. There has been a sustained increase in the prevalence of multidrug-resistance organisms (MDRO) over the last two decades, and this problem is compounded by the parching of the new antibiotic manufacturing pipeline. This problem of growing resistance and dearth of new drugs to combat resistance has raised alarms in various quarters. The World Health Organization (WHO) has flagged this as the top public health and development issue in the world. WHO estimates that in the year 2019, bacterial AMR directly resulted in 1.27 million deaths and had an indirect contribution in 4.95 million deaths.[1] The increase in AMR is not only the genetic ability of microbes but is largely driven by human and societal

issues. Overuse and misuse of antimicrobials in animals and humans are one of the biggest drivers of this epidemic. The mortality consequence is easily observable by practicing intensivists, but the financial burden is generally not easily appreciated. The World Bank estimates that by 2050, AMR would lead to an increase of 1 trillion $ in health care costs, and there will be a loss of 3.4 trillion $ in Gross Domestic Product per year by 2030.[2] Critical care medicine, where sepsis, infections, and use of antimicrobials are highly prevalent, is itself at the verge of annihilation due to the specter of AMR. All the good that science has achieved in health care will be undone if the spiral of AMR continues to gallop.

DEFINITIONS

There are a lot of terms in the literature, like MDR, extremely drug-resistant (XDR), and PDR, in the context of AMR. Multidrug-resistance, as the name implies, means resistance to more than one antimicrobial agent. Standardized definitions have been in place since 2011 following a consensus meeting of the Centers for Disease Control and Prevention of the USA and Europe.[3] The method advocated is based on in vitro antimicrobial susceptibility testing. The definition used for gram-positive and gram-negative bacteria is "resistant to more than or equal to one agent in three or more antimicrobial classes." The term XDR originated from the tubercular resistance nomenclatures, wherein XDR TB is defined as resistance to first-line medicines such as isoniazid and rifampicin, to fluoroquinolones, and to at least one of the three second-line medications. A similar approach is used in bacteria and is defined as "resistant to more than or equal to one agent in all but two or fewer categories." PDR implies that an organism is resistant to all the antimicrobials. The categories of antibiotic classes tested differ for various organisms; a few examples are shown in **Tables 1 to 3**. The more commonly used method to define MDR is, however, based on "resistance to one key antimicrobial agent." A common example is Methicillin-resistant *Staphylococcus aureus* (MRSA). With MRSA, resistance to one agent, i.e., methicillin, implies public health importance and cross- or coresistance to other classes of antimicrobial agents.

EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

Resistance to antimicrobials is increasing in a prolific fashion. Gram-negative bacteria lead this brigade of resistant pathogens. However, resistance is widespread across the microbial world. Gram-positive bacteria are not far behind *Staphylococcus* and *Enterococcus,* being the prime culprits. Other microorganisms concerned are *Mycobacterium tuberculosis*, parasites, such as *Plasmodium* species, and fungi. In this review, we will restrict ourselves to the epidemiology, management, and infection control of MDR bacteria and *Candida*.

TABLE 1: To define MDR, XDR, and PDR for *Staphylococcus aureus* isolates.

Antimicrobial class	*Antimicrobial drugs*	*Antimicrobial susceptibility result*
Ansamycins	Rifampicin	
Aminoglycosides	Gentamicin	
Antistaphylococcal β-lactam	Oxacillin or cefoxitin*	
Anti-MRSA cephalosporins	Ceftaroline	
Folate pathway inhibitors	Trimethoprim–sulfamethoxazole	
Fucoidanes	Fusidic acid	
Fluoroquinolones	Moxifloxacin, ofloxacin	
Glycylcyclines	Tigecycline	
Glycopeptides	Teicoplanin, vancomycin	
Lipopeptides	Daptomycin	
Lincosamides	Clindamycin	
Macrolides	Azithromycin	
Oxazolidinones	Linezolid	
Phosphonic acid	Fosfomycin	
Tetracyclines	Doxycycline, minocycline	
Streptogramins	Quinupristin–dalfopristin	

Note: Criteria for defining:

- *MDR*: (1) An MRSA is considered MDR and (2) Non susceptible to more than or equal to one drug in more than or equal to three antimicrobial classes.
- *XDR*: Nonsusceptible to more than one drug in all but less than or equal to two antimicrobial classes.
- *PDR*: Nonsusceptible to all the antimicrobial classes listed.

