National Guideline for the Management of Multidrug-Resistant Organisms (MDRO) – Carbapenem-Resistant Organisms (CRO)

Ministry of Health
Royal Government of Bhutan
1st Edition 2026

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FOREWORD

Bhutan has a long and proud history of meeting the Sustainable Development Goals, notably in the field of health. For many decades, our citizens have benefitted from access to the effective use of antibiotics, which have significantly reduced morbidity and mortality from bacterial infections. Antibiotics are essential for the provision of safe perinatal care, basic surgery, and the treatment of minor and serious infections. However, the rise of antimicrobial resistance (AMR), particularly multi-drug-resistant organism (MDRO) like carbapenem-resistant organism (CRO), poses an unprecedented threat to these healthcare advancements. Many experts believe that AMR poses a serious and growing threat to our health and society,one that can have more adverse effects than the COVID-19 pandemic if we don't take action. Unchecked AMR can affect not just individual patients but also the core of modern medicine, making it harder to provide safe and effective care. It is crucial that we respond quickly to this challenge to protect our health systems and future generations.

This guideline is a pioneering initiative in Bhutan, designed for all healthcare professionals working across the country involved in managing infections caused by MDRO, notably carbapenem-resistant organism (CRO). It will provide guidance on the identification and risk assessment of CRO; prevention and control measures to curb transmission; the isolation policies and infection prevention and control (IPC) measures in managing patients with MDRO-CRO infections. The guideline will also provide treatment guidelines for specific organisms, and highlight stewardship policies that aim to prevent MDRO from acquiring further antibiotic resistance. It will inform staff about their education and training obligations with respect to MDRO-CRO infection prevention and control, and where appropriate, their statutory duties to report, monitor and survey MDRO-CRO cases within the hospital.

Through these guidelines, we aim to minimize the spread of infections within the hospital and wider community, and thus improve patient outcomes. Our objectives include early identification of CRO infections, implementation of robust infection control measures, and fostering a culture of safety and accountability among healthcare workers.

We trust that you will closely adhere to these guidelines when assessing and caring for patients with suspected, or confirmed MDRO infection. The Ministry appreciates your commitment to caring for such patients, and thus helping to curb the spread of this major threat to public health in Bhutan. Together, we can combat the threat of AMR and ensure a healthier future for all Bhutanese.

Dasho Pemba Wangchuk
Hon'ble Secretary
Ministry of Health

LIST OF ABBREVIATIONS

ABHR	Alcohol-based Hand Rub
ADE	Adverse Drug Event
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
AST	Antibiotics Susceptibility Test
CLSI	Clinical Laboratory standard Institution
CP-CRO	Carbapenemase-producing carbapenem-resistant organism
CPE	Carbapenemase-producing Enterobacterales
CRAB	Carbapenem-resistant Acinetobacter baumannii
CRE	Carbapenem-resistant Enterobacterales
CRO	Carbapenem-resistant organism
CRPA	Carbapenem-resistant Pseudomonas aeruginosa
ECG	Electrocardiogram
ER	Emergency Room
ESBL	Extended-spectrum beta-lactamases
GES	Guiana-Extended Spectrum-β-Lactamase
HCP	Healthcare Personnel
HDU	High Dependency Unit
HH	Hand Hygiene
ICU	Intensive Care Unit
IMP	Imipenemase
IPC	Infection Prevention and Control
IPCT	Infection Prevention and Control Team
IV	Intravenous
KPC	Klebsiella pneumoniae Carbapenemase
LD	Loading Dose
MALDI-TOF	Matrix Assisted Laser Desorption Ionization Time-of-Flight
MBL	Metallo-β-lactamase
MD	Maintenance Dose
MDRO	Multidrug Resistant Organism
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin-resistant Staphylococcus aureus
MS	Medical Superintendent
NDM	New Delhi Metallo-β-lactamase
OXA	Oxacillinase
PO	Per os: by mouth
PPE	Personal Protective Equipment
QAD	Quality Assurance Division
SOP	Standard Operating Procedure
USG	Ultrasound Sonography
VIM	Verona Integron-encoded Metallo-beta-lactamase
VRE	Vancomycin-resistant Enterococci

ACKNOWLEDGEMENT

The development of this "National Guideline for the Management of Multidrug-Resistant Organism - Carbapenem Resistant Organism" would not have been possible without the invaluable contributions and collaborative efforts of several dedicated individuals and institutions.

We extend our sincere gratitude to the following key contributors whose expertise, commitment, and hard work were essential in the development of this guideline:

- Dr. Sonam Zangmo, Infectious Diseases Physician, AMS and IPC Center, JDWNRH
- Tshering Yangzom, Clinical Nurse, AMS and IPC Center, JDWNRH
- Khando Wangchuk, Pharmacist, AMS Focal, AMS and IPC Center, JDWNRH

We extend our sincere appreciation to the Microbiology Unit, Department of Pathology and Laboratory Medicine, JDWNRH, for their teamwork and continued support. We also acknowledge the Heads of Departments (HODs), clinician representatives, Nursing Superintendent, and nurse in-charges at JDWNRH, CRRH, ERRH, and PGH for their valuable comments, constructive suggestions, and sustained support throughout the development process. Their expert inputs were instrumental in shaping the final document and ensuring its clinical relevance and applicability.

Special acknowledgement is extended to the Fleming Fund for their generous financial and logistical support, and to the Health Promotion and Risk Communication Division for the design and layout, which were essential to the successful completion of this guideline.

This document is a result of collective expertise and dedication, and we hope it will serve as a valuable resource in improving the management of Multidrug-Resistant Organism, specifically Carbapenem-Resistant Organism, in our healthcare settings.

Thank you all for your invaluable contributions.

INTRODUCTION

Each year, 7.7 million people die from bacterial infections; 1.27 million of these deaths are caused by bacteria resistant to available antibiotics. The burden of Antimicrobial Resistance (AMR) is increasing worldwide, but the incidence of new cases, and mortality, are unequally distributed. Low- and middle-income countries are the most affected by AMR, and a recent Lancet Commission highlighted the pressing need for improved surveillance, infection control procedures, and access to antibiotics in these settings. Without concerted action, AMR will have substantial negative effects on human health and economic development, especially in resource-constrained environments.

In South Asia, the situation is stark, with an estimated 76.8 deaths per 100,000 population linked to AMR - only slightly lower than rates in sub-Saharan Africa. Notably, no studies have reported on the burden of AMR in Bhutan. However, significant strides are being made. In recent years, with support from the Fleming Fund, the national reference laboratory at the Jigme Dorji Wangchuck National Referral Hospital (JDWNRH) has enhanced its capacity for detecting multidrug-resistant organism (MDRO) using advanced technologies (VITEK MALDI-TOF and COMPACT machines). Although targeted screening is currently limited, these advancements are beginning to illuminate the hidden burden of MDRO in our hospitals, which have likely been circulating undetected for many years. Recent findings indicate a troubling scenario, with a significant prevalence of MDRO-CRO infections, particularly among vulnerable patient populations in medical, surgical, intensive care and high-dependency units. This alarming trend necessitates urgent action from healthcare professionals across Bhutan to address this threat.

