

# CLINICAL PEARLS IN THE MANAGEMENT OF INFECTIONS CAUSED BY MULTI-DRUG RESISTANT ORGANISMS

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## I. INTRODUCTION

In recent decades, the emergence and proliferation of multi-drug resistant organisms (MDROs) have posed formidable challenges to healthcare systems worldwide. These pathogens, armed with the ability to withstand multiple classes of antibiotics, have become a pressing concern for public health sectors globally. Understanding the importance of MDROs and the threats they pose is crucial for several reasons.

Primarily, MDROs represent a grave threat to human health, contributing to increased morbidity and mortality rates globally. Infections caused by these resistant pathogens are notoriously difficult to treat, often requiring prolonged hospitalization, specialized therapies, and in some cases, resulting in treatment failure. The escalating rates of MDRO infections have significant implications for patient outcomes, healthcare costs, and the overall burden on healthcare systems.

Moreover, MDROs play a pivotal role in the global antibiotic resistance crisis, which has been recognized as one of the most pressing public health threats of our time. The overuse and misuse of antibiotics have fuelled the development and spread of resistance among bacteria, rendering many once-effective antibiotics ineffective. MDROs represent a culmination of this phenomenon, posing a dire challenge to infectious disease management and threatening to regress modern medicine to a pre-antibiotic era.

Beyond the realm of healthcare, MDROs have broader societal and economic implications. They impact productivity, strain healthcare resources, and undermine efforts to achieve universal health coverage and sustainable development goals. The consequences of MDRO infections extend beyond individual patients to encompass entire communities and populations, particularly vulnerable groups who bear a disproportionate burden of disease.

Given the multifaceted nature of the threat posed by MDROs, it is imperative that we deepen our understanding of these organisms and the mechanisms driving their spread. By elucidating the epidemiology, transmission dynamics, and underlying factors contributing to MDRO emergence, we can develop targeted interventions and strategies to mitigate their impact on public health.

This chapter aims to explore the importance of knowing about multi-drug resistant organisms in detail, highlighting their significance, challenges, and implications for healthcare delivery, antibiotic stewardship, and global health security. Through a comprehensive examination of the topic, we seek to underscore the urgency of addressing the threat of MDROs and the critical need for coordinated action at local, national, and international levels.

## Topics

- What is the multi-drug resistant organisms (MDROs)?
- What is the epidemiology of MDRO?
- What are the antibiotic resistance mechanisms?
- How do MDROs spread?
- What are the infections caused by MDRO?
- How to treat MDRO infection?
- How to prevent and control infections caused by MDRO?
- What is the impact of MDRO on the public health?

### 1. What is the Multi-Drug Resistant Organisms (MDROs)?

These are the bacteria which develop resistant mechanism against antibiotics. Since 1980, this term was used without determination of either the type or the number of resistant antibiotics.

- **International Definition of MDRO:** Recently, the term of MDRO refers to resistance to at least one antibiotic in no less than three classes of antibiotics. Moreover, due to increased rate of resistance, other terms were developed including the extremely drug resistant organisms (XDRO) which refers to susceptibility of the organism to one or two classes of antibiotics only. In addition to the term, pan drug resistant organism (PDRO) which is defined as resistance to all antibiotics which are normally used to kill this organism.

Unfortunately, these definitions did not support the ideal surveillance system of MDRO for many reasons, which inspire the researchers to develop more useful definitions through more practical approaches. This approach depends on two factors:

- Categorization of antibiotics based on their route of administration, whether oral, which is commonly used in community settings, and parenteral which is majorly used in hospitals.
- Determination of susceptible agent rather than resistant one.

- **Practical Definition of MDROs**

**MDRO for Oral Antibiotics:** Bacteria is sensitive only to one or no oral antibiotic which is active against either systemic or upper urinary tract infections, which means that antibiotics that are only effective against lower urinary tract infections are not considered in this approach of definitions.

