SRH Newsletter

Pharmaco-Therapeutics Committee

Issue -12 **September -2025**

ECO PHARMACOVIGILANCE

- DR.K.KARTHIKA

We do not inherit the earth from our ancestors; we borrow it from our children.

- African proverb

Ecopharmacovigilance can be defined as science and activities concerning detection, assessment, understanding, and prevention of adverse effects due to the presence of pharmaceuticals in the environment. Many pharmaceuticals are resistant to degradation, surviving in acidic stomach environments or persisting for extended periods. Even the excipients used in the formulations may pose a threat to the environment.

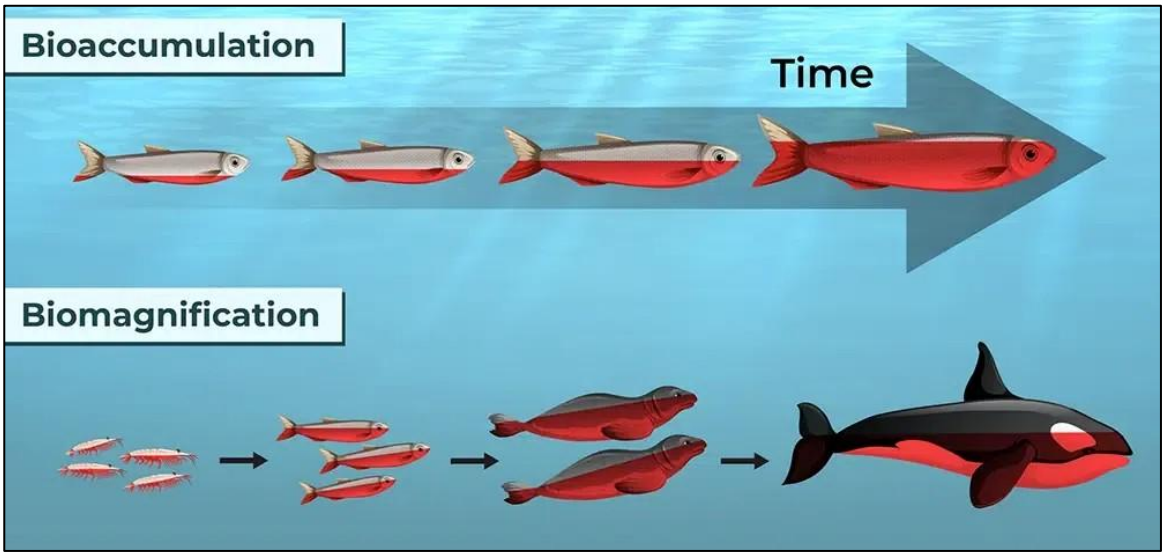
DDT, an insecticide commonly used during the 1940s and 1950s, led to the near extinction of bald eagles in USA. It accumulated in the fatty tissues and gonads, leading to infertility and interferes with the bird's ability to absorb calcium, leading to thinning of eggshells. It was banned in USA in 1972.

SOURCES OF ENTRY OF PHARMACEUTICALS INTO THE ENVIRONMENT:

- Drugs consumed by humans and animals are excreted after metabolism.
- Inadequate treatment of sewage and its release into environment by pharmaceutical industries
- Flushing unused or expired medications down the toilet
- Medications placed in the trash can leach into the environment from landfills (even from lined facilities)
- Runoff from farms
- Improper waste disposal of clinics and hospitals
- Direct release of pharmaceuticals from fish farms
- Conventional Wastewater Treatment Plants are not designed to fully remove pharmaceutical compounds.

CONSEQUENCES FOR ECOSYSTEMS & BIODIVERSITY:

- Chronic low-level exposure to pharmaceuticals can interfere with hormone signaling in aquatic organisms, causing abnormalities in growth, development, and reproduction, and leading to population declines.
- Drugs like Oxazepam can affect fish behavior, influencing feeding and other critical functions.
- Drugs lead to disruption of microbial ecosystems, cytotoxicity, mutagenicity and teratogenicity.
- Some pharmaceutical by-products can deplete oxygen in aquatic environments.
- Pharmaceuticals are bioactive and chemically stable, leading to bioaccumulation and biomagnification as they become more concentrated at higher trophic levels.