In 2017, the endorsement of a National Action Plan on Antimicrobial Resistance marked a pivotal step toward addressing this issue, culminating in the establishment of national antibiotic prescribing guidelines and surveillance systems. Despite these efforts, the need for ongoing improvement remains clear. A point prevalence survey carried out in June 2022 across four major hospitals suggests that antibiotic prescribing patterns are similar to those in other countries. Nonetheless, there is further work to be done. The Lancet Commission on AMR has identified improved use of personal protective equipment (PPE) and effective isolation and cohorting of confirmed cases as highly effective interventions to reduce the spread of AMR. Judicious use of antibiotics is key. Health workers have an important role to play in

identifying patients with a history of MDRO infection, and liaising with infection prevention and control (IPC) teams to cohort or isolate these patients pending further testing. However, tackling this multifaceted challenge requires a collective effort from all healthcare staff, emphasizing that every role is vital in our fight against this pressing public health threat.

1 General Information on Multidrug-Resistant Organism - Carbapenem Resistant Organism (MDRO-CRO)

Multi-drug-resistant bacteria are bacteria that are resistant to at least three different antibiotics. These bacteria are commonly found in the gut, where they do no harm, however, they can cause infection at other body sites, mainly in patients who are vulnerable due to other underlying diseases, injury or hospitalization. Infection often happens when the bacteria enter the body through an open wound or via a medical device such as a catheter. These infections are difficult to treat, and can cause additional pain to patients with slow wound healing and other complications such as pneumonia or infection in the blood. This can prolong the length of stay in hospital and, in some cases, can cause death.

Globally, there have been several notable outbreaks of MDRO infection, especially in high dependency and intensive care settings. MDRO of particular clinical significance include:

- Carbapenem-resistant *Enterobacterales* (CRE)
- Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
- Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. diff)*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococci* (VRE)
- Extended-spectrum beta-lactamases (ESBL)

1.1 Clinical Condition

Patients may be colonized or infected with these organisms:

- **Colonization** refers to the presence of MDRO on or in the body without causing clinical illness. Although asymptomatic, colonized individuals can still transmit the organism to others.

- **Infection** occurs when MDRO are present on or in the body and cause signs or symptoms of illness. The clinical presentation depends on the site of infection and may involve the skin, lungs, urinary tract, bloodstream, or other organs. Laboratory markers such as white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin can assist in distinguishing infection from colonization, particularly when correlated with clinical findings.

1.2 Mode of Spread

This group of organisms are spread by multiple routes depending on their location in the body and the type of infection.

- **Contact:** Via hands or contaminated equipment and environment.
- **Droplet:** With respiratory infection, droplets from the respiratory tract can travel short distances during coughing and sneezing
- **Airborne:** Some respiratory MDRO spread by the airborne route while others can become airborne during aerosol generating procedures.

1.3 Incubation Period

- No specific incubation period.

1.4 Period of Communicability

- As long as the organism is isolated.

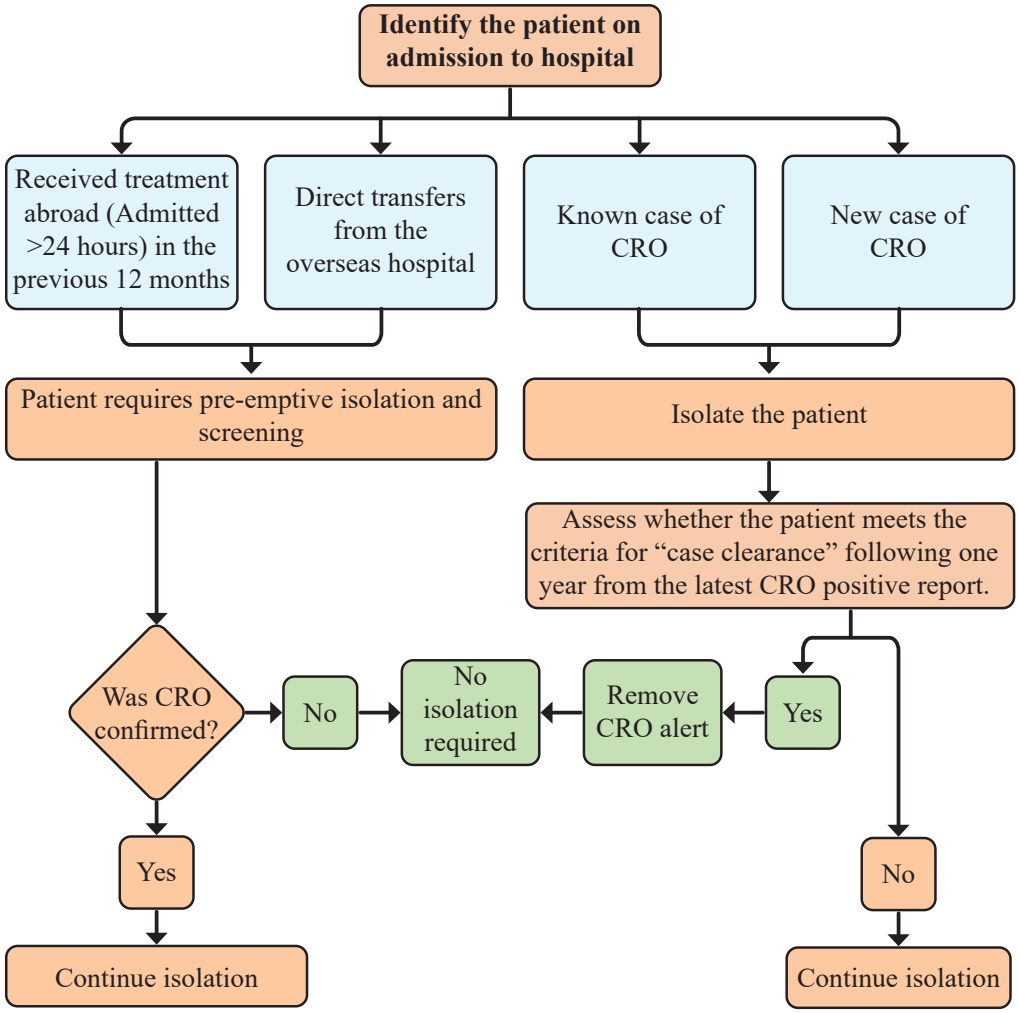
1.5 Persons most at-risk

- Patients in Intensive Care Units, High Dependency Units (HDU), Haemato-oncology and Renal Units.
- Patients who have had a variety of antibiotics and/or prolonged antibiotic therapy and prolonged hospital stay.
- Patients who have been admitted for medical treatment abroad within the last one year.

2 Identification and Screening of MDRO

2.1 High-Risk Patient Identification

- Patients with a history of recent healthcare exposure (e.g. Prolonged hospitalization, availed treatment in hospitals abroad within the last 1 year).
- Patients with a history of confirmed CRO infection or colonization.
- Patients placed in high-risk units (ICU, HDU, Oncology unit, Renal Unit).
- Patients who are on mechanical ventilation or have an indwelling medical device.
- Patients that are epidemiologically linked to an outbreak in the health facility.



#Patients with respiratory infections (MDRO isolated in sputum and tracheal aspirate) must be cohorted separately from non-respiratory cases.

Figure 1. Identification and isolation of known or suspected case with MDRO/CRO

2.2 Screening

- **Currently, routine screening for high-risk patients is not implemented due to the unavailability of selective culture plates, constraints in human resources for conducting routine screening, and lack of adequate isolation facilities.**
- All high-risk patients will be managed with stringent universal precautions to prevent the spread of infections.
- In the event of an outbreak of MDRO, screening will be carried out based on the recommendations provided by the Infection Prevention and Control Team (IPCT). The IPCT will specify the timing and procedures for screening patients who are at risk of MDRO during the outbreak.

