

Antibiotic Resistance

Antimicrobial Agents

CC – 14/ UNIT - 7

Azidothymidine Antibiotic Resistance

Zidovudine (AZT)

- A synthetic pyrimidine (thymidine) analogue
- AZT is converted to its triphosphate form by cellular thymidine kinase. It binds preferentially to HIV – reverse transcriptase resulting in chain termination.
- It is a potent inhibitor of HIV replication
- Used to treat patients with advanced HIV disease, with AIDS-related complex and with CD4 counts less than 500/mm³
- Has potent bactericidal activity against *E. coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Shigella flexneri*, *Enterobacter aerogenes* and vibrios.

- Side effects: Anaemia, neutropenia, leucopenia, increase in mean corpuscular volume, nausea, vomiting, headache, rash, abdominal pain, anorexia, fever, insomnia, malaise, nail, skin and oral mucosal pigmentation, diarrhoea, dizziness, sweating, dyspepsia, bad taste, chest pain, confusion, loss of mental activity, anxiety, depression
- Resistance: Associated with a sequential accumulation of mutations (at amino acids 41, 67, 70, 215, 219) in the HIV pol gene encoding reverse transcriptase

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- ◆ Zidovudine (ZDV), is an important drug used for treatment of HIV infection. It belongs to the family of nucleoside analogue reverse transcriptase inhibitors (NRTIs)
 - ◆ It is structurally related to the endogenous nucleoside thymidine with an azido group in place of the hydroxyl group at the 3' position of the deoxyribose ring.
 - ◆ Presence of azido group prevents formation of phosphodiester linkages needed for DNA replication, causing chain termination.

This is the mechanism by which ZDV interferes with viral replication. The effectiveness of ZDV in the treatment of HIV infection is due to its selective affinity for HIV reverse transcriptase as opposed to human DNA polymerases.

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- ◆ **Zidovudine** or **AZT (azidothymidine)** is the drug used to delay development of AIDS (acquired immunodeficiency syndrome) in patients infected with HIV (human immunodeficiency virus).
 - ◆ AZT belongs to a group of drugs known as nucleoside reverse transcriptase inhibitors (NRTIs).
 - ◆ **In 1987** AZT became the first drug to be approved by the U.S. Food and Drug Administration for the purpose of prolonging the lives of AIDS patients.
 - ◆ Since HIV is capable of mutating and thus of **developing resistance to the drug**. As a result, it is often given, either orally or intravenously, **in combination** with at least two or three other drugs in order to overcome drug resistance.

Zidovudine/Azidothymidine (AZT)



- Selective inhibition of viral reverse transcriptase
- Gets incorporated into growing viral DNA and terminates chain formation
- Zidovudine prevents infection of new cells
- No effect on already infected host cell
- Resistance occur by altered reverse transcriptase enzyme

MDR & XDR

- Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to it.
- According to WHO, these resistant microorganisms (like bacteria, fungi, viruses, and parasites) are able to combat attack by antimicrobial drugs, which leads to ineffective treatment resulting in persistence and spreading of infections.

- Although the development of MDR is a natural phenomenon, extensive rise in the number of immuno-compromised conditions, like HIV infection, diabetic patients, individuals who have undergone organ transplantation, and severe burn patients, makes the body an easy target for hospital acquired infectious diseases, thereby contributing to further spread of MDR.

TABLE 1: Common drug resistant microbes and diseases caused by them.

Name of Bacterium	Drug(s) resistant to	Typical diseases
<i>Escherichia coli</i>	Cephalosporins and fluoroquinolones	Urinary tract infections and blood stream infections
<i>Klebsiella pneumoniae</i>	Cephalosporins and carbapenems	Pneumonia, blood stream, and urinary tract infections
<i>Staphylococcus aureus</i>	Methicillin	Wound and blood stream infections
<i>Streptococcus pneumoniae</i>	Penicillin	Pneumonia, meningitis, and otitis
Nontyphoidal <i>Salmonella</i>	Fluoroquinolones	Foodborne diarrhoea, blood stream infections
<i>Shigella species</i>	Fluoroquinolones	Diarrhoea (bacillary dysentery)
<i>Neisseria gonorrhoeae</i>	Cephalosporins	Gonorrhoea
<i>Mycobacterium tuberculosis</i>	Rifampicin, isoniazid, and fluoroquinolone [4]	Tuberculosis
Name of Fungi		
<i>Candida spp.</i>	Fluconazole and echinocandins [5]	Candidiasis
<i>Cryptococcus neoformans</i>	Fluconazole [17]	Cryptococcosis
<i>Aspergillus spp.</i>	Azoles [18]	Aspergillosis
<i>Scopulariopsis spp.</i>	Amphotericin B, flucytosine, and azoles [19]	Onychomycosis
Name of Virus		
Cytomegalovirus (CMV)	Ganciclovir and foscarnet [20]	In AIDS and oncology patients
Herpes simplex virus (HSV)	Acyclovir, famciclovir, and valacyclovir [21]	Herpes simplex
Human immunodeficiency virus (HIV)	Antiretroviral drugs [22]	AIDS
Influenza virus	Adamantane derivatives (Amantadine and rimantadine) and neuraminidase inhibitors [23]	Influenza
<i>Varicella zoster virus</i>	Acyclovir and valacyclovir [21]	Chicken pox
Hepatitis B virus (HBV)	Lamivudine [24]	Hepatitis B