*Oxacillin resistance predicts resistance to all other β-lactams with the exception of anti-MRSA cephalosporins, which include all categories of penicillins, cephalosporins, β-lactamase inhibitors, and carbapenems.

(MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; PDR: pandrug-resistant; XDR: extensively drug-resistant)

Drug Resistance in Bacteria

Epidemiology of MDR bacteria is obtained from the WHO global antimicrobial resistance and use surveillance system (GLASS) report of 2022.[4] MDR *Escherichia coli,* i.e., extended spectrum β-lactamase (ESBL) production rates are as high as 41.8% and ESBL *K. pneumoniae* rates range from 59 to 64.7% and carbapenem resistance in *Acinetobacter* species (CRAB) ranges from 69 to 73.4%. Data regarding the epidemiology of MDRO in India is obtained from the annual report of the National Antimicrobial Surveillance Network

TABLE 2: To define MDR, XDR, and PDR for Enterobacteriaceae isolates.

Antimicrobial class	*Antimicrobial drugs*	*Antimicrobial susceptibility result*	*Intrinsic resistance to antimicrobials*
Aminoglycosides	• Gentamycin • Tobramycin • Netilmicin • Amikacin		*Providencia rettgeri*, *Providencia stuarti* *P. rettgeri*, *P. stuarti*, *P. rettgeri*, *P. stuarti*
Antipseudomonal penicillins + β-lactamase inhibitors	• Ticarcillin-clavulanic acid • Piperacillin-tazobactam		*Escherichia hermannii* *E. hermannii*
Anti-MRSA cephalosporin	• Ceftaroline		
Carbapenem	• Meropenem • Imipenem • Ertapenem • Doripenem		
First and second generation cephalosporins	• Cefazolin • Cefuroxime		*Morganella morganii*, *Proteus penneri*, *Proteus Vulgaris*, *P. rettgeri*, *P. stuarti*, *Serratia marcescens*, *Citrobacter freundii*, *Enterobacter aerogenes*, *and Enterobacter cloacae* *M. morganii*, *P. penneri*, *P. vulgaris*, *S. marcescens*
Third and fourth generation cephalosporins	• Cefotaxime or ceftriaxone • Ceftazidime and cefepime		
Cephamycins	• Cefoxitin		*C. freundi*, *E. aerogenes*, *E. cloacae*, *H. alvei*
Folate pathway inhibitors	• Trimethoprim–sulfamethoxazole		
Fluoroquinolones	• Ofloxacin		
Glycylcyclines	• Tigecyclines		*Proteus mirabilis*, *M. morganii*, *P. penneri*, *P. vulgaris*, *P. rettgeri*, *P. stuarti*
Monobactams	• Aztreonam		
Phenicols	• Chloramphenicol		
Phosphonic acid	• Fosfomycin		

Contd…

Contd…

Antimicrobial class	*Antimicrobial drugs*	*Antimicrobial susceptibility result*	*Intrinsic resistance to antimicrobials*
Penicillins	• Ampicillin		*C.freundii, E. aerogenes, E. cloacae, M. morgani, klebsiellae spp, P. vulgaris, P. penneri, P. rettgeri, P. stuarti*
Penicillins + β-lactamase inhibitor	• Amoxicillin clavulanic acid • Ampicillin-sulbactam		*C. freundii, E. aerogenes, E. cloacae, M. morgani, P. vulgaris, P. penneri, P. rettgeri, P. stuarti*
Polymyxins	Colistin		
Tetracyclines	• Tetracycline • Doxycycline/ Minocycline		*M. morganii, P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuarti* *M. morganii, P. penneri, P. vulgaris, P. rettgeri, P. stuarti*

Note: Criteria for defining:
- *MDR*: Nonsusceptible to more than or equal to one drug in more than or equal to three antimicrobial classes.
- *XDR*: Nonsusceptibility to more than or equal to one drug in all but less than or equal to two antimicrobial classes.
- *PDR*: Nonsusceptible to all antimicrobial drugs listed.

(MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; PDR: pandrug-resistant; XDR: extensively drug-resistant)

(NARS-Net), a part of the government of India's National Programme on AMR containment.[5] The last published report is from 2023, which includes data up to December 2022. The NARS-Net has identified seven pathogens, which pose a significant risk for AMR, and they include *S. aureus, Enterococcus species, E. coli, Klebsiella* species, *Pseudomonas species, Acinetobacter species, and Salmonella enterica* serotype *Typhi* and *Paratyphi*. The report noted consistency with previous years as *E. coli* remains the most commonly isolated pathogen (33% of all pathogens), the most common source being urine (43%). Most of the priority pathogens are isolated from in-patient wards (56%), with the remaining from the out-patient sites. ESBL *E. coli* rates have decreased from 86% in 2018 to 76% in the year 2022. This decreased trend in ESBL rates in *E. coli* may be attributed to more stringent microbiologic criteria and better-quality control on antibiotic discs for testing. The rates of carbapenem-resistant *Enterobacterales* (CRE) are static, and about 35% of

TABLE 3: To define MDR, PDR, and XDR for *Acinetobacter* spp. Isolates.