2.3 Screening Methods

2.3.1 Culture and Sensitivity Testing

- Obtain specimens from body sites of suspected cases at high risk for colonization.
- **CPE:** Multiple sites of rectal or perianal swabs, feces, aspirates from any tubes or drains, urine from catheterized patients and specimens from open wounds.
- **CRPA, CRAB:** rectal or perianal swabs, wounds, ostomy sites and respiratory secretions or tracheal aspirates.
- Cultures are analyzed for resistance patterns.

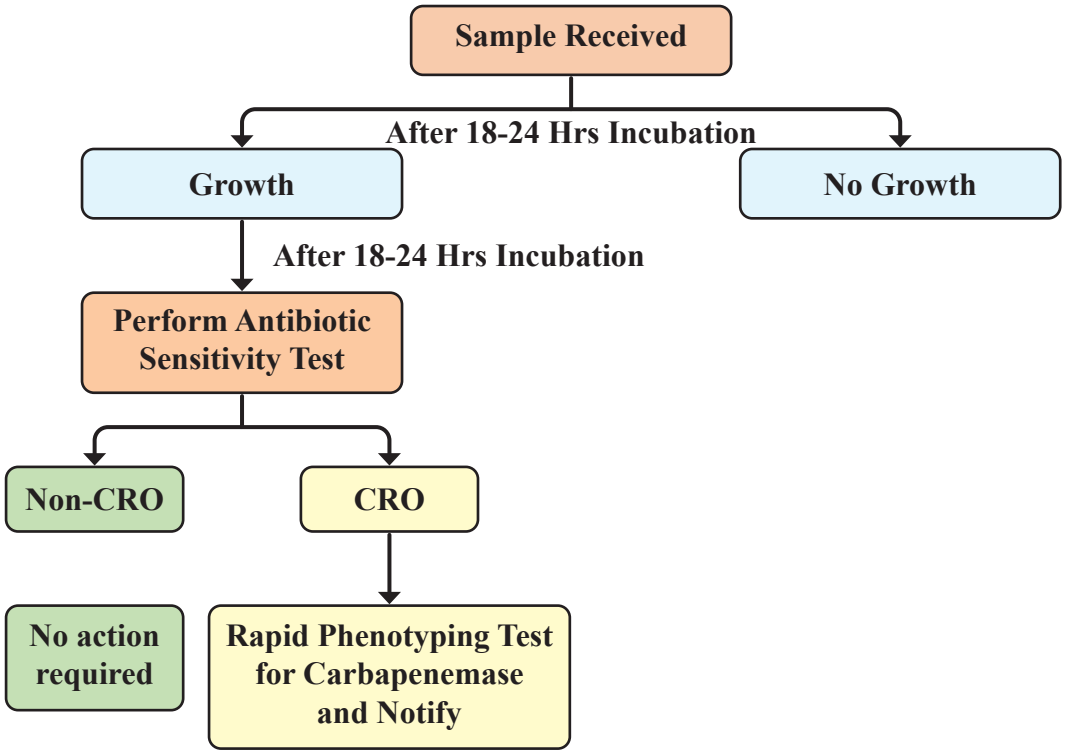
2.4 Laboratory Identification

2.4.1 Phenotypic Methods

- Identify the microorganisms using available methods (VITEK MS / Manual biochemical tests).
- Perform Antibiotics Susceptibility Test (AST) by Disk Diffusion method as per recommendation of Clinical Laboratory standard Institution (CLSI) and if Firstline antibiotics are sensitive then no further testing is required.
- In the AST report if all the antibiotics are resistant then second line testing is warranted. The second line testing includes higher generation antibiotics including carbapenems (Meropenem).
- If the organism identified is a CRO, perform a phenotypic test to distinguish between CP-CRO and non-CP-CRO, provided a test kit is available.
- If required and reagents are available, the CRO may be subject to MIC testing.

2.4.2 Genotypic Methods

- **In vitro rapid diagnostics test:** Detect specific resistance genes (e.g., OXA-48, KPC, NDM, VIM, IMP and OXA-40/58) using O.K.N.V.I. RESIST-5 and RESIST ACINETO



#Reporting: Notify Infection Control Teams and physician about identification on MDRO/CRO

Figure 2. Laboratory identification methods of MDRO/CRO

3 Roles and Responsibility

3.1 IPC and AMS Team

- Develop and implement protocols to prevent and control MDRO spread.
- Educate healthcare personnel and visitors about the organism and necessary precautions to be taken.
- Coordinate with other stakeholders to prevent and control MDRO spread.
- Monitor adherence to infection control practices and provide feedback to Healthcare Personnel (HCP).
- Maintain a surveillance system for timely recording, reporting, and notification of CRO cases or outbreaks.

- Manage CRO outbreaks and implement appropriate infection control strategies.
- Review and update protocols based on emerging evidence and surveillance data.
- Evaluate and improve the effectiveness of current infection control interventions through regular audits and feedback.

3.2 Clinician

- Adhering to SOPs/guidelines, including proper hand hygiene, isolation, contact precautions, and antibiotic stewardship.
- Notify the IPC team about the new MDRO cases in their respective units.
- Identify and flag affected patients using their old medical records to promptly implement isolation and contact precautions.
- Patients with a documented history of CRO should be placed in isolation and assessed to determine if they have met the appropriate clearance criteria.
- **Patients with respiratory infections (MDRO isolated in sputum and tracheal aspirate) must be cohorted separately from non-respiratory cases.**
- **Patients who received treatment abroad (hospitalized for more than 24 hours within the past 12 months) should be flagged as high-risk for CRO upon presentation at the ward/ER, and placed under pre-emptive isolation with appropriate precautions and measures implemented.Since no active screening like rectal swab is conducted, baseline cultures (blood, urine, sputum, and pus/wound culture if an open wound is present) should be sent on admission of these patients to the Ward/ED.**
- **Patients who are newly confirmed cases of CRO should be placed in isolation immediately, with necessary precautions and measures implemented.**
- Notify the transferring facility clinician if the MDRO was present on admission for appropriate follow-up.
- Notify the receiving unit's clinician of the patient's transfer for necessary arrangements and appropriate follow-up measures.
- Inform patients about their results and the infection control measures being implemented.
- Collaborate with the AMS team to review and adjust treatment plans.

3.3 Nurse

- Adhere to relevant SOPs/guidelines, including proper hand hygiene, isolation, contact precautions, and antibiotic stewardship.
- Notify the IPC team about the new CRO cases in their respective units.
- Notify the transferring facility if the CRO was present on admission for appropriate follow-up.
- Notify the receiving unit nurse of the patient's transfer to facilitate necessary arrangements and appropriate follow-up.
- Identify and flag affected patients using their old medical records to promptly implement isolation and contact precautions.
- **Patients with respiratory infections (MDRO isolated in sputum and tracheal aspirate) must be cohorted separately from non-respiratory cases.**
- **Patients with a documented history of CRO should be placed in isolation and assessed to determine if they have met the appropriate clearance criteria.**
- **Patients who received treatment abroad (hospitalized for more than 24 hours within the past 12 months) should be flagged as high-risk for CRO upon presentation at the ward/ER, and placed under pre-emptive isolation with appropriate precautions and measures implemented. Since no active screening like rectal swab is conducted, baseline cultures (blood, urine, sputum, and pus/wound culture if an open wound is present) should be sent on admission of these patients to the ward/ED.**
- **Patients who are newly confirmed cases of CRO should be placed in isolation immediately, with necessary precautions and measures implemented.**

3.4 Laboratory Staff

- Ensure timely and accurate identification of CRO using available identification methods.
- Alert the IPC unit and relevant department of positive culture reports.