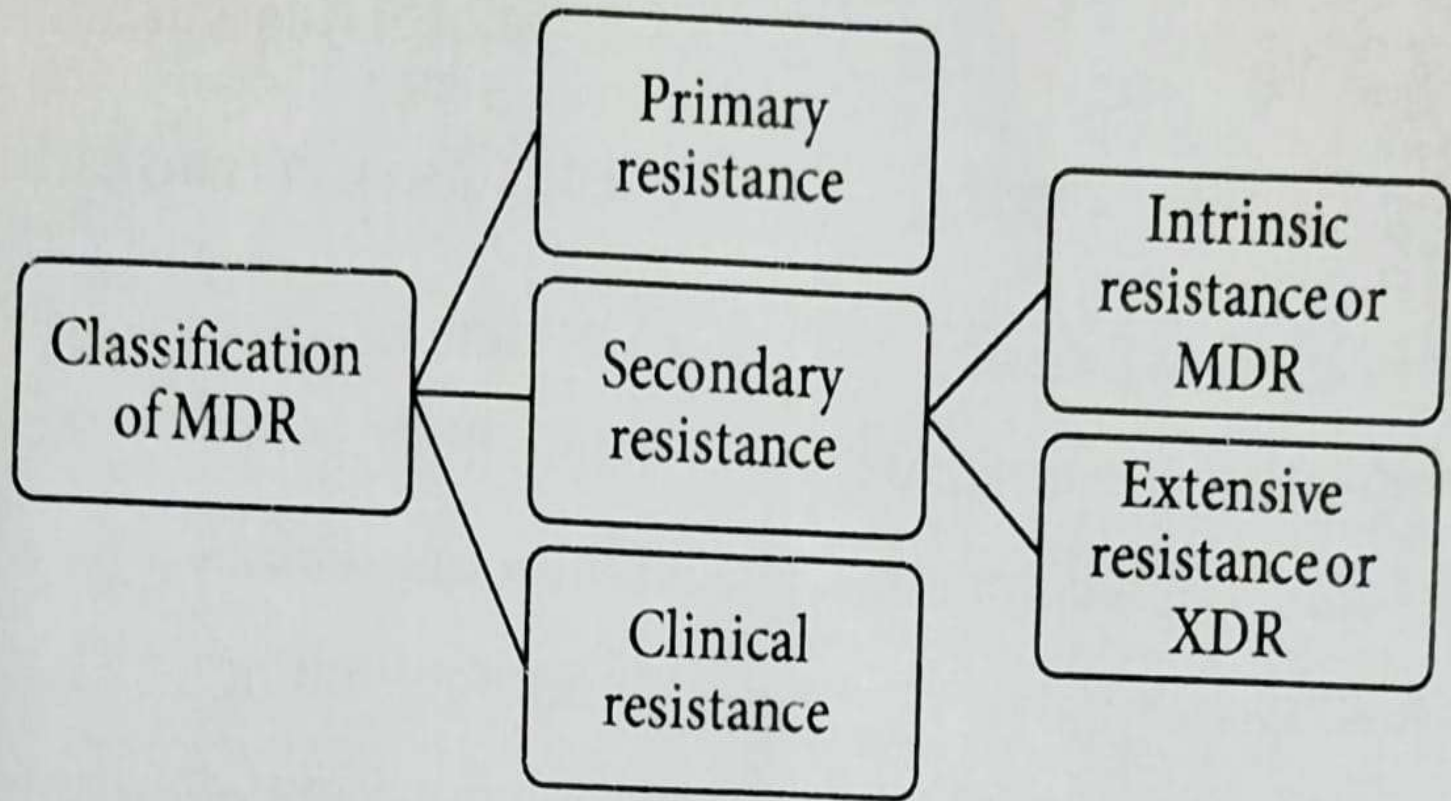


FIGURE 2: Classification of MDR.

- *Primary Resistance:*

It occurs when the organism has never encountered the drug of interest in a particular host.

- *Secondary Resistance:* Also known as “acquired resistance.” This term is used to describe the resistance that only arises in an organism after an exposure to the drug.

- It may further be classified as follows -
 - (i) *Intrinsic resistance:* it refers to the insensitivity of all microorganisms of a single species to certain common first-line drugs, which are used to treat diseases based on the clinical evidence of the patient.

- It is also known as multidrug resistance (MDR), for example, *Mycobacterium tuberculosis* to rifampicin and isoniazid or *Candida* spp. to fluconazole.
- (ii) *Extensive resistance*: it defines the ability of organisms to withstand the inhibitory effects of at least one or two most effective antimicrobial drugs.
- Also termed as XDR, this seemed to arise in patients after they have undergone a treatment with first line drugs, for example, XDR-TB resistance against fluoroquinolone

- *Clinical Resistance:*

In addition to the above-mentioned types, clinical resistance is defined by the situation in which the infecting organism is inhibited by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic failure or reappearance of infections within an organism due to impaired host immune function.

In other words, the pathogen is inhibited by an antimicrobial concentration that is higher than could be safely achieved with normal dosing

Mechanisms

1. Cell wall, in both bacteria and fungi, plays a crucial role in their survival. As discussed above, drugs inhibit the cell wall synthesis by binding with the peptidoglycan layer in bacteria or affecting ergosterol synthesis (e.g., polyenes) in fungi, thus, blocking the cell growth and division. These organisms undergo certain chromosomal mutations or exchange of extrachromosomal DNA elements through conjugation or transformation (horizontal gene transfer) such as in *K. pneumoniae*, which can cause alteration in the cell membrane composition (e.g., a reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell.

2. Altered membrane composition (such as β -1,3-glucan and lipid content in fungal cell membrane) also leads to lack of active target sites for the drugs (e.g., echinocandins in fungi) to bind.
3. Mutations in the genes encoding for the target cause modifications at the molecular level and retain cellular function by reducing susceptibility to inhibition.
4. Another mechanism of MDR was found to be an overexpression of drug target enzymes leading to target bypass due to modification in certain metabolic pathways (e.g., azoles and allylamines in fungi), which causes production of alternate target molecules and interference in some protein synthesis. This can influence the access of drugs to the target sites.