Antimicrobial class	*Antimicrobial drug*	*Antimicrobial susceptibility result*
Antipseudomonal carbapenem	• Imipenem • Meropenem • Doripenem	
Antipseudomonal fluoroquinolones	• Ciprofloxacin • Levofloxacin	
Antipseudomonal penicillin + β-lactamase inhibitors	• Piperacillin–tazobactam • Ticarcillin–clavulanic acid	
Aminoglycosides	• Amikacin • Gentamicin • Tobramycin • Netilmicin	
Extended-spectrum cephalosporin	• Ceftriaxone • Ceftazidime • Cefotaxime • Cefepime	
Folate pathway inhibitors	• Trimethoprim–sulfamethoxazole	
Polymixins	• Colistin • Polymyxin B	
Tetracyclines	• Tetracycline • Minocycline • Doxycycline	
Penicillins + β-lactamase inhibitors	Ampicillin–sulbactam	

Note: Criteria for defining:
- *MDR:* Nonsusceptibility to more than or equal to 1 drug in more than or equal to 3 antimicrobial class.
- *XDR:* Nonsusceptibility to more than or equal to 1 drug in all but less than or equal to 2 antimicrobial class.
- *PDR:* Nonsusceptible to all antimicrobial drug listed.

(MDR: multidrug-resistant; PDR: pandrug-resistant; XDR: extensively drug-resistant)

E. coli and 47% of *Klebsiella* species are CRE. Amongst the nonfermenting gram-negative bacilli, *Pseudomonas* had MDR rates of 50% and carbapenem resistance of 27%, while amongst *Acinetobacter*, carbapenem resistance was 65–69%. *Staphylococcus* species were predominantly seen in pus cultures, and MRSA rates of 59% and vancomycin-resistant *Enterococcus* rates were at 13%. Unfortunately, these resistance rates were reported by government hospitals, mostly medical colleges providing tertiary care. If private hospitals were to be involved, the rates would be far more than those reported in this data. This data is still reflective of the burden of MDRO in India.

Drug Resistance in *Candida*

Antifungal resistance in *Candida* is the non-susceptibility to an antifungal agent based on in vitro susceptibility testing, when comparing with isolates of the same *Candida* species. Resistance in *Candida* is intrinsic or acquired. Many *Candida* species are intrinsically resistant to antifungal agents. There has been an uptick in the prevalence of invasive *Candida* infections across the world, and now *Candida* is the fourth most common cause of bloodstream infections (BSI), especially in the ICU.[6] There has been a steady shift in the species of *Candida* causing invasive infections over the last two decades, and non-albicans *Candida* species are the predominant pathogens in many ICUs.[7] Fungal susceptibility testing across *Candida* species in the US revealed a rate of 7% fluconazole resistance.[8] In India, MDR rates in *Candida* species are 1.9%. A significant proportion of the non-albicans *Candida* have reduced susceptibility to antifungal drugs and are MDR. There is now a plethora of MDR *Candida* species, including *Candida glabrata, Candida guilliermondii, Candida krusei, Candida lusitaniae,* and the most prominent amongst these being *Candida auris*. *Candida auris* was initially misidentified as *Candida haemulonii* species, but was identified as a separate species from 2015 onward. It has become a notifiable disease because of its MDR nature, and worldwide, there is an increasing number of infections due to *Candida auris*. *Candida auris* is a critical priority organism as per the WHO.[9] One of the main reasons for this is the almost 100% resistance to fluconazole and 43% resistance to polyene antifungals, making it very difficult to treat MDRO.