**Example**

<b>Organism: E. coli</b>			
<b>Antibiotic (PO)</b>	<b>S / R</b>	<b>Antibiotic (PO)</b>	<b>S / R</b>
Co amoxiclav	<b>Resistant</b>	Nitrofurantoin	<b>Sensitive</b>
Cephalosporins	<b>Resistant</b>	Mecillinam	<b>Sensitive</b>
Quinolones	<b>Resistant</b>	Fosfomycin	<b>Sensitive</b>
Trimethoprim	<b>Resistant</b>		

**According to this AST, E. coli is considered MDRO.**

- **MDRO for Parenteral Antibiotics:** Bacteria is sensitive only to two or less antibiotics from different classes which are taken parenterally such as, carbapenems, cephalosporins, aztreonam, ceftolozane/tazobactam, ceftazidime/avibactam, temocillin, piperacillin/tazobactam, colistin, quinolones, Fosfomycin, tigecycline and aminoglycosides.

**Example**

<b>Organism: Klebsiella spp., Enterobacter spp., Serratia spp. and Citrobacter spp.</b>			
<b>Antibiotic</b>	<b>S / R</b>	<b>Antibiotic</b>	<b>S / R</b>
Carbapenems	<b>Sensitive</b>	Aminoglycosides	<b>Resistant</b>
3rd Gen- cephalosporins	<b>Resistant</b>	Quinolones	<b>Resistant</b>
Temocillin	<b>Resistant</b>	Colistin	<b>Resistant</b>
Tigecycline	<b>Resistant</b>		

**According to this AST, these organisms are considered MDRO.**

**What is the Epidemiology of MDRO?**

There are several factors including temperature, geographical area, type of healthcare setting, infected age group and treatment of long-term infections, which affect the epidemiology of MDROs which influence their existence worldwide. Also, there is evidence that the rate of antimicrobial resistance has a direct relationship to the hospital size in addition to selective resistance due to overuse of specific antibiotics.

Here are some examples of increased prevalence of MDROs

- **Vancomycin Resistant Enterococci VRE:** It was isolated from clinical samples in eastern United States in 1990s and appeared 7 years later in the western side of the USA, with increased prevalence from 1% to 15% over these 7 years.
- **Meticillin Resistant Staphylococcus Aureus MRSA:** It is one of the models of increased prevalence over years, where it was first isolated in 1968 then by early 1990 it accounted for >25% of isolates from hospital admitted patients. After a decade, it was isolated from >50% of patients.

## 2. What are the Antibiotic Resistance Mechanisms?

Bacteria develop several mechanisms of resistance against antibiotics to protect itself, where these mechanisms vary between different species of bacteria.

- **Resistance Mechanisms of Gram-Positive Bacteria Against Antibiotics:** There are two main mechanisms of resistance which are:
  - **Enzyme Secretion:** These enzymes which are responsible for the breakdown of antibiotic structural rings.
  - **Modifying Antibiotic Binding Sites:** Mutations and structural changes in the binding sites of antibiotic, lead to decreasing affinity of these sites to antibiotic binding, which ends up in low effectiveness and resistance to these antibiotics, e.g. mutation in the penicillin binding protein PBP.

### Example

Enzyme Secretion	Modifying Antibiotic Binding Sites
<b>Penicillinase</b> which are $\beta$ -lactamase against $\beta$ -lactam antibiotics, e.g. Penicillin.	<b>MRSA</b> Meticillin resistance Staphylococcus aureus, which caused by alteration in the PBP, the binding sites of penicillins.
<b>Phosphotransferases, Nucleotidyltransferases, and Acetyltransferases</b> are enzymes which cause destruction of the aminoglycoside structure leading to their inactivation.	<b>VRE</b> Alteration of the peptidoglycan synthesis pathway due to attainment of genes, e.g. Van A and B genes in enterococci, leading to decrease in the target affinity to vancomycin and development of resistance.

- **Resistance Mechanisms of Gram-Negative Bacteria Against Antibiotics:** There are several mechanisms of resistance in the gram-negative bacteria including:
  - **Enzyme Secretion:** Secreted enzymes can inactivate antibiotics, they have a wide range of activity from narrow spectrum to extended spectrum effect e.g. the inactivation of  $\beta$ -lactams by  $\beta$ -lactamases.
  - **Efflux Pumps:** These systems pump antibiotics from inside to outside cells which help bacteria in removing the antibiotics before its action to protect itself, leading to development of resistance against these agents.
  - **Reduced Entry of Antibiotics:** Through either reducing permeability of cell membrane, blocking entry portals, loss of porins and loss of active transport mechanisms.
  - **Mutation of Target Sites for Antibiotic Binding:** There are several sites of binding considered target site for antibiotics including ribosomes, cell wall, chromosomes, and cell membranes according to the mechanism of action of each antibiotic, where the structural mutation of these targets make the binding of antibiotics insufficient.