5. Inactivation or enzymatic degradation of antimicrobials by hydrolysis of ester or amide bonds (such as resistance to β -lactams due to β -lactamases, etc.) and chemical transformation of these compounds by acetylation, phosphorylation, adenylation, glycosylation, and hydroxylation have also become increasingly apparent as causes of MDR.
6. The resistant strains of clinical isolates of different microorganisms have developed the ability to oxidize or reduce the antimicrobial compounds to prevent their interaction with the respective target.

7. Antiviral drugs usually target viral DNA polymerase having the reverse transcriptase activity to inhibit the viral replication. Drug resistant mutant strains undergo mutations in the reverse transcriptase domains of the polymerase gene which affects the interaction between the drug and the enzyme.
8. Resistance to the inhibitory effects of drug on the enzyme can also emerge due to any conformational changes or altered binding of substrate to the viral polymerase.

9. MDR mediated by drug efflux pumps remains the predominant mechanism of MDR. The overexpression of genes encoding for ATP-binding cassette (ABC) transporter membrane proteins (e.g., P-glycoprotein (Pgp)), also known as the multidrug efflux pumps which are responsible for the export or expulsion of drugs out of the cell, usually generates MDR and continues cellular functions without any interference.
10. Overexpression of P-glycoprotein, in *Entamoeba* spp. and *Leishmania* spp. membrane or multidrug resistant proteins (MRP), affects the fluidity and permeability, leading to an ATP-dependent efflux of the antimicrobials and decreasing their intracellular concentration

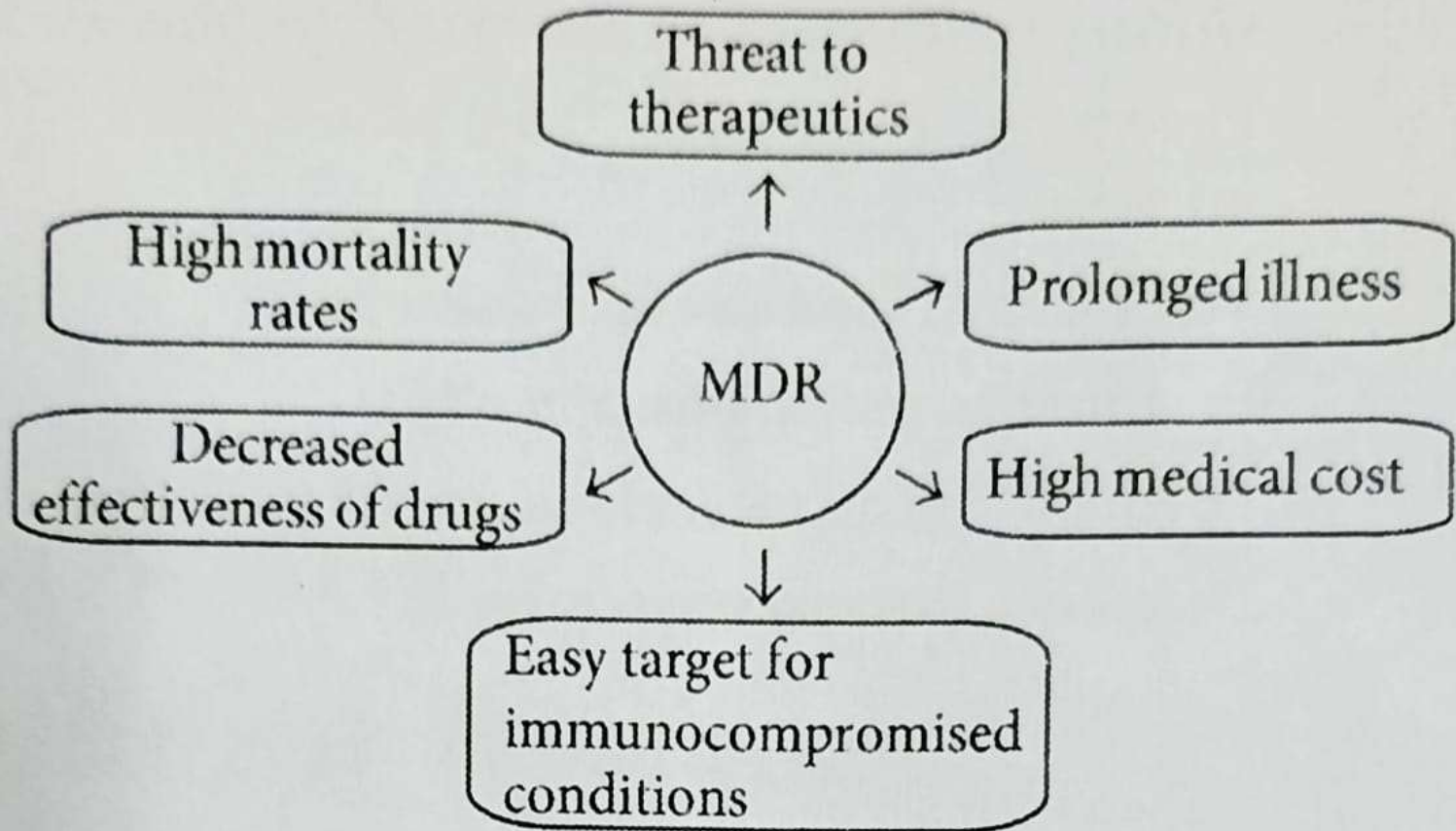


FIGURE 1: Problems associated with MDR.