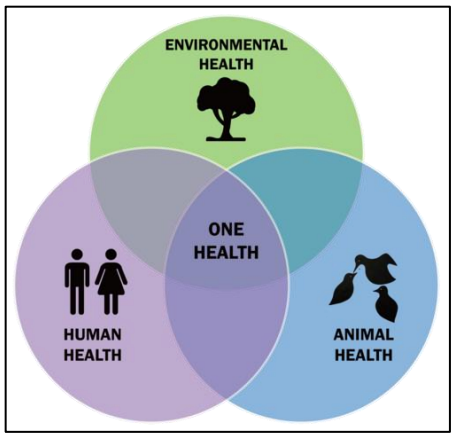


BIOACCUMULATION	BIOMAGNIFICATION
Bioaccumulation refers to the accumulation of substances within an organism's body over its lifetime, regardless of its position in the food chain.	Biomagnification refers to the concentration increase of harmful substances as they move up the food chain, affecting organisms at higher levels.

HUMAN HEALTH CONCERNS:

- Many pharmaceutical compounds are not fully removed by standard wastewater treatment, leading to contaminated drinking water.

- Antibiotics can reduce the effectiveness of beneficial sewage bacteria and contribute to the proliferation of superbugs.
- Some antibiotics, like Quinolones, can interfere with crucial glutamatergic and GABAergic systems.
- Some pharmaceuticals could decrease fertility and cause breast and testosterone cancers.
- Special populations like pregnant women, children, geriatric population, renal or hepatic failure patients have a greater risk - the pharmacokinetics gets altered and even minor doses may prove to be toxic



THE ONE HEALTH CONCEPT:

It is a collaborative approach recognizing that human, animal, and environmental health are interconnected and interdependent. By uniting different sectors and disciplines, it aims to foster well-being and tackle health challenges, such as pandemics, zoonotic diseases, antimicrobial resistance, and climate change.

REMEDIAL MEASURES:

1. During drug development, Environmental Risk Assessment should be mandatory.
2. Regular environmental monitoring of contamination
3. Implement regulations and guidelines to control the release of pharmaceuticals into the environment - setting limits for permissible concentrations of drugs in industrial and household wastewater.
4. Raise awareness among healthcare professionals and the public about the proper use, disposal, and environmental impact of pharmaceuticals.
5. Enact laws to ensure that all the clinics and hospitals should obtain an authorization from the Pollution Control Board and submit an annual report regarding their waste management.
6. Implement drug take-back programs for redistribution and proper disposal of unused, unexpired medicines.

7. Safely destroy pharmaceutical waste through high-temperature incineration to break down complex pollutants.
8. Implement policies like the "Polluter Pays Principle" and Extended Producer Responsibility, making the pharmaceutical producers responsible for managing and treating waste.
9. Invest in research to develop advanced wastewater treatment technologies and greener pharmaceuticals
10. International cooperation is crucial, as pharmaceutical pollution is a global issue that transcends national borders.

The Namami Gange program was started in 2014 to clean the Ganga River, the biggest river of India. It has shown positive outcomes, including a reduction in river pollution, increased sewage treatment capacity, improved river water quality, a rise in Gangetic River dolphin populations (an indicator species) and the restoration of ghats and crematoria. These achievements led to the program being recognized as one of the Top 10 World Restoration Flagship Initiatives by the UN Decade on Ecosystem Restoration.

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MEROPENEM AND COLISTIN: LIGHTS AND SHADOWS OF OLDER ANTIBIOTICS

- SR.Y.J.SALOMY SUHIRTHARANI, DR.K.KARTHIKA

This article delves into the latest research done on Meropenem and Colistin, older antibiotics still used in our hospitals and how they can be relevant even today.