### 3. How do MDROs Spread?

Antibiotic resistance can be transmitted from generation to another of the same species or between bacterial cell to another from different species, this occurs through transmission of genetic elements carrying the resistance genes.

- **What are these Genetic Elements?**

The genetic elements responsible for the spread of antibiotic resistance are:

- **Plasmids:** They are extrachromosomal small circular pieces of double stranded DNA which reside in the cytoplasm of bacteria and can replicate independently and move between bacterial cells.
- **Transposons:** They are part of chromosomes, but they can change their positions within the genome sequence and move in and out through plasmids, leading to mutations and transfer of genetic materials.
- **Phages:** They are viruses that attack bacteria to kill them and can transfer genetic materials from bacterial cell to another.

- **How do these Genetic Elements Work?**

- **Transduction:** Where an external DNA is introduced into the bacterial cell through phage.
- **Conjugation:** Which occurs when bacterial cells come in a direct contact with each other where a bridge-like structure is formed to facilitate transfer of genetic element from cell to another.
- **Transformation:** Where the resistance genes released from a live or dead cells and can be picked up directly by another bacterial cell.

### 4. What are the Infections Caused by MDRO?

MDRO can cause infections in all sites of the human body, on a wide scale of severity, starting from mild superficial infections up to invasive life threatening infections, which depends upon multiple factors. There are several risk factors which stand behind this wide range of infection severity, some of these risk factors are:

- The underlying cause of infection.
- Comorbidities and immune status of the patient
- History of prolonged intake of antibiotics.
- History of surgical or invasive procedures.
- Prolonged length of stay in healthcare facilities.
- Prolonged contact with healthcare providers.
- Contact with confirmed MDRO infected patients, especially those in the same household.
- Previous infection with MDRO.

Therefore, most of community acquired infections are less severe than those acquired in the healthcare facilities, where the patient may acquire severe infections such as blood stream infections, surgical wound infections, and ventilator acquired infections which end up in a life-threatening infection.

## 5. How to Treat MDRO Infection?

Enterobacterales are the frequently isolated organisms from clinical samples, and consequently they have the highest rate of resistance between different species of bacteria. Here we are trying to summarise the treatment approaches of the multi-drug resistant Enterobacterales with the following resistant mechanisms:

- Extended-spectrum  $\beta$ -lactamase-Producing Enterobacterales
- AmpC  $\beta$ -Lactamase-Producing Enterobacterales
- Carbapenem-Resistant Enterobacterales

### Extended-Spectrum $\beta$ -Lactamase ESBL Producing Enterobacterales

**1. ESBL Definition:** These enzymes which can put the following antibiotics out of action:

- Penicillins
- Cephalosporins
- Aztreonam

## 6. Treatment Options

- Urinary tract infections
- Uncomplicated cystitis

Preferred Options	First Alternative	Second Alternative
Nitrofurantoin	Ciprofloxacin	Aminoglycosides (Single dose)
Cotrimoxazole	Levofloxacin	Fosfomycin (PO) (E. coli only)
	Carbapenems	

### Clinical Pearls

- Ofloxacin is less active against Enterobacterales than ciprofloxacin and levofloxacin, so not included in first options.
- Fosfomycin (PO) is used only for E. Coli infections but not for other Enterobacterales, due to high probability of treatment failure due to carriage of fosA hydrolase genes.
- Amoxicillin-clavulanate is not recommended in the treatment of ESBL especially in females due to persistent urogenital bacterial colonization.

**Complicated UTI/ Pyelonephritis:** Complicated urinary tract infection occurs due to congenital anomaly or structural dysfunction in the genitourinary tract of adolescent or adult males.