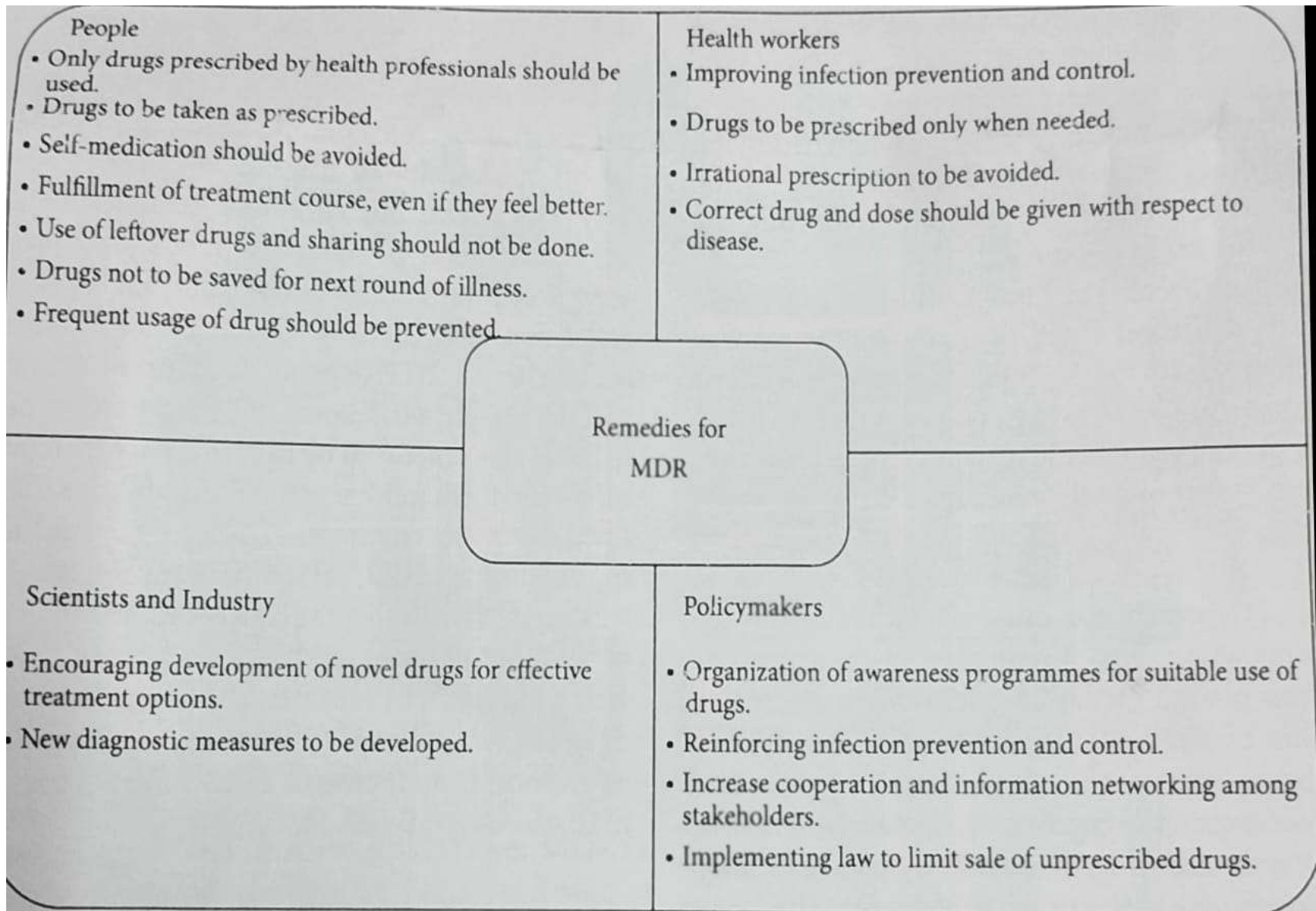


FIGURE 4: Remedies of MDR.

How do bacteria become resistant to an antibiotic

- ❖ Resistance happens when an infection is treated with antibiotics but all the bacteria are not killed the ones that remain learn how to outlive that antibiotic and are now resistant
 - Not finishing the whole prescription
 - Not taking the proper dosage or at the proper times
 - Taking someone else's prescription
 - Taking antibiotics when not needed

MDR

- MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories.
- Bacteria that resist treatment with more than one antibiotic are called multidrug-resistant organisms
- Multidrug-resistant organisms are found mainly in hospitals and long-term care facilities.
- They often affect people who are older or very ill and can cause bad infections
- Penicillin resistance in *Staphylococcus aureus*, a common type of bacteria, was first found in the 1940s.
- The more often the antibiotics are used, the more likely it is that resistant bacteria will develop.

Common multi-drug-resistant organisms (MDROs)

- MDROs are microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents
 - ❑ Methicillin-resistant *Staphylococcus aureus* (MRSA)
 - ❑ Vancomycin-intermediate *Staphylococcus aureus* (VISA)
 - ❑ Vancomycin-resistant *Staphylococcus aureus* (VRSA)
 - ❑ Vancomycin-resistant *enterococcus* (VRE)
 - ❑ *Streptococcus pneumoniae* resistant to penicillin and other broad-spectrum agents
 - ❑ MDR-TB
 - ❑ (ESBLs) producing Gram-negative bacteria

- ❖ The most serious concern with antibiotic resistance is that some bacteria have become resistant to almost all of the easily available antibiotics.
- ❖ For example, *Staphylococcus aureus* ('golden staph') and *Neisseria gonorrhoeae* (the cause of gonorrhoea) are now almost always resistant to benzyl penicillin.
- ❖ These bacteria are able to cause serious disease and this is a major public health problem.

XDR

- ❑ XDR is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories).
- ❑ Multidrug-resistant tuberculosis (MDRTB)
- ❑ Resistance to Isoniazid and Rifampicin
- ❑ Extensively (extremely) drug-resistant (XDR-TB)
- ❑ MDR-TB plus resistance to a second line injectable drug such as amikacin plus a quinolone.