MECHANISM OF RESISTANCE

Antimicrobial resistance can be either intrinsic resistance or acquired resistance. Intrinsic resistance is the ability of bacteria to deny the activity of an antimicrobial agent via its inherent functional and structural properties, which will allow resistance to that antimicrobial class of drug. It can be due to drug inaccessibility into the cell wall, presence of gene-encoded active export channels or pumps, production of antimicrobial-degrading enzymes, and lack of affinity for the target site. For example, aerobic bacteria have innate resistance to metronidazole due to the inability of the drug to reduce to its active form in aerobic conditions.[10]

Acquired resistance happens when a particular organism acquires the ability to resist the activity of a particular antimicrobial agent to which it was previously susceptible to. This may happen from gene mutation and transfer across species via vertical or horizontal gene transfer by transformation, transduction, or conjugation.[11]

There are various ways by which gram-negative bacteria become resistant to antibiotics[12] **(Fig. 1)**. They include the following mechanisms:

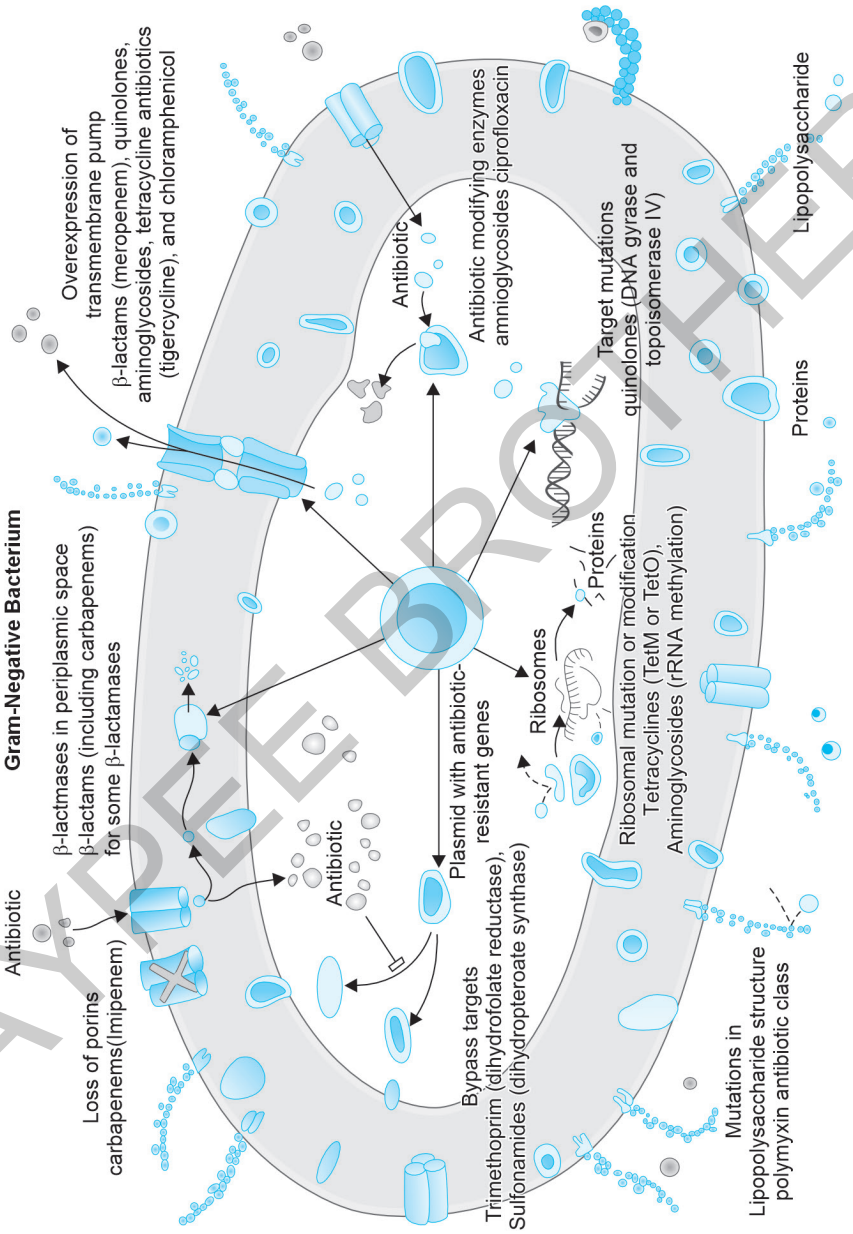

Fig. 1: Gram-negative bacteria. (DNA: deoxyribonucleic acid)