3.5 Emergency Department staff

- To identify and flag CRO patients using their old medical records to implement isolation and contact precautions without delay.

- **Patients with respiratory infections (MDRO isolated in sputum and tracheal aspirate) must be cohorted separately from non-respiratory cases.**
- **Patients with a documented history of CRO should be placed in isolation and assessed to determine if they have met the appropriate clearance criteria.**
- **Patients who received treatment abroad (hospitalized for more than 24 hours within the past 12 months) should be flagged as high-risk for CRO upon presentation at the ward/ER, and placed under pre-emptive isolation with appropriate precautions and measures implemented. Since no active screening like rectal swab is conducted, baseline cultures (blood, urine, sputum, and pus/wound culture if an open wound is present) should be sent on admission of these patients to the ward/ED.**
- **Patients who are newly confirmed cases of CRO should be placed in isolation immediately, with necessary precautions and measures implemented.**

3.6 Hospital Management

- Provide the necessary resources and support to ensure effective CRO prevention, including the availability of adequate supplies to facilitate proper patient care and management.
- Ensuring staff training and compliance with AMR protocols.
- Facilitating regular reviews and updates of infection control policies.

3.7 AMS Team

- Develop and regularly update standard treatment protocols for CRO patients based on the latest evidence.
- Provide expert guidance to clinicians on the treatment of CRO.
- Utilize CRO surveillance data to ensure the availability of appropriate antibiotics for specific organisms and genotypes (when testing is available).
- Incorporate AMS principles into the management of CRO.
- Conduct Prescription Audits of CRO patients and provide immediate feedback and corrective actions, when required.

3.8 Supporting Staff

- Follow detailed cleaning and disinfection protocols for surfaces and equipment in patient areas, focusing on high-touch surfaces to prevent MDRO spread.
- Wear and properly dispose of PPE (e.g., gloves, gowns, masks) as required to protect themselves and prevent CRO transmission.
- Adhere to strict personal hygiene and hand hygiene practices to minimize the risk of spreading MDRO.
- Ensure proper waste disposal.
- Notify the respective supervisor of any cleaning-related issues or concerns, including damaged surfaces or insufficient supplies.
- Engage in ongoing training on IPC, CRO management, and safe cleaning techniques.
- Support surveillance efforts by assisting in monitoring and documenting cleaning activities and compliance with infection control protocols.

4 Infection Prevention and Control Practices in CRO management

In the management of MDRO, in addition to standard precautions, Transmission Based Precautions should be applied.

4.1 Patient Placement

4.1.1 In Isolation Ward/Cabin

- A single-patient room (cabin) with en-suite toilet is recommended when there are two or less CRO patients.
- When there are more than two patients colonized or infected with CRO in a hospital, cohorting them into dedicated units with en-suite toilets is recommended to prevent transmission. Ideally, CP-CRO should be cohorted separately from Non-CP-CRO. However, due to the lack of continuous supply of rapid tests for detecting carbapenemase enzymes and the challenges in establishing separate isolation for CP-CRO and Non-CPCRO, they will currently be cohorted together.
- **Patients with respiratory infections (MDRO isolated in sputum and tracheal aspirate) must be cohorted separately from non-respiratory cases, preferably in a dedicated single isolation room (if available) or in a separate cohort room.**

- Choose rooms with greater physical separation (3 – 6 feet) and use privacy curtains.
- Treat each bed space in multi-occupancy rooms as separate.
- Change PPE and perform hand hygiene between each patient.
- Cohort patients with CRO throughout their admission.
- These precautions should remain in place until the patient is discharged from the facility.
- Make sure rooms have proper CRO contact precaution signage ***(Annexure I: MDRO Signage and sticker)*** placed.
- Since dedicated staff cannot be provided to patients in a CRO cohort, one should care for patients without CRO first and then CRO patients, whenever feasible.
- Use dedicated medical equipment for CRO cohorts. If equipment is shared, ensure it is thoroughly cleaned with an appropriate disinfectant after use and allowed to dry before being used for another patient.
- For shared equipment, use different sets for MDRO and non-MDRO patients whenever feasible, such as dressing trolley sets and ECG machines.
- Any medical devices/equipment (e.g., portable USG machine/portable echo machine) should be thoroughly cleaned with suitable disinfectant before taking it to other units.
- Keep doors closed.
- Limit patient movement to reduce transmission.
- Hand hygiene must be performed when exiting the room.
- Clean and disinfect patient care areas using a 0.5% bleach solution at least three times daily, with emphasis on high-touch surfaces.

4.1.2 In Isolation ICU/HDU

- **Since dedicated isolation rooms are not available in the ICU or HDU, it's crucial to implement standard precautions and practices while caring for every patient.**
- Treat each bed space in multi-occupancy rooms as separate.
- Change PPE and perform hand hygiene between each patient.
- These precautions should remain in place until the patient is discharged from the unit.

- In an event of an outbreak, try to Cohort patients with CRO throughout their admission in one side of the ICU or HDU (i.e. ICU and HDU have 2 rooms with 4-5 beds in each room).
- Make sure each bed has proper CRO contact precaution signage placed ***(Annexure I: MDRO Signage and sticker)***.
- Since dedicated staff cannot be provided to care for patients in an CRO cohort, staff should care for patients without CRO before those with CRO, whenever feasible.
- Use dedicated medical equipment for CRO cohorts. If equipment is shared, ensure it is thoroughly cleaned with an appropriate disinfectant after use and allowed to dry before being used for another patient.
- For shared equipment, use different sets for MDRO and non-MDRO patients whenever feasible, such as dressing trolley sets and ECG machines.
- Any medical devices or equipment (e.g., portable USG or portable echocardiography machines) must be thoroughly cleaned with an appropriate disinfectant before being taken to other units.
- Keep doors closed.
- Limit patient/bystander movement to reduce transmission.
- Perform hand hygiene immediately after leaving the room.
- Clean and disinfect patient care areas using a 0.5% bleach solution at least three times daily, with emphasis on high-touch surfaces.
- Terminal Cleaning of ICU/HDU following directions given by IPC Team, in coordination with the Administration and other departments after a formal notification by the administration.

4.2 Contacts

- Contacts may be screened on the advice of IPCT during the event of an outbreak.

4.3 Hand Hygiene

- Hand hygiene is the single most important measure to prevent CROs infection.
- All staff must strictly adhere to the 7-step hand hygiene technique at each of the 5 moments of hand hygiene ***(Annexure II: Steps of Hand Hygiene, Annexure III: 5 moments of Hand Hygiene)***.

- Hand hygiene must be performed before and after each patient contact using alcohol-based hand rub (ABHR) or soap and water.