MDR & XDR TB

- ✓ The term XDR TB appears to have been used for the first time in March 2006.
- ✓ WHO describing strains of TB, referred to as XDR TB, that were resistant not only to isoniazid and rifampicin (that is they were MDR TB) but they were also resistant to at least three of the six classes of second line anti TB drugs.
- ✓ In 1980 50% of TB bacilli were resistant to 1 drug.
- ✓ Multi-drug resistant TB (MDR-TB) began to emerge. There are now an estimated 1.5million MDR cases worldwide.
- ✓ Extreme drug resistance (XDR-TB) was reported in 2006.

- ✓ The first completely drug resistant (CDR-TB) case was reported in Italy in 2007.
- ✓ MDR-TB has emerged and spread due to the inadequacy of treatment. Today, treatment for drug-resistant TB can take up to two years, and is so complex, expensive, and toxic that a third of all MDR-TB patients die.
- ✓ WHO treatment standards require that at least four drugs be used to treat TB in order to avoid the development of further resistance.
- ✓ According to the WHO, Eastern Europe's rates of MDR-TB are the highest, where MDR-TB makes up 20% of all new TB cases.
- ✓ In some parts of the former Soviet Union, up to 28% of new TB cases are multidrug-resistant.

- ✓ Among previously treated cases in the same region, reported rates of drug resistance are commonly above 50% and as high as 61%.
- ✓ During the late 1980s and early 1990s, outbreaks of MDR-TB in North America and Europe killed more than 80% of those who contracted the disease.
- ✓ During a major TB outbreak in New York City in the early 1990s, one in 10 cases proved to be drug-resistant.
- ✓ Today, drug-resistant TB is also quite common in India and China –the two countries with the highest MDR-TB burdens.
- ✓ Treatment for MDR-TB consists of what are called second-line drugs. These drugs are administered when first-line drugs fail.

- ✓ Treatment for MDR-TB is commonly administered for 2 years or longer and involves daily injections for six months. Many second-line drugs are toxic and have severe side effects.
- ✓ The World Health Organization has issued a target of treating 80% of MDR-TB cases by 2015.
- ✓ The cost of curing MDR-TB can be literally thousands of times as expensive as that of regular treatment in some regions.

- ❖ **Extensively drug-resistant TB (XDR-TB)**, also known as Extremely Drug-Resistant TB, is emerging as an even more ominous threat.
- ❖ This makes XDR-TB treatment extremely complicated, if not impossible, in resource-limited settings.
- ❖ In a 2006 XDR-TB outbreak in South Africa, 52 of 53 people who contracted the disease died within months.
- ❖ It is estimated that 70% of XDR-TB patients die within a month of diagnosis.
- ❖ The most recent drug-resistance surveillance data issued by the WHO estimates that an average of roughly 5 % of MDR-TB cases are XDR-TB.
- ❖ Estimating the incidence of XDR-TB is extremely difficult because most laboratories are ill-equipped to detect and diagnose it; it is thought that the majority of XDR-TB cases go undocumented.

Prevent of MDR & XDR?

- Hand Hygiene – The Most Important Way to Prevent Transmission of Microorganisms and Infection
- Use the appropriate antimicrobial for an infection; e.g. no antibiotics for viral infections
- Identify the causative organism whenever possible
- Select an antimicrobial which targets the specific organism, rather than relying on a broad-spectrum antimicrobial



- Complete an appropriate duration of antimicrobial treatment (not too short and not too long)
- Use the correct dose for eradication; subtherapeutic dosing is associated with resistance, as demonstrated in food animals.
- Minimize unnecessary prescribing and overprescribing of antibiotics.



Methicillin-resistant *Staphylococcus aureus*
(MRSA)

Staphylococcus aureus

- Gram Positive
- Non-motile
- Spherical
- Grows in clumps
- Resembles clumps of grapes
- Golden color- colonies
- Some produce hemolysis
- Some produces coagulase
- Produce catalase enzymes



What Is MRSA?

- MRSA is the term used for any strain of *Staphylococcus aureus* that has developed resistance to β -lactam antibiotics, which include the penicillins (methicillins, oxacillin, dicloxacillin etc.) and cephalosporins
- MRSA causes a variety of disseminated, lethal infections in humans.
- Has the ability to easily transfer resistant genes to other species directly and indirectly

how MRSA is resistant to methicillin?

- Resistance of MRSA to β - lactam antibiotics including penicillinase stable β - lactam is mediated by the *mecA* gene.
- This gene is expressed in bacterial cell wall and encodes for a penicillin binding protein (PBP2a) which has a low affinity for β - lactam antibiotics (Leonard and Markey, 2008).
- SCCmec element is a genomic island of unknown origin containing this antibiotic resistant *mecA* gene (Batabyal et al., 2012).

- Methicillin-resistant *Staphylococcus aureus* (MRSA) strains or multidrug-resistant *S. aureus*, initially described in 1960s, emerged in the last decade as a cause of nosocomial infections responsible for rapidly progressive, potential fatal diseases including life-threatening pneumonia, necrotizing fasciitis, endocarditis, osteomyelitis, severe sepsis, and toxinoses such as toxic shock syndrome.

- A multifactorial range of independent risk factors for MRSA has been reported in literature and include immunosuppression, hemodialysis, peripheral malperfusion, advanced age, extended in-hospital stays, residency in long-term care facilities (LTCFs), inadequacy of antimicrobial therapy, indwelling devices, insulin-requiring diabetes, and decubitus ulcers, among others

- Evolution of methicillin resistance by *S. aureus* has been traced to the acquisition of the exogenous gene (*mecA*) which is part of the staphylococcal cassette chromosome *mec* (SCC*mec*) (types I–VII) and is under the control of *MecI* (a repressor) and *MecR1* (a transducer) and, when present, the regulatory/signalling proteins of the *blaZ* system

- The *mecA* gene codes for additional penicillin-binding protein (PBP2a), a peptidoglycan transpeptidase, can confer resistance to all β -lactam antibiotics (penicillins, cephalosporins, and carbapenems). Other isolates containing a particular variant of SCCmec types II and III have expanded range of resistance due to the presence of additional resistance genes. The presence of PBP2a, or *mecA* positivity, can be typed using methicillin or oxacillin (isoxazolyl penicillin), hence the acronym MRSA- or oxacillin-resistant *S. aureus* (ORSA)