- *Loss of porin channels:* Gram-negative bacilli have an outer cell membrane, which confers protection and a barrier to penetration of antibiotics to target the penicillin-binding proteins (PBPs) in the peptidoglycan layers. As a result, the antibiotic molecules need to pass through the hydrophilic porin channels situated in the outer membrane of the bacterial cell wall to reach the inner cell membrane. Mutations that result in decreased amounts of porin channels confer resistance to antibiotics like carbapenems.
- β-*lactamases:* The presence of enzymes like β-lactamases in the periplasmic space results in degradation of β lactam antibiotics and prevents them from exerting their action on the PBPs in the inner cell membrane. These enzymes are classified based on their structure into four molecular classes (A to D), may be classified based on their substrate, and lastly based on their response to inhibitors **(Flowchart 1)**. This is the major defense mechanism of gram-negative organisms against β-lactam antibiotics. These enzymes have evolved alongside the development of β-lactam antibiotics. Ever since the discovery of penicillin, there has been an increase in the prevalence of β-lactamases in organisms that naturally possess these enzymes, like *S. aureus*. Subsequently, these enzymes spread to organisms that did not naturally possess these enzymes, such as *Hemophilus influenzae* and *Neisseria gonorrhoeae,* to become broad-spectrum β-lactamases. Introduction of a multitude of cephalosporins about 30 years ago resulted in an explosion of β-lactamases, such as extended-spectrum β-lactamases (ESBL) and carbapenem-hydrolyzing β-lactamases (carbapenemase) **(Table 4)**.
- *Efflux pump overexpression:* Overexpression of the transmembrane efflux pump in bacteria can result in expulsion of the drug from the bacterium

Flowchart 1: Classification of β-lactamases.

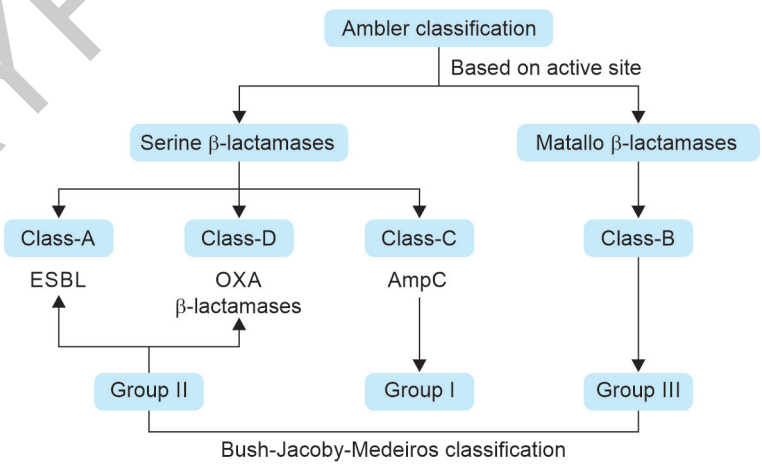

TABLE 4: Description of selected β-lactamases of gram-negative bacteria.

β-lactamases	*Examples*	*Substrates*	*Inhibition by clavulanic acid*	*Molecular class*
Broad spectrum	TEM-1, TEM-2, SHV-1 OXA family	• Benzylpenicillin, aminopenicillins, carboxypenicillins, piperacillin, narrow-spectrum cephalosporins, such as cefuroxime, cefazolin, and other • Substrates of the broad-spectrum group, plus cloxacillin, methicillin, and oxacillin	+++ +	A D
Expanded spectrum	TEM family and SHV family Others(BES-1, GES/IBC family, PER-1, PER-2, SFO-1, TLA-1, VEB-1 and VEB-2) CTX-M family OXA family	• Substrates of the broad-spectrum group PLU oxyimino cephalosporins (ceftazidime, cefpodoxime, cefotaxime, and ceftriaxone) and monobactams (aztreonam) • Same as for the TEM family and the SHV family • Substrates of the expanded spectrum group, plus, for some enzymes, cefepime • Same as for the CTX-M family	++++ ++++ ++++ +	A A A D
Amp c	ACC-1, ACT-1, CFE-1, CMY family,DHA-1, DHA-2, FOX family, LAT family, MIR-1, MOX-1, and MOX-2	Substrates of expanded-spectrum group plus cephamycins (cefotetan, cefoxitin, and others)	0	C
Carbapenemase	IMP family, VIM family, GIM-1, and SPM-1 KPC-1, KPC-2, and KPC-3 OXA-23,OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, and OXA-48	• Substrates of the expanded-spectrum group plus cephamycins and carbapenems • Same as for IMP family, VIM family, GIM-1, and SPM-1 • Same as for IMP family, VIM family, GIM-1, and SPM-1	0 +++ +	B A D

Note: Table above showing the type of β-lactamases produced by the gram-negative bacteria with examples and the substrates it acts on, along with the degree of inhibition by β-lactamase inhibitor such as clavulanic acid, with a plus(+) sign denoting the relative sensitivity to inhibition.

before it can have an effect. This is an important mechanism for resistance against carbapenems, quinolones, aminoglycosides, tetracyclines, and chloramphenicol.