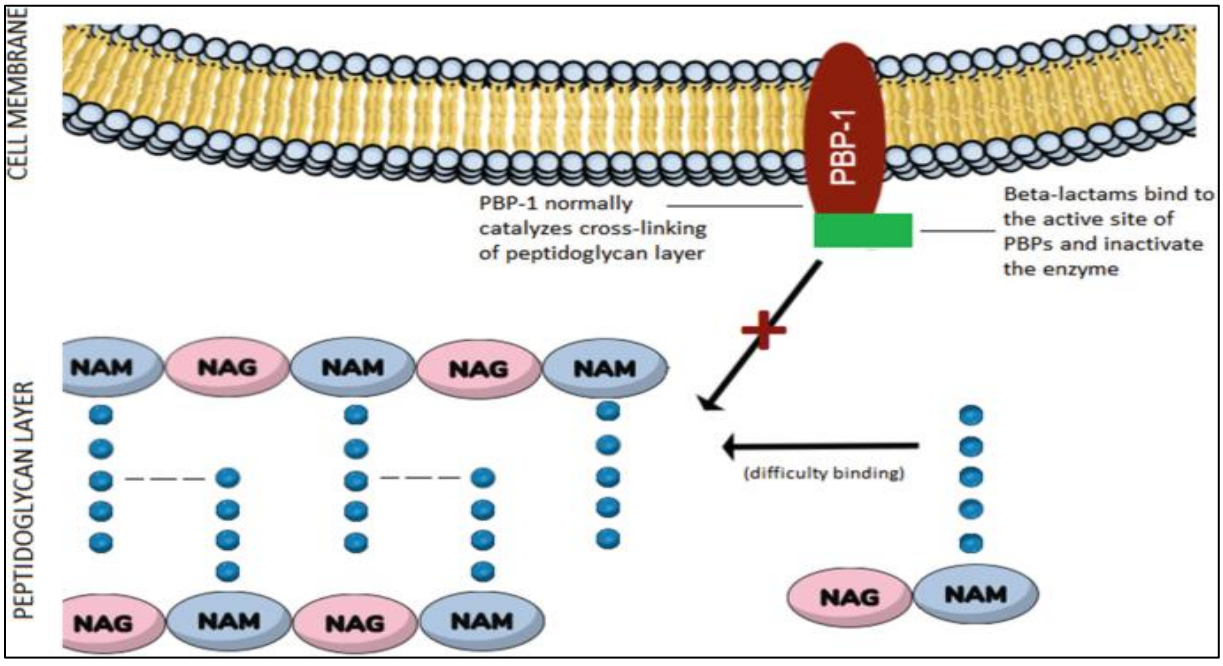
MEROPENEM

CLASS: Carbapenem β-lactam antibiotic.

SPECTRUM: Broad spectrum (effective against Gram-positive, Gram-negative)

MECHANISM:

Meropenem exerts its bactericidal action by binding to penicillin-binding proteins (PBPs) in the bacterial cell wall and inhibiting peptidoglycan cross- linking associated with cell wall synthesis, which ultimately leads to cell death.



CLINICAL USES:

- Ω Severe bacterial infections

- Ω Intra-abdominal infections
- Ω Meningitis (especially pediatric)
- Ω Complicated skin & soft tissue infections
- Ω Hospital-acquired pneumonia
- Ω Septicemia
- Ω Used when multidrug resistance is suspected.

ADVERSE REACTIONS:

- ❖ **Skin**:
  Rash, pruritus (itching), urticaria (red spots on arms/trunk)
- ❖ **Gastrointestinal** (**GI**):
  Diarrhea, nausea, abdominal pain → highlighted around stomach area.
- ❖ **Neurological**:
  Headache, dizziness, seizures (rare) → highlighted around brain/head.
- ❖ **Local Reactions**:
  Pain, redness, swelling at injection site → shown as inflamed area near arm vein.
- ❖ **Allergic/Severe**:
  Anaphylaxis (rare but serious) → could be represented as airway/lung involvement.

RESEARCH AREAS:

1. Antimicrobial Resistance (AMR):
Increasing resistance due to carbapenemase-producing organisms (KPC, NDM, VIM, OXA-type).
Studies on molecular epidemiology of resistant strains.

2. Combination Therapy:
Meropenem + Colistin / Tigecycline / Fosfomycin studied for multidrug-resistant Klebsiella pneumoniae and Pseudomonas aeruginosa.
Meropenem-Vaborbactam (a new β-lactam/β-lactamase inhibitor) is a major area of current research.

3. Pharmacokinetics/Pharmacodynamics (PK/PD):
Extended/prolonged infusion of Meropenem shows better efficacy against resistant strains.
Research into dosing in neonates, critically ill, and renal impairment patients.

4. Neurotoxicity & Safety:
Studies suggest Meropenem is safer than Imipenem (less risk of seizures).

5. Recent Advances
Meropenem-Vaborbactam & Meropenem-Nacubactam are new combinations showing promise against carbapenem-resistant Enterobacteriaceae (CRE).