Preferred options	First alternative	Second alternative
Cotrimoxazole	Ertapenem	Aminoglycosides (Full course)

Ciprofloxacin	Meropenem	
Levofloxacin	Imipenem-cilastatin	

### Clinical Pearls

- Do not use the following antibiotics:
  - Antibiotics with limited parenchymal concentration:
    - Fosfomycin
    - Nitrofurantoin
  - Antibiotics with limited urinary excretion:
    - Doxycycline

### Infections Outside Urinary Tract

<b>Preferred</b>
Meropenem
Imipenem-cilastatin
Ertapenem

### Clinical Pearls

- **Do not use Ertapenem in Patients with Hypoalbuminemia or Critically Ill Patients, Why?**

Because Ertapenem is highly protein bound unlike other carbapenem agents which prolong its serum half-life, so in these patients, the free fraction of ETP increased which lower its half-life and make its dose interval ineffective.

- **Do Not Step-Down to the Following Oral Antibiotics Due to their Poor Serum Concentration**
  - Nitrofurantoin
  - Fosfomycin
  - Amoxicillin-Clavulanate
  - Doxycycline.

## 7. Role of Other Antibiotics in Treatment of Infections Caused by ESBL Producing Enterobacterales

### 3. Piperacillin-Tazobactam

In UTI	Outside UTI
<b>Not Suggested</b> unless the patient improved, in this case continue this antibiotic but with no extension of duration of treatment.	<b>Not suggested</b> even if sensitive in vitro, <b>Why?</b> Several reasons stand behind this suggestion, including:
	1. In the presence of ESBL or other $\beta$ -lactamases, the MIC of Pip/Taz is inaccurate which make it hard to decide if it is sensitive

	<p>or not.</p> <p>2. Increased bacterial inoculum in the infection sites e.g. abscess, make the Pip/Taz penetration ineffective in comparison with carbapenems.</p> <p>3. Excessive production of ESBL decreased the effectiveness of Pip/Taz.</p>
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#### 4. Cefepime

In UTI	Outside UTI
<b>Not Suggested</b> unless the patient improved, in this case continue this antibiotic but with no extension of duration of treatment.	<b>Not suggested</b> even if sensitive in vitro, <b>Why?</b>
	<p>Cefepime is hydrolysed by ESBL, so when it is sensitive in vitro, it might be due to:</p> <ul style="list-style-type: none"> <li>• Inaccurate MIC</li> <li>• Poor AST</li> </ul>

5. **Cephamycin:** Do not use cephamycin although they are stable against ESBL, this is because there are little studies about it to recommend their effectiveness.

#### 8. AmpC β-Lactamase-Producing Enterobacterales

**AmpC Definition:** They are enzymes that encoded by chromosomes of several members of Enterobacterales. They hydrolyse β-lactams through either their basal or increased production through three main mechanisms:

- **Inducible Chromosomal Gene Expression:** Which gives in vitro sensitive third generation cephalosporins while they are ineffective in vivo.
- **Stable Chromosomal Gene De-Repression**
- **Constitutively Expressed AmpC Genes:** Both mechanisms (b and c) give in vitro resistant third generation cephalosporins which makes the identification of AmpC production followed by prescribing the most effective antibiotic much easier than in the mechanism (a).

#### 9. Organisms Producing AmpC Enzymes

Currently Considered AmpC producers	Previously considered AmpC producers
<b>Mnemonic: Ec Ka Cf</b>	<b>Mnemonic: ESCPPM</b>
<p><i>Enterobacter cloacae complex</i></p> <p><i>Klebsiella aeruginosa</i></p> <p><i>Citrobacter freundii</i></p>	<p><i>Enterobacter spp.</i></p> <p><i>Serratia spp.</i></p> <p><i>Citrobacter freundii</i></p> <p><i>Proteus vulgaris</i></p> <p><i>Providencia spp.</i></p> <p><i>Morganella morganii</i></p>



**Clinical Pearls**

- *Enterobacter cloacae* complex, *Klebsiella aeruginosa*, *Citrobacter freundii* are at moderate to substantial risk for clinically significant AmpC production.
- Do not treat infections caused by **EcKaCf** using third generation cephalosporins even if it is sensitive in vitro, due to resistance development in 20% of cases.
- *Serratia spp.*, *Providencia spp.*, *Morganella morganii*, do not overexpress AmpC, that is why they are not included in the currently considered AmpC producers, and should be treated according to the results of AST.