- *Antibiotic-modifying enzymes:* Certain gram-negative organisms possess enzymes in the cytoplasm that can modify the antibiotics, making them incapable of interacting with their target. This mechanism is important to prevent the actions of aminoglycosides and quinolones.
- *Target site mutations:* Mutations in certain targets, like deoxyribonucleic acid (DNA) gyrase and topoisomerase intravenous (IV) in certain gram-negative bacteria, can lead to resistance to quinolone antibiotics.
- *Ribosomal mutations:* Antibiotics that act on ribosomes, like aminoglycosides and tetracyclines, are affected by mutations or modifications of the ribosomes, leading to the antibiotic not being able to bind to the ribosome and inhibiting protein synthesis.
- *Metabolic bypass mechanisms:* Certain gram-negative bacteria develop an alternative resistant enzyme to bypass the inhibitory effect of antibiotics like trimethoprim and sulfonamides.
- *Lipopolysaccharide mutation:* A mutation in the lipopolysaccharide structure in certain gram-negative organisms results in resistance to the polymyxin class of antibiotics.

Mechanism of Resistance in Gram-positive Organisms

National Antimicrobial Resistance Surveillance Network (NARS-Net): NARS-Net has identified two gram-positive pathogens, which pose a significant risk for AMR, and they include *S. aureus* and *Enterococcus* species and the discussion of the mechanism of resistance will be restricted to these two gram-positive organisms.

Staphylococcus aureus: Ever since the introduction of penicillin, *S. aureus* has been quick to develop resistance and has been the quintessential smart organism that develops resistance to any introduced antibiotic. Resistance to penicillin is due to β-lactamase production. Resistance to methicillin, which epitomizes MDR status, is due to production of PBP2a, a homologue of PBP, which is resistant to β-lactams.[13] Vancomycin resistance in *S. aureus* (VRSA) is due to the acquisition of the vanA operon from *enterococci*, which allows *S. aureus* to alter the structure of peptidoglycan precursors, leading to reduced affinity to vancomycin.

Enterococcus species: Enterococcus species are intrinsically resistant to β-lactams because their PBP has low affinity for β-lactams. Vancomycin-resistant *enterococci* (VRE) are the MDR of concern, and the mechanism of resistance is the same as that of VRSA, i.e., possession of vanA operons.

Mechanism of Antifungal Resistance

Like bacteria, some species of *Candida* are intrinsically resistant to certain antifungals. This is due to the ineffective binding to drug targets and/or efflux activities in all members of a given species. For instance, *C. krusei* and *C. auris* are intrinsically resistant to fluconazole; similarly, environmental molds are resistant to fluconazole. The problem, however, is acquired resistance, i.e., the ability of the fungal cells to grow at a higher concentration of antifungal drugs as compared to the fungal cells of the wild type of population. Another characteristic observed in fungal cells, like bacteria, is tolerance, also called heteroresistance. This is the ability of a susceptible isolate to grow slowly in the presence of drug concentrations above the minimum inhibitory concentrations (MICs). Acquired resistance results in changes in the interaction between the drug and the target[14] **(Fig. 2)**. This may arise due to:

- Genetic changes to the binding site of the antifungal agent. For example, mutation of the genes encoding the synthesis of lanosterol demethylase results in azole resistance, and mutation of genes encoding for β-glucan synthase results in echinocandin resistance.
- *Increased abundance of target:* Overexpression of ERG11 can lead to azole resistance to *C. albicans*, by increasing target abundance, which would require more drug to be available for effectiveness.
- Altering the effective drug concentration acts by increasing drug efflux pumps, leading to decreased intracellular concentration of drugs like azoles or inhibition of prodrugs like flucytosine.