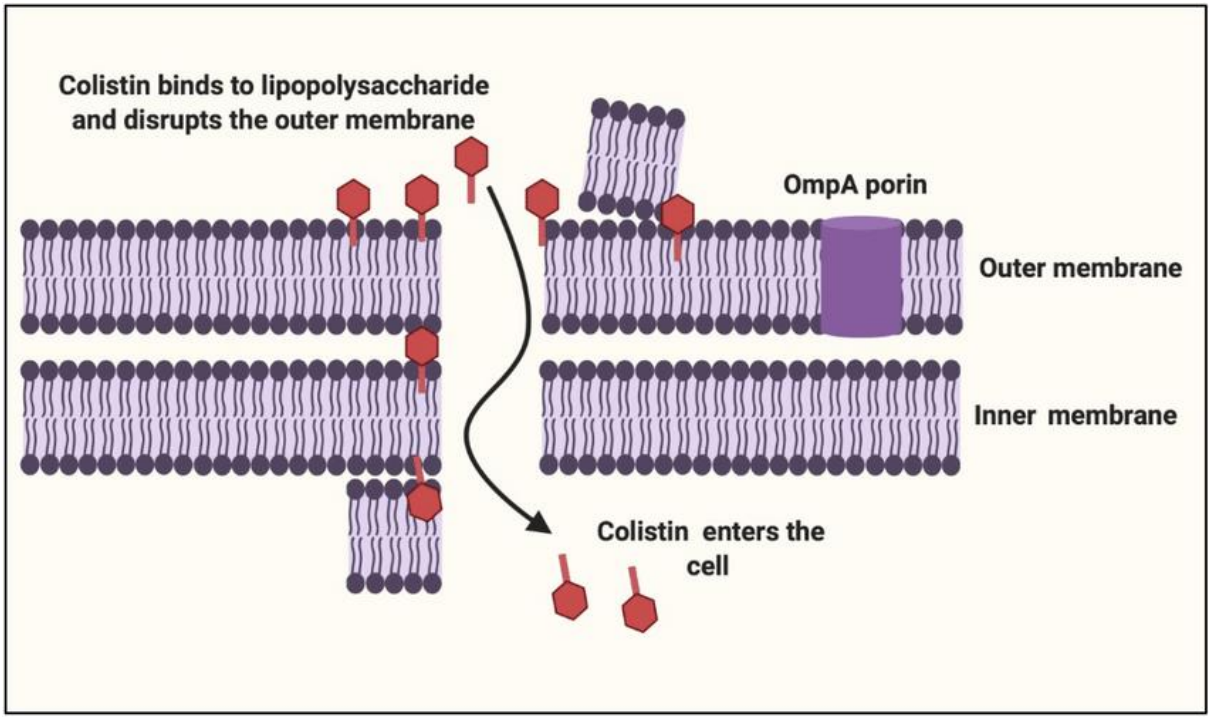
In vitro synergy studies with Polymyxins and Aminoglycosides show improved bacterial killing.
Novel dosing regimens (continuous infusion, high-dose therapy) explored in ICUs.

6. Key Challenges
Rapid spread of Carbapenem-resistant Enterobacteriaceae (CRE).
Limited new β-lactams in pipeline.
Need for rapid diagnostic tests to guide Meropenem use.

COLISTIN

(COLISTIMETHATE SODIUM, POLYMYXIN E)

CLASS: Polymyxin antibiotic.
FORM: Injection is given as Colistimethate sodium (CMS), which is converted in the body to active Colistin.
SPECTRUM: Active mainly against multidrug-resistant Gram-negative bacteria such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae.
MECHANISM: Disrupts bacterial cell membrane (acts like a detergent), leading to cell death.



CLINICAL USES:

- Severe hospital-acquired infections due to multidrug-resistant Gram-negative bacilli
- Ventilator-associated pneumonia

- Bacteremia / septicemia
- Urinary tract infections (complicated)
- Intra-abdominal infections
- Often used as a last-line / salvage therapy

ADVERSE REACTIONS:

- Nephrotoxicity (most important): Acute kidney injury is common.
- Neurotoxicity: Dizziness, paresthesia, muscle weakness, confusion, seizures (rare).
- Local reactions: Pain, inflammation at injection site.
  Allergic reactions, bronchospasm (if inhaled form).