4.4 Personal Protective Equipment (PPE)

- To prevent spread through direct contact, PPE (disposable gloves and apron) must be worn for all direct contact with the patient or the patient's environment/ equipment.
- If there is a risk of splashing/spraying of blood or body fluid, a fluid repellent surgical face mask and eye protection should be worn.
- Remove PPE before leaving the isolation area and discard it as an infectious waste.
- Hand hygiene must follow removal of PPE.
- Change PPE and perform hand hygiene between each patient.
- Contact your IPCT for advice on when/if transmission-based precautions can be discontinued.

4.5 Linen Management

- The CRO's linen and clothing are classified as infectious linen that require disinfection by soaking in a 0.5% bleach solution for 10 – 15 minutes and then thoroughly rinsing before being sent to the laundry unit for final processing.

4.6 Moving between Wards, Hospitals and Departments (Including Operation Theater)

- The patient should only be transferred to another department for essential procedures and investigations.
- All patient movement should be kept to a minimum.
- Prior to transfer, the ward should inform the receiving department/ward/hospital of the patient's infectious condition.
- The receiving area should put in place arrangements to minimize contact with other patients and arrange for additional domestic cleaning if required.

4.7 Patient Attendant/Visitors

- Limit attendants to one per patient; the attendant should be healthy and not on any form of immunosuppression.

- Restrict visitors.
- Educate patient attendants and visitors on hand hygiene, mandatory use of face masks and contact precautions.
- Educate and encourage patients to maintain hand hygiene and follow proper cough etiquette.
- Limit the movement of patient attendants within the hospital.
- Ensure hand hygiene is performed by family members and visitors before leaving the room of a patient infected with MDRO.

5 Environmental Cleaning and Disinfection

5.1 Environmental Cleaning

- Clean and disinfect patient care areas using a 0.5% bleach solution at least three times daily, with emphasis on high-touch surfaces.
- Clean and disinfect the patient environment using a 0.5% bleach solution.

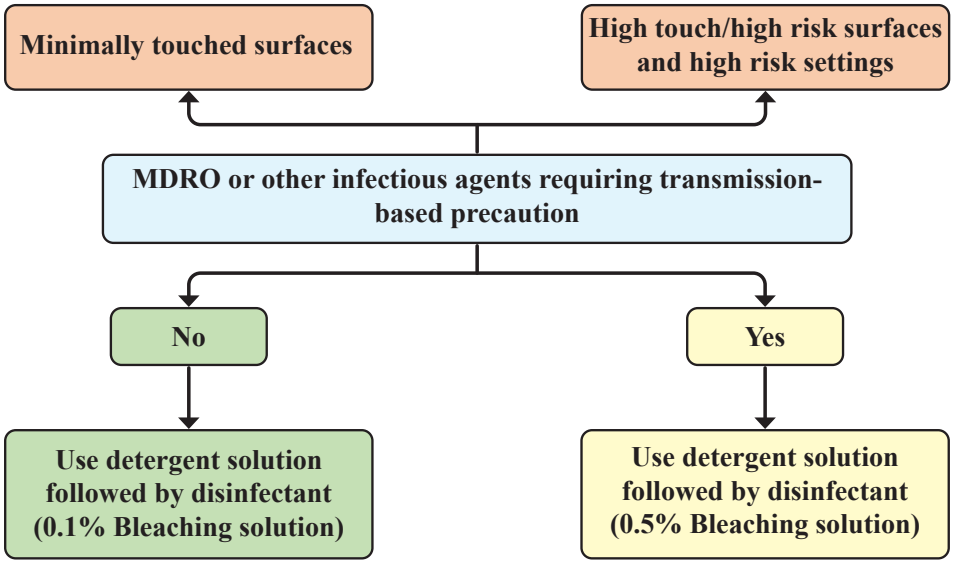


Figure 3. Environmental cleaning processes of touch surfaces in hospitals

5.2 Terminal Cleaning

- When indicated, terminal cleaning of the isolation ward/cabin shall be performed using the recommended disinfectant solution (e.g., 10% hydrogen peroxide with 0.01% silver nitrate), in accordance with standard procedures.

- Patient care areas shall be cleaned and disinfected using a 0.5% bleach solution.
- After terminal cleaning, the bed or room must remain vacant for at least one hour before admitting a new patient.

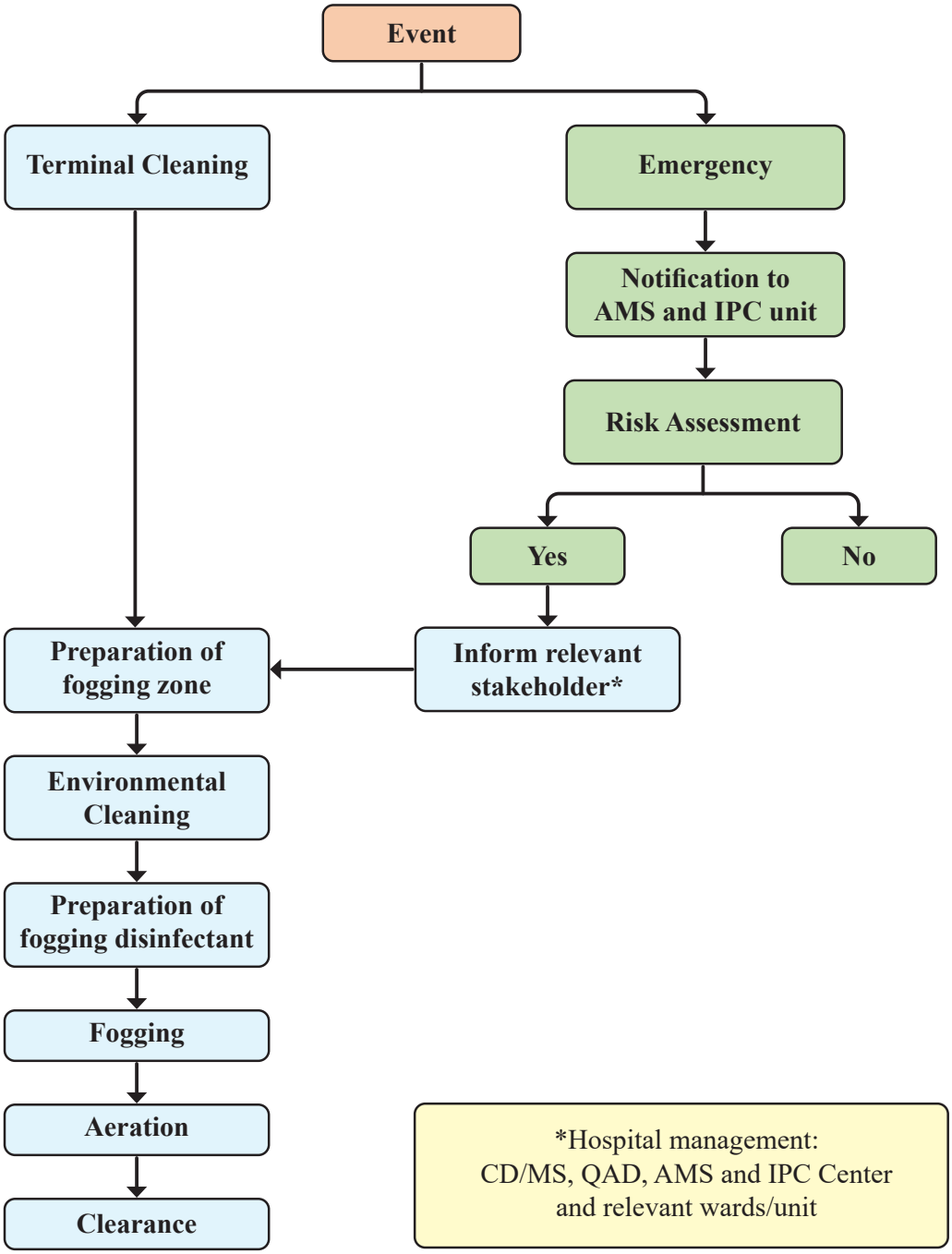


Figure 4. Terminal cleaning procedure and issuance of clearance of re-use of MDRO/CRO Isolation Ward/Cabin

6 Patient Education

6.1 Patient Information

- Inform the patient/parent/guardian/next-of-kin (as appropriate) of the patient's condition and the necessary precautions.
- Educate them well about their condition and their role in preventing the spread within the health facility and community.
- If relatives or carers wish to take personal clothing home, staff must place clothing in a plastic bag, explain and mention the steps of washing clothes at home.