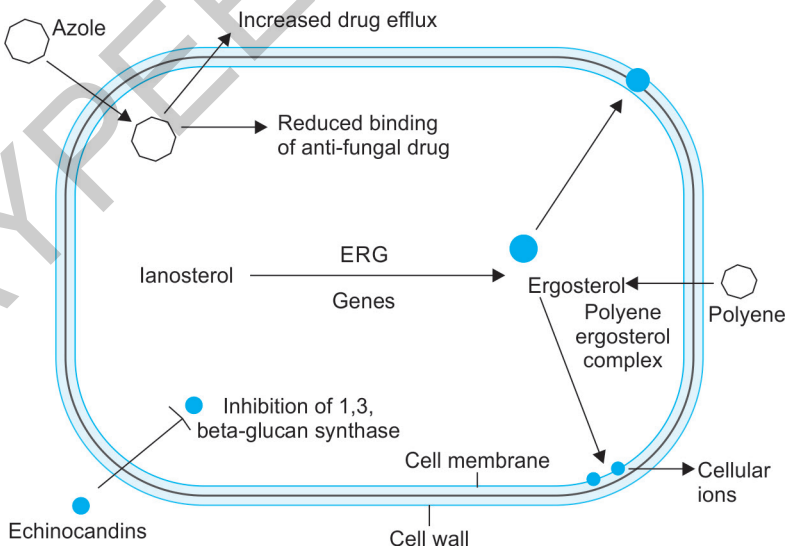

Fig. 2: Resistance results in changes in the interaction between the drug and the target.

MANAGEMENT OF INFECTIONS WITH MULTIDRUG-RESISTANT ORGANISMS

The management of infections caused by MDR gram-negative infections is based on the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Society of Intensive Care Medicine (ESICM).[15]

- *Infections caused by third-generation resistant Enterobacterales (ESBL):* In patients with BSI and sepsis/septic shock, the MERINO trial has clearly demonstrated the superiority of meropenem as compared to piperacillin–tazobactam and is the drug of choice.[16] In patients with low-risk infections (this Classification into low-risk and high-risk infections is based on the INCREMENT score), that is originating from a urinary tract source or biliary infections after source control, use of piperacillin–tazobactam, amoxicillin–clavulanic acid, or quinolones can be used with close monitoring. For a nonsevere complicated urinary tract infection, which is in the absence of sepsis or septic shock, cotrimoxazole can also be considered. In case of complicated UTI without septic shock, use of a short-duration course of aminoglycosides or IV fosfomycin may be useful. In the management of infections caused by third-generation resistant *enterobacterales*, it is considered good practice to step down therapy to a targeted drug following the use of carbapenem and patient stabilization.
- *Carbapenem-resistant enterobacterales (CRE): The recommendation for treatment of severe CRE infections is the use of meropenem-vabor*bactam or ceftazidime-avibactam; this may not be useful in critical care practice in countries like India, where there is a high prevalence of metallo-β-lactamase (MBL) producing organisms. In such situations, a combination of ceftazidime-avibactam with aztreonam or treatment with cefiderocol may be considered. For the treatment of non-severe CRE infections, use of an antibiotic from among the in vitro active drugs on a case-by-case basis is a good practice. In case of complicated UTI, aminoglycosides, including plazomicin, are preferred. Tigecycline should be avoided in cases of complicated UTI and bloodstream infection. In patients with pneumonia, tigecycline can be used at high doses. The practice of using a combination of polymyxins, tigecycline, aminoglycosides, or fosfomycin in combination is recommended in the absence of new beta-lactamase inhibitor (BLBLI) agents. Monotherapy with these agents can be used in nonsevere and low-risk carbapenem-resistant Enterobacterales (CRE) infections based on in vitro susceptibility and source of infection.
- *Carbapenem-resistant Pseudomonas aeruginosa (CRPA):* In severe infections due to CRPA, ceftolozane–tazobactam is recommended if active in vitro. If this agent is not available, then a combination of polymyxins,

aminoglycosides, or fosfomycin can be used. While in non-severe, low-risk infections, monotherapy with these agents can be considered.

- *Carbapenem-resistant Acinetobacter baumanii (CRAB):* In patients with CRAB infections susceptible to sulbactam, using high-dose sulbactam is preferred. If strains are not susceptible to sulbactam, then polymyxin or high-dose tigecycline can be used if there is in vitro susceptibility. For severe and high-risk infections with CRAB, A combination of two in vitro active antibiotics among the following drugs, i.e., polymyxin, aminoglycoside, tigecycline, and sulbactam, is preferred.
- *MRSA:* The initial treatment recommended for management of MRSA BSI consists of monotherapy with glycopeptides, such as vancomycin and teicoplanin. Daptomycin is an alternative for the treatment of BSI with MRSA. Other alternative agents include ceftaroline, ceftobiprole, telavancin, linezolid, tedizolid, dalbavancin, and oritavancin.
- *VRE:* The preferred treatment of enterococcal infections with resistance to vancomycin (VRE) includes daptomycin and linezolid. In the setting of BSI with VRE and possible endocarditis, daptomycin is the preferred agent.
- *Fluconazole-resistant Candida:* The initial therapy in critically ill patients with BSI with *Candida species* is with echinocandins as per the recommendation of the Infectious Disease Society of America guidelines (IDSA).[17] However, treatment depends on the species identified and in vitro susceptibility. In patients with infections due to *Candida auris*, initial treatment is with echinocandins, but if there is no response or there is persistent candidemia, then a switch to the lipid formulation of amphotericin B is suggested.