RESEARCH AREAS:

1. Colistin Resistance:

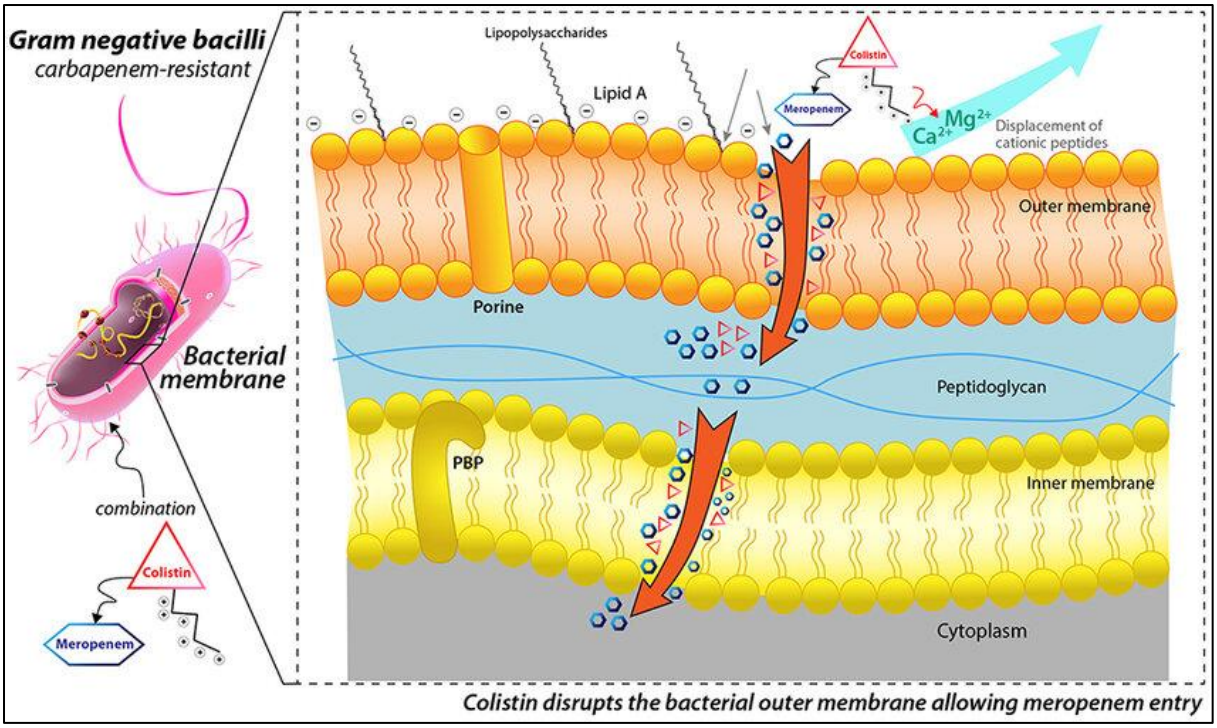
Resistance is rising due to mcr genes (plasmid-mediated), making infections harder to treat.

Research focuses on molecular mechanisms and global spread of mcr-1 to mcr-10 genes

2. Combination Therapy:

Colistin + Meropenem, Tigecycline, Fosfomycin, Rifampicin studied for synergy against resistant Klebsiella and Pseudomonas.

Colistin + Carbapenems has shown variable outcomes.



Eg: Colistin + Meropenem combination:

The cationic Colistin binds to anionic lipopolysaccharide molecules by displacing Calcium and Magnesium from the outer membrane of Gram-negative bacilli, resulting in increased permeability of the bacteria's membrane. This allows Meropenem to more effectively reach its target, the PBPs, leading to a more potent inhibition of cell wall synthesis and ultimately bacterial cell death. The combination can lead to a significant decrease in the minimum inhibitory concentration (MIC) of Colistin. It may also help to prevent the development of resistance and reduce the need for higher, potentially more toxic, doses of Colistin.

3. Pharmacokinetics / Pharmacodynamics (PK/PD):
Complex drug: given as inactive CMS → hydrolyzed to colistin in vivo.
Research on optimal dosing (especially in critically ill, neonates, renal impairment).
Prolonged infusion regimens tested for improved efficacy.