6.2 Patient Education on Discharge

- Educate them well about their condition and their role in preventing the spread within the health facility and community.
- Their MDRO status should be clearly flagged on the discharge summary.
- Staff must place the patient's clothing in a plastic bag, explain and mention the steps of washing clothes at home.

Discharge Leaflet

Precautions be taken at home to prevent the spread of Multidrug Resistant Organism

- Clean your hands often, especially after any contact with the area of your body where the Multidrug Resistant Organism has been found.
- Caretakers, people living with you and visitors should also clean their hands often.
- Avoid sharing personal items such as towels or razors.
- Avoid using public toilets where possible.
- Wash and dry clothing, bed linens and towels in the warmest temperatures recommended on labels.
- Keep your environment clean by using household cleaners and disinfectants following label instructions.

7 Clearance of CRO

- Most CRO patients remain colonized for at least 12 months and some considerably longer. **Therefore, it is crucial for isolation and contact precautions for subsequent admission to a healthcare facility, at least for one year from the latest CRO positive culture report.**
- While it is a requirement **that an alert remain in the patient's medical record** noting that CRO has been isolated, an assessment must be made at **each subsequent** admission to determine if additional IPC measures are warranted to determine **'clearance criteria'**.

7.1 Clearance Criteria

- Patients with a documented positive CRO result within the previous 12 months shall be placed in isolation with MDRO precautions upon readmission, irrespective of any negative results obtained during that period.
- Patients whose most recent positive CRO result occurred more than 12 months ago should undergo a clearance assessment. This assessment requires collection of appropriate clinical specimens (e.g., sputum, blood, urine, or wound swabs) on two separate occasions, at least 24 hours apart. If all specimens are negative, additional IPC precautions may be discontinued for subsequent admissions. Clearance must be determined in consultation with the IPCT and an infectious diseases physician.
- Any individual considered cleared must be re-screened at each subsequent overnight admission to a healthcare facility to detect possible recurrence of CRO colonization.

8 Antimicrobial Stewardship and Treatment Protocol

8.1 Antimicrobial Stewardship

8.1.1 Optimize Antimicrobial Use

- Use Narrow-Spectrum Agents: Prefer narrow-spectrum antibiotics based on susceptibility testing to limit resistance development.
- Avoid Overuse: Avoid using broad-spectrum antibiotics when not necessary. Overuse can promote resistance.

8.1.2 Guideline Adherence

- Follow Protocols: Adhere to established Antibiotic guidelines and local protocols for prescribing antibiotics.
- Update Protocols: Regularly review and update guidelines based on current resistance patterns and new evidence.

8.1.3 Review and Adjust Therapy

- Regular Reviews: Conduct regular reviews of antimicrobial therapy to ensure it remains appropriate based on patient response and culture results.
- De-escalation: De-escalate therapy as soon as possible based on culture and susceptibility results to the most effective and narrow-spectrum antibiotic.

8.1.4 Education and Training

- Staff Education: Provide ongoing education to healthcare providers about antimicrobial stewardship and the implications of MDRO.
- Patient Education: Educate patients about the importance of completing prescribed antibiotic courses and the risks of misuse.

8.2 Treatment Protocol: Specific Recommendations

8.2.1 Treatment Options for Carbapenem-resistant *Enterobacterales* (CRE): (*Escherichia coli* and *Klebsiella pneumoniae*)

- Ceftazidime + Avibactam
- Tigecycline (Do not use for bloodstream infection, urinary tract infections and hospital acquired pneumonia)
- Cefiderocol
- Polymyxin B (for infections in which no other treatment option is available, do not use in urinary tract infections)

8.2.2 Treatment of Carbapenemase-producing *Enterobacterales* (CPE) depending on the type of Carbapenemase produced:

A. New Delhi Metallo-β-lactamase (NDM)

- Prolonged infusion of (Ceftazidime+Avibactam) and Aztreonam (over 3 hours). (ceftazidime-avibactam) and aztreonam to be administered simultaneously)
- Cefiderocol as monotherapy.

B. *Klebsiella pneumoniae* Carbapenemase (KPC)

- Ceftazidime+Avibactam
- Cefiderocol is an alternative option.

C. Oxacillinase-48 (OXA-48)

- Ceftazidime+Avibactam
- Cefiderocol is an alternative option.

8.2.3 Carbapenem-resistant Non-*Enterobacterales* (*Acinetobacter baumannii, Pseudomonas aeruginosa)*

A. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) Treatment Options

- It is recommended to use combination therapy with at least two agents for CRAB infections, even if a single agent demonstrates activity at least until a positive response is seen. In situations when prolonged durations of therapy may be needed (e.g., osteomyelitis), step-down therapy to a single active agent can be considered.
- Ampicillin-sulbactam (18-27 grams of Ampicillin-sulbactam per day,equivalent to 6-9 grams of sulbactam component per day in Combination therapy with another agent for CRAB infection (can be combined with Amikacin, Meropenem, Polymyxin, Minocycline, Tigecycline, Cefiderocol).
- Polymyxins (cannot be used in urinary tract infections, use colistin instead of polymyxin B for urinary tract infections) in combination with high dose Ampicillin-sulbactam.
- Minocycline in combination with high dose Ampicillin-sulbactam (Minocycline is preferred over Tigecycline). Minocycline is not for children below 8 years old.
- Tigecycline (do not use for urinary tract infections and blood stream infection) used in combination with high dose Ampicillin-sulbactam.
- Cefiderocol in combination with high dose Ampicillin-sulbactam (keep it as the last resort).

B. Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

- Ceftazidime + Avibactam
- Ceftolozane-tazobactam
- Cefiderocol is an alternative option.
- Polymyxins (for infections in which no other treatment option is available, do not use in urinary tract infection)

i. Verona Integron-encoded Metallo-beta-lactamase (VIM), NDM

- Cefiderocol is the preferred antibiotics for the treatment of Difficult-to-treat (DTR) *P. aeruginosa* that produce metallo-β-lactamase enzymes (VIM, NDM).
- Both ceftolozane- tazobactam and ceftazidime-avibactam is ineffective against MBL- producing *P. aeruginosa* (e.g., VIM, NDM enzymes)

ii. KPC

- Ceftazidime-avibactam is preferred.
- Cefiderocol is another option
- Ceftolozane-tazobactam remains ineffective against KPC-producing *P. aeruginosa*

iii. GES-producing P. aeruginosa:

- Ceftazidime-avibactam is preferred
- Cefiderocol is another option

8.3 Duration of Therapy

- Tailor Duration: The duration of antibiotic therapy should be determined by the site of infection, clinical response, and antimicrobial susceptibility results, with shorter courses often being sufficient.