**10. Antibiotics Inducing AmpC vs their Stability against AmpC**

Antibiotic	AmpC induction	Stability
Aminopenicillin	Induce	Unstable
First gen Cephalosporins	Induce	Unstable
Carbapenems	Induce	Highly stable
Third gen Cephalosporins	Induce (weak)	Unstable
Piperacillin Tazobactam	Induce (weak)	Unstable
Aztreonam	Induce (weak)	Unstable
Cefepime	Induce (weak)	Stable
Non-B lactams	No induction	Stable

**Clinical Pearls**

- On choosing antibiotic to treat the EcKaCf organisms, follow this scheme:

Do not use: (even if sensitive in vitro)	Do use:
Aminopenicillin	Cefepime
First -3 <sup>rd</sup> Generation cephalosporins	Carbapenems
Aztreonam	
Piperacillin-tazobactam	
Amoxicillin- Clavulanate	
Ampicillin-sulbactam	

- Cefepime is the first choice unless AmpC production is combined with ESBL production or porin loss.
- All B-lactam induce AmpC production.
- Tazobactam is less effective in B lactam protection than other B-lactamase inhibitors e.g. Vaborbactam.

**10. Carbapenem-Resistant Enterobacterales**

**CRE Definition:** According to CDC, CRE can be defined as, Enterobacterales that test resistant to at least one of the carbapenem antibiotics or produce a carbapenemase.

**Clinical Pearl:** When the following organisms are isolated from the clinical samples, you should take in consideration that these organisms have intrinsic elevated MIC to imipenem,

so to apply the CDC definition of CRE, you should use the AST results of carbapenems other than imipenem to identify CRE. These organisms are *Proteus spp.*, *Providencia spp.*, *Morganella spp.* with **mnemonic PPM**.

**CRE Mechanism or Resistance:** From the CDC definition of CRE we can find out two types of resistant mechanisms which can be detected either phenotypically or genotypically.

**Carbapenemase Production:** Enterobacterales can produce carbapenemase enzyme that is responsible for carbapenem breakdown. There are a lot of carbapenemase which is varying in their epidemiology and distribution worldwide. The most isolated carbapenemase are:

- **KPC**, which was isolated first from *Klebsiella*, but it is currently not limited to it, and can be isolated from several species of Enterobacterales.
- **NDM**, New Delhi metallo- $\beta$ -lactamases
- **VIM**, Verona integron-encoded metallo- $\beta$ -lactamases
- **IMP**, imipenem-hydrolysing metallo- $\beta$ -lactamases
- **OXA-48 like**.

**Non Carbapenemase Production:** This can occur due to amplification of non-carbapenemase  $\beta$ -lactamase genes in combination with other resistance mechanisms. Example of this type of resistance is the overproduction of ESBL enzymes in combination with porin loss.

## Clinical Scenarios

### Scenario 1: How to Treat a Patient with Isolated *Klebsiella Pneumoniae* from a Surgical Wound, Which has the Following AST Result

Antibiotic	AST result
Ertapenem	Resistant
Imipenem-cilastatin	Sensitive
Meropenem	Sensitive
Ciprofloxacin	Resistant
Gentamycin	Sensitive
Ceftriaxone	Resistant
Carbapenemase production	Negative

**Clinical Pearl:** The previous AST shows that this organism is fulfilling the CDC definition of CRE, due to resistance to one agent of tested carbapenems. On testing carbapenemase production, it came with negative results, which means that this mechanism of resistance is non carbapenemase producing type. In this case, the recommended treatment will be:

### Extended Infusion of Meropenem or Imipenem-Cilastatin Over 3 Hours.

### Scenario 2: How to Treat a Patient with Isolated *E. Coli* from a Clinical Sample of Admitted Patient, Which has the Following AST Result

Antibiotic	AST result
Ertapenem	Resistant
Imipenem-cilastatin	Resistant
Meropenem	Sensitive
Ciprofloxacin	Resistant
Gentamycin	Sensitive
Ceftriaxone	Resistant

**Clinical Pearl:** The previous AST shows that this organism is fulfilling the CDC definition of CRE, due to resistance to two out of three agents of tested carbapenems. In this scenario, the severity of infection will be the cornerstone in choosing the treatment plan. Examples of infection severity:

- **Cystitis:** in this case, extended infusion of Meropenem can be used.
- **Complex Intra-Abdominal Infection:** in this case, **DO NOT** use neither carbapenems nor carbapenem-B lactamase inhibitor combinations.