Emergence of methicillin-resistant *S. aureus* (MRSA)

- Penicillin was the first beta-lactam antibiotic developed for the treatment of *S. aureus* infections. Which is usually fatal.¹
- The introduction of penicillin to treat infections caused by *S. aureus* greatly improved the prognosis of patients with severe staphylococcal infections.¹² these strains resistant to penicillin soon appeared following its clinical use.¹²
- Penicillin resistance is due to the production, by the bacteria, of penicillinase, which inactivates the antibiotic. Penicillinase hydrolyses the beta-lactam ring that is central to the antimicrobial activity of these drugs.
- The emergence of penicillin resistance in *S. aureus* stimulated the development of new antibiotics such as streptomycin, tetracycline, erythromycin, and chloramphenicol in the 1950s.¹²

- These new antibiotics were developed and put into clinical use, resistance to them also appeared.⁴ The continuous search for antibiotics active against penicillin-resistant *S. aureus* led to the development of methicillin also known as methicillin or Staphcillin.⁵
- Methicillin is a semisynthetic derivative of penicillin, developed in the late 1950s, by a modification of the penicillin structure which conferred resistance to penicillinase.⁹ It kills bacteria by inhibiting bacterial cell-wall synthesis, a mechanism of action similar to that of other penicillins.
- Methicillin resistance occurs due to the acquisition of *mecA* or *mecC* gene by previously susceptible strains.⁶ The *mecA* gene codes for an altered penicillin-binding protein called penicillin-binding protein-2a (PBP2a) with reduced affinity to the entire beta-lactam class of antibiotics including penicillin, cephalosporin and carbapenems,¹¹ except the recently approved beta-lactams, ceftaroline and ceftobiprole.⁷

- mecC carrying MRSA was identified in 2007, a retrospective search of archived collections found mecC in isolates collected as early as 1975. indicating that these strains have been around for a long time possibly as long as the mecA-MRSA strains.⁶
- MecC gene is a homolog of mecA. It was initially designated mecALGA251. It shares 69% nucleotide homology with mecA.⁶ MRSA isolates carrying mecC have been isolated from human as well as animal hosts.³
- the mecA PCR or PBP2a latex agglutination test fails to detect mecC. In sensitivity testing, using both cefoxitin and oxacillin, mecA-MRSA show resistance to both antibiotics whereas the majority of mecC MRSA will express resistance only to cefoxitin.³ This discrepancy is explained by the observation that PBP2a produced by mecC strains have higher affinity to oxacillin than cefoxitin.³

Types of MRSA

- When MRSA strains first occurred, they were usually confined to elderly patients admitted to healthcare facilities especially those with previous antibiotic use. The MRSA strains were also isolated from apparently healthy individuals in the communities of no previous contact with healthcare facilities.
- MRSA strains circulating in the healthcare settings and the community were classified as either nosocomial or healthcare associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA).¹⁰
- This was followed by a new type of MRSA that arose from animals, designated Livestock-associated MRSA (LA-MRSA) has recently been described.¹⁰

Community-associated MRSA (CA-MRSA)

- Community-associated MRSA (CA-MRSA) strains were initially reported in the late 1980s among individuals living in remote communities in Western Australia with no previous history of hospitalization.⁹
- CA-MRSA were mostly associated with skin and soft tissue infections such as impetigo, cellulitis, folliculitis and boils and those at risk were the young patients.¹⁰
- some CA-MRSA strains have been reported to cause severe infections including necrotizing fasciitis, post-influenza pneumonia, septic thrombophlebitis, septic arthritis, and bacteremia.¹⁰
- CA-MRSA are usually susceptible to non-beta lactam antibiotics carry smaller-sized SCC mec types IV, V and VI.¹⁰
- CA-MRSA strains often express lower levels of resistance to oxacillin (MIC; 8–32 mg/L) and multiply faster than HA-MRSA strains with significantly shorter doubling times which may help CA-MRSA achieve successful colonization by enabling it to out compete commensal bacterial flora.¹⁰

Community-Associated (CA)-MRSA

- CA-MRSA has only been known since the 1990s.
- CA-MRSA is of great concern to public health professionals because of who it can affect.
- CA-MRSA skin infections are known to spread in crowded settings

- CA-MRSA is resistant to penicillin and methicillin.
- Lead to redness, swelling and pain resembling to spider bite.
- Minor skin problems pimples, insect bites, cuts, and scrapes especially in children may lead to MRSA colonization.



Healthcare-associated MRSA

- Healthcare-associated MRSA (HA-MRSA) were isolated from patients admitted to healthcare facilities such as nursing homes and long-term care facilities.
- the infections caused by HA-MRSA include bloodstream infections, urinary tract infections, respiratory tract infections, surgical-wounds and device-associated infections.²
- Risk factors for acquiring HA-MRSA include previous admission to healthcare facilities, impaired immune system, use of multiple antibiotics, use of invasive medical devices and old age.¹¹
- Genetically, the HA-MRSA carried SCC mec types I, II and III, are usually multi resistant to antibiotics, and tend to multiply slowly in culture.¹¹

Livestock-associated MRSA

- *Staphylococcus aureus* is also an important cause of infections in live stock resulting in economic losses in the food industry.¹¹
- Livestock-associated MRSA (LA-MRSA) strains were initially identified because they were non-typeable by pulsed-field gel electrophoresis following digestion with *Sma*I restriction enzyme.¹²
- The molecular typing revealed that LA-MRSA defined to a new lineage of MRSA that belonged to clonal complex 398 (CC398).¹⁶ the LA-MRSA ST398 was initially reported among livestock,^{11,12}
- it has also appeared in the community among human patients in contact with infected or colonized animals which is considered the major risk factor for LA-MRSA colonization.¹²
- Other LA-MRSA lineages reported in humans include ST9, ST97 and ST433.¹⁸ LA-MRSA has also caused invasive infections including endocarditis, osteomyelitis, and ventilator-associated pneumonia in humans.^{13, 14}

Can Healthy People Get MRSA?