4. Novel Delivery Methods:
Inhaled colistin for ventilator-associated pneumonia.
Liposomal formulations under research to reduce toxicity.

5. Key Challenges
Narrow therapeutic window (efficacy vs toxicity).
Rapid development of resistance during monotherapy.
Limited alternatives for extensively drug-resistant (XDR) Gram-negative infections.

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POTASSIUM CHLORIDE INJECTION (KCL)

-DR.A.VIGNESH, DR.K.KARTHIKA

CLASS: Electrolyte replenisher & High-alert medication

MECHANISM OF ACTION: Potassium chloride is used to prevent or treat low levels of potassium (hypokalemia) in the body. Potassium chloride is in a class of medications called electrolytes. It works by to provide potassium to the body to maintain fluid and electrolyte balance.

INDICATIONS:

- Treatment of severe hypokalemia (serum potassium level ≤ 2.5 mmol/litre, marked muscular weakness or rhabdomyolysis)
- Prevention of hypokalaemia in patients on:

  - Diuretics, Digoxin, Total parenteral nutrition (TPN), Prolonged vomiting or diarrhoea

- Treatment of arrhythmias due to low potassium
- Correcting potassium loss from metabolic alkalosis or ketoacidosis

SERUM POTASSIUM (K^+) LEVELS AND CLINICAL SIGNIFICANCE:

- Normal range: 3.5 – 5.0 mEq/L - Physiologically normal
- Mild Hypokalemia: 3.0 – 3.4 mEq/L – Often asymptomatic
- Moderate Hypokalemia: 2.5 – 2.9 mEq/L - Muscle weakness, fatigue
- Severe Hypokalemia: < 2.5 mEq/L - Risk of arrhythmias, paralysis

FORMS AND STRENGTHS, ROUTE OF ADMINISTRATION:

- Ampoule containing 10% potassium chloride hypertonic solution (100 mg/ml, 10 ml), i.e. 1 g of potassium chloride (KCl) per 10 ml ampoule
- Ionic composition:
    - potassium (K^+): 13.4 mmol per 10 ml ampoule (*13.4 mEq*)
    - chloride (Cl^-): 13.4 mmol per 10 ml ampoule (*13.4 mEq*)
- CHECK CONCENTRATION BEFORE USE: potassium chloride also comes in ampoules containing 7.5%, 11.2%, 15% and 20% solutions.
- NEVER USE BY IV OR IM OR SC INJECTION. Potassium chloride must always be administered by slow IV infusion, diluted in 0.9% sodium chloride.
- For dilution:
    - The potassium concentration in the infusion fluid should not exceed 40 mmol/litre.
    - Mix thoroughly the potassium and the 0.9% sodium chloride solution by inverting at least 5 times the infusion bottle or bag.

DOSAGE REGIMEN (Adult):

1. Peripheral IV Line

- Max concentration: 40 mEq/L

- Max infusion rate: 10 mEq/hour

- Not to exceed 200 mEq dose/24hr

2. Central IV Line (with ECG monitoring)

For serum potassium less than 2 mEq/L and electrocardiographic changes and/or muscle paralysis

- Max concentration: 80 mEq/L

- Max rate: 40 mEq/hour (only in ICU/monitored settings)

- In presence of continuous ECG monitoring and frequent lab monitoring;

- Patients may require up to 400 mEq/24hr

3. Daily Maximum Dose

- Standard: 100–200 mEq/day

- **NEVER GIVE INJECTABLE POTASSIUM CHLORIDE UNDILUTED**
- **CHECK CONCENTRATION BEFORE USE: POTASSIUM CHLORIDE COMES IN AMPOULES CONTAINING 7.5%, 10%, 11.2%, 15% AND 20% SOLUTIONS.**

DOSING MODIFICATIONS:

HEPATIC IMPAIRMENT:

- Patients with cirrhosis should usually be started at low end of dosing range, and serum potassium level should be monitored frequently

RENAL IMPAIRMENT:

- Patients with impaired renal function, particularly if patient is on RAAS inhibitors or nonsteroidal anti-inflammatory drugs, should usually be started at low end of dosing range because of potential for development of hyperkalemia; serum potassium level should be monitored frequently; renal function should be assessed periodically.
- Use of the dextrose containing injection may cause hyperkalemia, hyponatremia, and/or fluid overload in renally impaired patients; monitor for these reactions.