8.4 Dosing Regime and Extended Infusion of Antimicrobial Agents

Sl no	Antibiotics	Dose	Dosing frequency	Infusion time
1	Piperacillin -Tazobactam	4.5 g	Every 8 hours	4 hours
2	Meropenem	2 g	Every 8 hours	3 hours
3	Ceftazidime -Avibactam	2.5 g	Every 8 hours	3 hours
4	Ampicillin- Sulbactam	9 g	Every 8 hours	4 hour
5	Minocycline (PO/IV)	200 mg LD, 100 mg MD	Every 12 hours	1 hour
6	Tigecycline	200 mg LD, 100 mg MD	Every 12 hours	0.5 - 1 hour
7	Polymyxin B	20k - 25k IU/kg LD 12.5k - 15k IU/kg MD	Every 12 hours	0.5 - 1 hour 1 - 2 hour
8	Aztreonam	2 g	Every 8 hours	3 hours
9	Ceftolozane-tazobactam	3 g	Every 8 hours	3 hours
10	Cefiderocol	2 g	Every 6 hours	3 hour
11	Colistin	9 million IU LD, 4.5 million IU MD	Every 12 hours	0.5 - 1 hour 1 - 2 hours
12	Sulbactam (High dose)	3 g	Every 8 hours	4 hours
LD = loading dose; MD = maintenance dose				

8.5 Polymyxins doses conversion

Can be expressed in mg or IU

Sl no	Polymyxins	Dose in mg	Dose in international units (IU)
1	Polymyxin B	1 mg	10,000 IU
2	Colistin (expressed as colistin base activity)	1 mg CBA ~ 2.67 mg Colistimethate Na.	30,000 IU

8.6 Dosing in Special Situation: Renal Dosing

Antibiotics	Creatinine clearance (CrCl)	Dose	Dosing interval	Infusion time
Piperacillin-tazobactam	>20 mL/min	4.5 g	Every 8 hours	4 hours
	≤20 mL/min or IHD/PD	4.5 g	Every 12 hours	4 hours
Meropenem	≥50 mL/min	1 or 2 g	Every 8 hours	3 hours
	25 to 49 mL/min	1 or 2 g	Every 12 hours	3 hours
	10 to 24 mL/min	500 mg or 1 g	Every 12 hours	3 hours
	<10 mL/min or IHD	500 mg or 1 g	Every 24 hours, given after HD	3 hours
Polymyxin B	Renal dosing not required	20k - 25k iu/kg LD 12.5k - 15k iu/kg MD	Every 12 hours	1 - 2 hours
Colistin	CrCl ≥90 mL/min	360 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 80 to <90 mL/min	340 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 70 to <80 mL/min	300 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 60 to <70 mL/min	275 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 50 to <60 mL/min	245 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 40 to <50 mL/min	220 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 30 to <40 mL/min	195 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 20 to <30 mL/min	175 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 10 to <20 mL/min	160 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl 5 to <10 mL/min	145 mg CBA/day	Every 12 hours	1 - 2 hours
	CrCl <5 mL/min	130 mg CBA/day	Every 12 hours	1 - 2 hours
Ceftazidime - avibactam	>50 mL/min	2.5 g	Every 8 hours	2 - 3 hours
	31 to 50 mL/min	1.25 g	Every 8 hours	2 - 3 hours
	16 to 30 mL/min	0.94 g	Every 12 hours	2 - 3 hours
	6 to 15 mL/min	0.94 g	Every 24 hours	2 - 3 hours
	≤5 mL/min or IHD	0.94 g	Every 48 hours, given after HD	2 - 3 hours
Ampicillin-sulbactam (6/3) g	≥90 mL/min	9 g	Every 8 hours	4 hours
	60 to <90 mL/min	6 g	Every 8 hours	4 hours
	30 to <60 mL/min or	3 g	Every 6 hours	4 hours
	15 to 29 mL/min	3 g	Every 8 hours	4 hours
	<15 mL/min	3 g	Every 12 hours	4 hours

Antibiotics	Creatinine clearance (CrCl)	Dose	Dosing interval	Infusion time
Tigecycline	No dosage adjustment necessary for any degree of kidney dysfunction			
	Mild-to-moderate hepatic impairment (Child-Pugh Class A or B)		No dosage adjustment necessary.	
	Severe hepatic impairment (Child-Pugh Class C)		Initial: 100 mg single dose; Maintenance: 25 mg every 12 hours.	
Ceftolozane-tazobactam	>50 mL/min	3 g	Every 8 hours	3 hours
	30 to 50 mL/min	750 mg or 1.5 g	Every 8 hours	3 hours
	15 to 29 mL/min	375 or 750 mg	Every 8 hours	3 hours
	<15 mL/min or IHD	150 or 450 mg	Every 8 hours (start after loading dose)	3 hours
Aztreonam (in combination with ceftazidime-avibactam)	≥30 mL/min	2 g	Every 6 to 8 hours	3 hours
	10 to 29 mL/min	1 g	Every 6 to 8 hours	3 hours
	<10 mL/min or I HD	2 g	Every 24 hours	3 hours
Cefiderocol	≥120 mL/min	2 g	Every 6 hours	3 hours
	60 to 119 mL/min	2 g	Every 8 hours	3 hours
	30 to 59 mL/min	1.5 g	Every 8 hours	3 hours
	15 to 29 mL/min	1 g	Every 8 hours	3 hours
	<15 mL/min or IHD	750 mg	Every 12 hours	3 hours

CBA: colistin based activity; **LD:** loading dose; **MD:** maintenance dose; **HD:** hemodialysis; **PD:** peritoneal dialysis, **IHD:** Intermittent hemodialysis

8.7 Adverse Drug Reactions

- Monitor for potential adverse effects of antibiotics, particularly those used in the treatment of MDRO.
- In the event of an adverse drug reaction (ADR), immediately discontinue the antibiotic, inform the prescribing clinician, and initiate appropriate management.
- Notify the pharmacy department for appropriate follow-up.

8.7.1 Ampicillin -Sulbactam

- Antibiotic associated diarrhoea
- Pseudomembranous colitis
- Thrombophlebitis
- Drug induced liver injury (DILI)

8.7.2 Ceftazidime Avibactam

- Antibiotic associated diarrhoea
- Pseudomembranous colitis

8.7.3 Minocycline

- DRESS is common side effect,
- Photosensitivity reactions
- Hepatotoxicity less common but fatal
- Tooth discoloration
- Vestibular symptoms

8.7.4 Tigecycline

- Hepatotoxicity
- Safety and efficacy not established in Pediatrics

8.7.5 Cefiderocol

- Hepatotoxicity
- Safety and efficacy not established in Pediatrics

8.7.6 Aztreonam

- Hepatotoxicity
- Neutropenia in children, less common in adults

8.7.7 Polymyxin B: Neurotoxicity

- Confusion, headache and seizures
- Visual disturbances, Dizziness,
- Ataxia, Paresthesias
- Muscle weakness