PREVENTION AND CONTROL OF INFECTIONS WITH MULTIDRUG-RESISTANT ORGANISMS

Multidrug-resistant organisms control can be discussed under the following six headings:[18]

1. *Improve hand hygiene compliance:* MDR organisms are transmitted through direct or indirect contact from health care workers, environmental surfaces, as well as medical equipment. WHO, in its 2009 guidelines on improving hand hygiene, promulgated the "five moments of hand hygiene." Despite the obvious importance of hand hygiene, results from the 2019 WHO "hand hygiene self-assessment" global survey showed a poor implementation of hand hygiene practices. Focusing on education and training, improving the infrastructure to promote hand hygiene, having reminder tools, providing feedback on hand hygiene techniques, and conducting audits are the mainstay to improve compliance. Newer technologies like the automated hand hygiene monitoring systems are

in place in certain countries and have shown substantial improvement in hand hygiene compliance. Such innovations need to be brought in to control the menace of MDRO.

2. *Environmental cleanliness:* It is well known that CRAB, CRE, MRSA, and VRE can persist in the environment for extended periods of time. To prevent their spread having thorough surface cleaning and equipment are essential. Regular surface cleaning followed by disinfection is the standard care practice as advocated by CDC.[19] Low-level disinfectants like quaternary ammonium compounds and intermediate-level disinfectants, either alcohol based or chlorine-based based are suggested based on the nature of the surface and equipment. Recent research is pointing towards using hydrogen peroxide devices (intermediate level disinfectants) and the use of ultraviolet light for disinfecting patient rooms, a process known as automated whole room disinfection (WRD).
3. *Contact isolation:* CDC also advocates contact isolation for all patients infected or colonized with MDRO. These precautions entail a single room, donning isolation gowns and gloves before encountering the patient or his surroundings, and doffing personal protective equipment before exiting the isolation room. Implementing such guidelines in open plan ICUs is a challenge, and most of the ICUs in India are open plan, making contact isolation methods non-compliant with guidelines.
4. *Decolonization:* Decolonization involves treating colonized patients to eliminate their carriage. This is well documented for treating MRSA carriage in hospitalized patients. Chlorhexidine bathing and nasal mupirocin have been used for eliminating the carriage of MRSA. However, no data exists for eliminating the problem of MDRO that plagues our country.
5. *Cluster intervention:* Clustering or bundling means doing a set of evidence-based interventions together to improve outcomes. Bundling hand hygiene practices and disinfection of the hospital environment is an example of clustering.
6. *Early screening for pathogens:* Early detection of pathogenic microorganisms can lead to appropriate antibiotic use and thereby result in decreasing the emergence of MDRO infections. Pneumonia diagnosis with polymerase chain reaction (PCR) testing, as compared to conventional cultures, shortens the duration of inappropriate antimicrobial use; whether this will lead to a reduction in the emergence of MDRO is uncertain as of now.

CONCLUSION

Multidrug-resistance is a growing epidemic, and prevalence is increasing leaps and bounds in both gram-positive and gram-negative organisms, parasites, mycobacterium species, and in yeasts. CRE is the main Gram-negative

threat in our ICUs. Rising fluconazole-resistant *Candida species* is also an emerging threat. Production of β-lactamases is the main mechanism driving gram-negative MDR, and this may happen from gene mutation and transfer across species via vertical or horizontal gene transfer. The mechanism of drug resistance is complex and involves multiple mechanisms, which differ in various organisms. A clear understanding of the mechanism of resistance is necessary for targeting therapy with antimicrobial agents. Treatment regimens for CRE, CRAB, and MRSA are evolving, and some new molecules are being introduced. Prevention remains the cornerstone for management of MDRO, and decreasing the emergence of MDRO focuses primarily on hand hygiene and environmental sanitation.

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