- Yes. MRSA skin infections are showing up more frequently in healthy people, with none of the usual risks factors.
- This type of MRSA - called community-associated MRSA (CA MRSA) - has been reported among athletes, prisoners, and military recruits.



How is MRSA spread?

1. Direct contact with infected or colonized host
-human-to-human contact
2. Contaminated intermediate surfaces
 - hand towels
 - faucets
 - tub/shower
3. Airborne fluid droplets

Transmission

- MRSA is transmitted from person to person by contaminated hands. Lack of access to hand hygiene products can increase the risk of transmission.
- Additional risk factors includes, sharing personal products such as shampoo or nail clippers, infrequent showers and hand washing.
- Another mode of transmission noted within the federal prison system is illicit, unsanitary tattoo practices.
- In other settings close physical contact, body shaving, turf burns and sharing athletic equipment have been associated with MRSA transmission.
- Persons with asymptomatic MRSA nasal carriage can shed MRSA resulting in transmission to other persons or contamination of food that may cause toxin mediated acute gastroenteritis.

- Some MRSA strains, CC398 are readily transmitted within the host species to which they are adopted.
- Inhalation of contaminated dust, which can contain large no. of organisms, is thought to be a major route of spread in confinement operations.

Who is at risk for MRSA?

- ANYONE can get MRSA – those most at risk:
 - Spend a lot of time in crowded places such as hospitals, schools or dorms
 - Share sports equipment
 - Share personal hygiene items
 - Play contact sports
 - Overuse or misuse antibiotics

Drugs against MRSA

- Daptomycin
- Linezolid(belonging to oxazolidiones class)

Daptomycin

- It is more active against MRSA/MSSA.
- MSSA/MRSA MIC's = 0.5 mcg/ml.
- Daptomycin is inactivated by calcium in alveolar surfactant fluid and not be used for pneumonia, but useful for septic pulmonary emboli or lung abscess.
- An initial dose of gentamycin, which increases the intracellular entry or effectiveness of daptomycin when treating with MSSA/MRSA infections.

TMP- SMX (same spectrum of ceftriaxone)

- It is inactivate against most streptococci, it is an excellent antibiotic against MSSA.
- TMP- SMX is active against CA-MRSA, but it is suboptimal against HA-MRSA.

Linezolid

- Highly effective against major G_{+ve} pathogens. Including, MSSA,MRSA .

Tetracyclines

- MRSA is sensitive to doxycycline invitro. But, it is delayed or incomplete response in vivo.
- Clinically, minocycline IV for treatment of MRSA/MSSA is more effective than doxycycline.
- oral Minocycline to treat serious systemic infections due to MRSA/MSSA. i.e. Osteomyelitis, meningitis.
- Minocycline is the most cost effective oral anti-MRSA antibiotic.

Quinupristin/ dalfopristin

- Highly effective against MRSA/MSSA.

Clindamycin

- It is one of the few antibiotics, able to penetrate or dissolve staphylococcal biofilms.
- It is effective against CA-MRSA but not HA-MRSA.
- With CA-MRSA, inducible clindamycin resistance should be suspected. if erythromycin is resistant and clindamycin is sensitive.
- The D test will conform the clindamycin resistant.

Cephalosporins

- ceftaroline is the only cephalosporin active in vivo against MRSA.
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- **Vancomycin**

- vancomycin is one of the major antibiotic for MRSA use.
- The MRSA is sensitive to vancomycin with MIC being 1 ug/ml.
- MIC values of vancomycin against MRSA has been increasing worldwide, leading to the emergence of VISA.
- The combination therapy mainly included the combined regimen of vancomycin and carbapenems with other aminoglycoside drugs, which increase the risk of developing nephrotoxicity and ototoxicity.
- If combined therapy is needed for MRSA infection, the third generation cephalosporins should be administrated.

Combination therapy

- **Combination with vancomycin**

- The Synergetic interactions between the vancomycin and wide variety of beta-lactams are there, but the mechanism is still not clear.

- The **see-saw effect**

(if decreased vancomycin susceptibility, which results, decreased transcription of *mecA* gene and increase the susceptibility of beta-lactams).

- **Combination with daptomycin**

- Daptomycin with beta-lactams, which kills the daptomycin susceptible and daptomycin non-susceptible MRSA.
- Increases the daptomycin binding to the bacterial cell membrane.
- Prevents the development of daptomycin resistant strains.
- It is proved in rabbit model of endocarditis.

Preventing HA-MRSA

Preventing HA-MRSA

- In the hospital, people who are infected or colonized with MRSA often are placed in contact precautions as a measure to prevent the spread of MRSA.
- Visitors and health care workers caring for people in isolation may be required to wear protective garments and must follow strict hand hygiene procedures.
- Contaminated surfaces and laundry items should be properly disinfected.

Preventing CA-MRSA

- **Wash your hands.** Careful hand washing remains your best defence against germs. Carry a small bottle of hand sanitizer containing at least 62 percent alcohol for times when you don't have access to soap and water.
- **Keep wounds covered.** Keep cuts and abrasions clean and covered with sterile, dry bandages until they heal. The pus from infected sores may contain MRSA, and keeping wounds covered will help prevent the bacteria from spreading.
- **Keep personal items personal.** Avoid sharing personal items such as towels, sheets, razors, clothing and athletic equipment. MRSA spreads on contaminated objects as well as through direct contact.
- **Shower after athletic games or practices.** Shower immediately after each game or practice. Use soap and water. Don't share towels.
- **Sanitize linens.** If you have a cut or sore, wash towels and bed linens in a washing machine set to the hottest water setting (with added bleach, if possible) and dry them in a hot dryer. Wash gym and athletic clothes after each wearing.