8.7.8 Colistin: Neurotoxicity and Nephrotoxicity

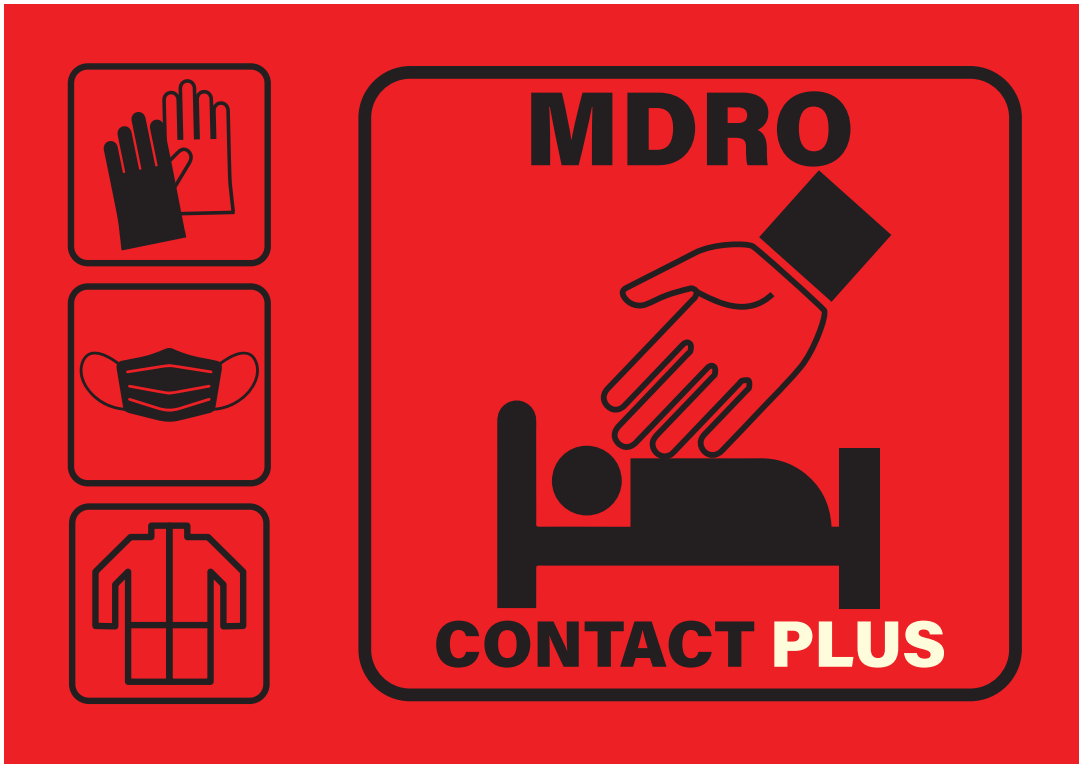
- Management: Mild ADE are reversible
- Lowering the dose
- Slow infusion

9 Education and Training for Healthcare Staff

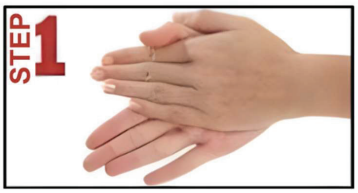
- IPCT should offer healthcare facilities with workshops centered on MDRO and IPC and AMS practices.
- Include AMR, MDRO, IPC, and AMS in the curriculum for the nursing and medical students in collaboration with the Khesar Gyalpo University of Medical Sciences of Bhutan.
- Implement a mandatory online course covering MDRO, IPC and AMS for all in-service healthcare providers and new recruits.

10 Annexures

10.1 Annexure I: MDRO Signage and Sticker

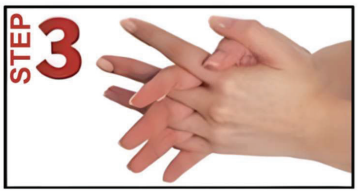


10.2 Annexure II: Steps of Hand Hygiene



Rub palms together.

Rub the back of both hands.



Interlace fingers and rub hands together.

Interlock fingers and rub the back of fingers of both hands.

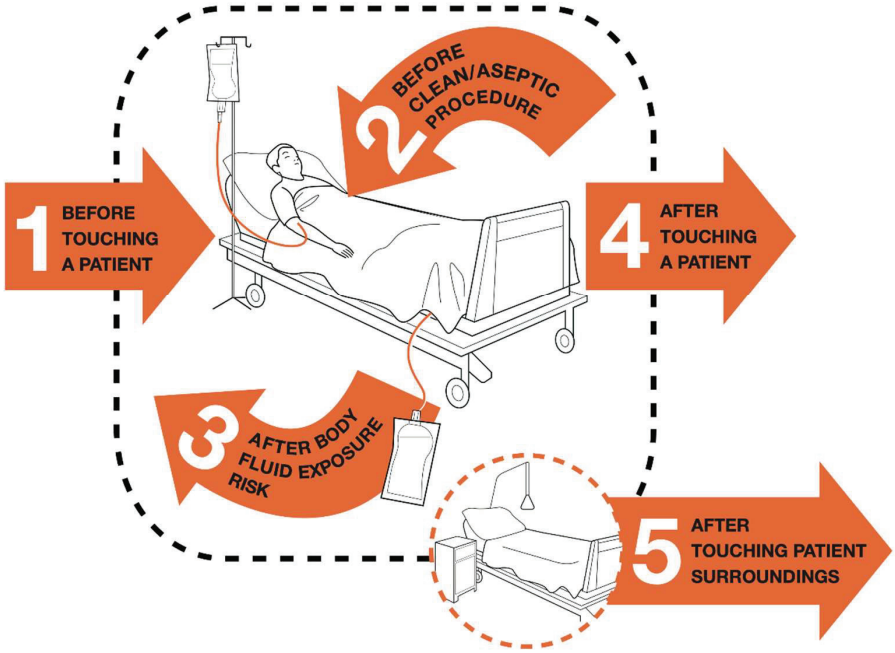
Rub thumb in a rotating manner followed by the area between index finger and thumb for both hands.

Rub fingertips on palm for both hands.

Rub both wrists in a rotating manner. Rinse and dry thoroughly.

10.3 Annexure III: 5 Moments for Hand Hygiene

Your 5 Moments for Hand Hygiene



1	BEFORE TOUCHING A PATIENT	WHEN?	Clean your hands before touching a patient when approaching him/her.
		WHY?	To protect the patient against harmful germs carried on your hands.
2	BEFORE CLEAN/ ASEPTIC PROCEDURE	WHEN?	Clean your hands immediately before performing a clean/aseptic procedure.
		WHY?	To protect the patient against harmful germs, including the patient's own, from entering his/her body.
3	AFTER BODY FLUID EXPOSURE RISK	WHEN?	Clean your hands immediately after an exposure risk to body fluids (and after glove removal).
		WHY?	To protect yourself and the health-care environment from harmful patient germs.
4	AFTER TOUCHING A PATIENT	WHEN?	Clean your hands after touching a patient and her/his immediate surroundings, when leaving the patient's side.
		WHY?	To protect yourself and the health-care environment from harmful patient germs.
5	AFTER TOUCHING PATIENT SURROUNDINGS	WHEN?	Clean your hands after touching any object or furniture in the patient's immediate surroundings, when leaving – even if the patient has not been touched.
		WHY?	To protect yourself and the health-care environment from harmful patient germs.

World Health Organization | Patient Safety — A World Alliance for Safer Health Care | SAVE LIVES Clean Your Hands

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