CAUTION:

May cause:

- in the event of rapid or excessive administration: hyperkalaemia, cardiac conduction and rhythm disorders, potentially fatal.
- in the event of extravasation: necrosis.

DOSAGE REGIMEN (PAEDIATRIC):

1. General IV Replacement (Maintenance or Mild Hypokalemia):

- Dosage: 1–2 mEq/kg/day (usually in maintenance IV fluids)

- Route: IV infusion (always diluted)

2. Moderate to Severe Hypokalemia:

- Dose: 0.3–0.5 mEq/kg/dose, repeated as needed

- Max single dose: 1 mEq/kg/dose

- Max rate (Peripheral IV): 0.5 mEq/kg/hr

- Max rate (Central IV): 1 mEq/kg/hr (with continuous ECG monitoring)

- Maximum daily dose: Typically, 3 mEq/kg/day

CONTRAINDICATIONS:

- Hyperkalaemia
- Hyperadrenalism associated with adrenogenital syndrome.
- Tissue breakdown.
- Acute dehydration
- Renal impairment with oliguria and azotaemia.
- Untreated Addison's disease.
- Ventricular fibrillation.
- Atrioventricular or intraventricular heart block.
- Conditions with increased sensitivity to potassium: Adynamia episodica hereditaria, congenital paramyotonia

MONITORING:

- Serum potassium (before and during therapy)

- Renal function (Urine Output, creatinine)

- ECG monitoring (especially for IV administration)

COMPATIBLE IV FLUIDS WITH KCL:

Sodium chloride 0.9%, sodium chloride 0.45%, Hartmann's, pre-mixed amino-acid formulations, Dextrose 5% in Water (D5W), Dextrose Saline (D5NS)

Ringer's Lactate (with caution) - Compatible (with lower doses; watch for calcium interaction)

Sterile Water for Injection (SWFI) - only for dilution, not for infusion directly

❌ INCOMPATIBLE OR CAUTION REQUIRED:

- Calcium-containing fluids (e.g., Calcium Gluconate)

- ❖ Sodium Bicarbonate
- ❖ Phosphate-containing fluids

INJECTABLE FORMS (IV USE ONLY):

Ampoules – 2 mEq/mL: 20 mEq/10 mL =150mg/ml: 1.5gm/10ml = 2mmol/ml: 20mmol/10ml – Must be diluted before use

Premixed IV Bags – 20, 30, 40, 60 mEq in 500–1000 mL NS/D5W – Ready-to-use infusion

ORAL FORMS:

Tablets (ER) – 600 mg (8 mEq), 750 mg (10 mEq)

Capsules (ER) – 8 mEq, 10 mEq

Oral Solution – 10%, 20% (1 mEq/mL or 2 mEq/mL) – Potassium chloride syrup

Oral Powder for Solution – 20 mEq/sachet – Dissolved in water/juice

SAFE HANDLING PROTOCOLS:

1. Dilute before administration

2. Use infusion pump

3. Administer via central line if needed

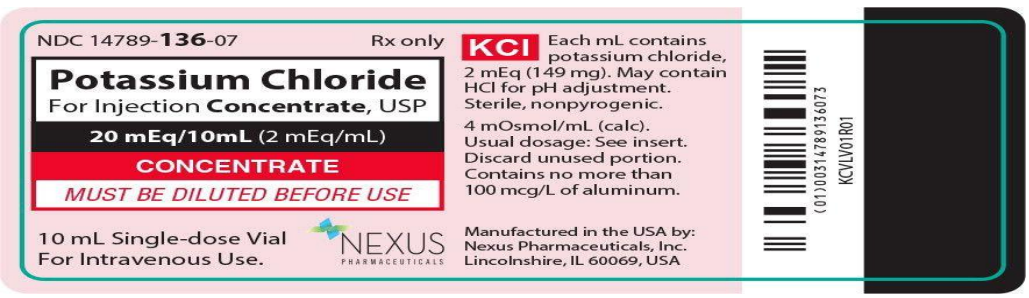
4. Label clearly (e.g., "High Alert: Dilute Before Use")

5. Double-check dose & rate

6. Monitor ECG, electrolytes, and renal function

STORAGE:

Store at 20 to 25°C (68 to 77°F).



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