Antibiotic stewardship

- Antimicrobial stewardship is defined as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance”.²⁴
- The goals of antibiotic stewardship are to work with health care practitioners to help each patient receive the most appropriate antimicrobial with the correct dose and duration, to prevent antimicrobial overuse, misuse, abuse and minimize the development of resistance.²⁴
- An added benefit of programs that aim to optimize antibiotic use is that they generally experience cost savings. Because, fewer doses of antibiotic are used and less expensive antibiotics are chosen.

- Both at the individual patient level and at the community level, antibiotic use changes susceptibility patterns.
- Patients exposed to antibiotics are at higher risk of becoming colonized or infected by resistant organisms.
- As hospitalized patients become more complex to treat, the increasing prevalence of antimicrobial resistance in both healthcare and community settings represents a daunting challenge.
- Antimicrobial stewardship can provide all practitioners with tools to prevent the overuse of valuable resources and help to control the increase in antimicrobial resistance.^{24,25}

NDM – 1 Antibiotic Resistance

- NDM-1 stands for New Delhi metallo- β -lactamase-1
- NDM-1 refers to a gene product present in some bacteria that counters antibiotics. If bacteria expressing this gene start to spread, treatment using currently available measure will not be possible
- The NDM-1 protein product itself does not cause disease, but it has the potential to change the characteristics of bacteria
- The NDM-1-expressing superbug is a potentially dangerous bacterium that could become resistant to many types of antibiotic, spreading quickly

- The gene makes bacteria resistant to antibiotics. In this way, it can lead to a range of conditions, such as a urinary tract, bloodstream, or wound infections and [pneumonia](#)
- Carbapenems are among the most powerful antibiotics. Healthcare professionals use them as a last resort for many bacterial infections, such as those that *E. coli* and *Klebsiella pneumoniae* cause
- The NDM-1 gene allows the bacterium to produce an enzyme that neutralizes the activity of these antibiotics

- The Centers for Disease Control and Prevention (CDC) have classified NDM-1 and another similar protein called KPC as [emerging issues](#) in the field of infectious diseases
- The NDM-1 protein is different from the protein product that characterizes methicillin-resistant *Staphylococcus aureus* ([MRSA](#)), another superbug
- MRSA are a Gram-positive bacteria, while the bacteria that carry NDM-1 are Gram-negative, a different classification of bacteria

- The NDM-1 gene causes bacteria to produce an enzyme called a carbapenemase. Carbapenemase renders many preferred types of antibiotic ineffective, including carbapenems
- Carbapenem antibiotics are extremely powerful drugs that can counter the activity of highly resistant bacteria for which other antibiotics have not been effective. Even carbapenems are ineffective in cases of NDM-1
- The plasmid containing the genetic code for NDM-1 can move from one strain of bacteria to another through a process known as horizontal gene transfer (HGT)

- A bacterium with a plasmid containing the NDM-1 protein product has the potential to be resistant to many current antibiotics, as well as newer antibiotics that could become available in the near future
- If NDM-1 jumps to a bacterium that is already antibiotic-resistant, dangerous infections could emerge. These would spread rapidly between people and might not be treatable
- NDM-1 efficiently hydrolyses a broad range of β -lactams including penicillins, cephalosporins, and carbapenems, just sparing monobactams such as aztreonam

- Systematic association with other antibiotic resistance determinants is observed in almost all NDM producers (Enterobacteriaceae, *Acinetobacter*, and *Pseudomonas*)
- Those associated resistance determinants are AmpC cephalosporinases, clavulanic acid inhibited expanded-spectrum β -lactamases (ESBLs), other types of carbapenemases (OXA-48-, VIM-, and KPC-types), and resistance to aminoglycosides (16S RNA methylases), to quinolones (Qnr), to macrolides (esterases), to rifampicin (rifampicin-modifying enzymes), to chloramphenicol, and to sulfamethoxazole

- Bacteria expressing NDM-1 [have surfaced](#) in countries around the world, including the United States, Japan, Australia, and the United Kingdom, in patients who spent time in India, travelled through it, or have family members there
- Some people carried the infection home after travelling to India or Pakistan for cosmetic surgery
- Since therapeutical options are limited to very few antibiotics such as colistin, tigecycline, and fosfomycin, hospital- and community acquired infections caused by NDM-1 producers are difficult to eradicate

- Since NDM producers were mainly described in Enterobacteriaceae, infections caused by NDM producers include urinary tract infections, peritonitis, septicemia, pulmonary infections, soft tissue infections, and device-associated infections
- Protective measures available at present—
 1. Surveillance
 2. quickly identifying and isolating patients with the bacteria
 3. disinfecting hospital equipment following hand-hygiene procedures in hospitals

- Similar to the other MBLs, the active site of NDM-1 contains two metal ion binding sites: the His and Cys sites.
- Accordingly, a 3D-structure modelling of the NDM-1 enzyme showed that two zinc ions were present at both the His and Cys sites with a distance of 4.20 Å
- Indeed, the hydrolysis activity of MBLs depends on the interaction of the β -lactam molecule with Zn^{2+} ion(s) in their active site.
- Consequently, their activity is inhibited by chelators of divalent cations, such as EDTA.

- Accordingly, the efficacy of EDTA (Ca-EDTA) has been evaluated in a mouse model of sepsis caused by an NDM-1-producing *Escherichia coli*.
- It has been shown that a combination therapy using imipenem/ cilastatin sodium (IPM/CS) and Ca-EDTA reduced the bacterial inoculum, as compared to IPM/CS alone suggesting the possibility to use Ca-EDTA in clinical therapeutics

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