### How to Prevent and Control Infections Caused by MDRO?

**1. Basics of IPC Programs in Health Care Facilities:** Application of the following principles will facilitate the execution of detailed strategies responsible for tackling the MDRO infections. Therefore, the following principles are:

- Education of the healthcare workers about the importance of IPC measures.
- Organised distribution of the approved guidelines through printed posters and materials.
- Enhancement of the role of the Microbiology laboratory, through restricted reporting of antibiotics based on trending antibiogram of each healthcare facility.
- Using good clinical practice in prescribing the needed antibiotics and avoidance of unneeded use.
- Empirical antibiotics should be reviewed daily and to be changed either through escalation or de-escalation based on clinical condition of the patient and the culture-based results.

### 2. Strategies for Tackling MDROs

- Application of the antimicrobial stewardship programme and setting up a responsible committee to follow up the execution of programme principles.
- Active surveillance to detect patients with MDRO as soon as possible and start measures needed to stop the spread of their infections to other patients such as patient isolation or contact precautions.
- Restriction of movement of the identified infected patients is one of the effective measures to stop the spread of infection.
- Cleaning and decontamination of all patient's items.

## What is the Impact of MDRO on the Public Health?

Multi-drug resistant organisms (MDROs) have a significant impact on public health sectors globally. Here are some key aspects of their impact:

- 1. Increased Morbidity and Mortality:** MDROs pose a serious threat to public health by causing infections that are more difficult to treat. Patients infected with MDROs are at higher risk of complications, prolonged hospital stays, and increased mortality rates compared to infections caused by susceptible organisms.
- 2. Healthcare Costs:** Treating infections caused by MDROs is often more expensive due to the need for prolonged hospitalization, specialized treatments, and the use of costly antibiotics. MDRO infections can strain healthcare resources and lead to increased healthcare expenditures for both individuals and healthcare systems.
- 3. Antibiotic Resistance Crisis:** MDROs contribute to the global antibiotic resistance crisis by acquiring resistance to multiple classes of antibiotics. The spread of MDROs limits treatment options, leading to the emergence of "superbugs" that are resistant to all available antibiotics, posing a serious challenge to infectious disease management.
- 4. Impact on Healthcare Delivery:** MDRO outbreaks in healthcare settings can disrupt healthcare delivery by necessitating ward closures, implementing strict infection control measures, and diverting resources to outbreak management. At the same time, Healthcare-associated transmission of MDROs can erode patient trust and confidence in healthcare facilities, leading to reduced utilization of healthcare services.
- 5. Community Transmission:** MDROs are not confined to healthcare settings but can also spread within communities through various mechanisms, including person-to-person transmission, contaminated food and water, and environmental contamination. Community-acquired MDRO infections contribute to the burden of infectious diseases in communities and may lead to outbreaks in community settings such as schools, prisons, and long-term care facilities.
- 6. International Spread:** MDROs know no borders and can spread across countries and continents through travel and trade. International dissemination of MDROs poses challenges for global health security, requiring coordinated efforts among countries to prevent and control the spread of these pathogens.
- 7. Impact on Vulnerable Populations:** Vulnerable populations such as the elderly, immunocompromised individuals, and those with chronic medical conditions are particularly susceptible to MDRO infections. MDROs exacerbate health disparities by disproportionately affecting marginalized and underserved communities with limited access to healthcare resources and infection prevention measures.
- 8. Economic and Societal Impact:** The impact of MDROs extends beyond the healthcare sector to encompass broader economic and societal consequences, including lost productivity, disability, and reduced quality of life for affected individuals and their families. MDROs can undermine sustainable development efforts by impeding progress

towards achieving universal health coverage and other health-related Sustainable Development Goals (SDGs).

Therefore, multi-drug resistant organisms pose a multifaceted threat to public health sectors worldwide, highlighting the urgent need for comprehensive strategies to prevent and control their spread. Addressing the impact of MDROs requires concerted efforts from governments, healthcare providers, researchers, and communities to preserve the effectiveness of antibiotics, safeguard public health, and ensure equitable access to healthcare services for all.

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