

Polymyxins

Cationic detergent antibiotics that tear open the gram-negative outer membrane - last-line therapy for multidrug-resistant organisms, limited by nephrotoxicity and neurotoxicity.

Online guide: <https://www.medguideglobal.com/pharmacology/antibiotics/polymyxins>

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Quick revision

One Liner: Polymyxins are positively charged detergents that bind the negatively charged lipid A of gram-negative LPS, displace calcium and magnesium and blow a hole in the outer membrane - bactericidal, gram-negative only, and reserved as a last line because of nephrotoxicity and neurotoxicity.

1. Mechanism: the positively charged polymyxin binds the phosphate groups of negatively charged lipid A, displacing divalent calcium and magnesium and disrupting the outer membrane. [1]
2. Bactericidal, and because the target is the outer membrane the class is active against gram-negative organisms only. [1]
3. Two agents are used clinically: polymyxin B and polymyxin E, which is colistin. [1]
4. Colistin is given parenterally as the inactive prodrug colistimethate sodium; polymyxin B is given in its active form. [1][3]
5. Last line of treatment for infections resistant to other antibiotics, especially carbapenem-resistant Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. [1]
6. Nephrotoxicity has the highest incidence of the adverse effects and is the dose-limiting problem. [1]
7. Neurotoxicity occurs in around 7% of patients; paresthesia is the most common manifestation, and neuromuscular blockade can cause respiratory failure. [1]
8. *Proteus*, *Serratia*, *Morganella*, *Providencia* and *Burkholderia* are intrinsically resistant. [2]
9. mcr-1 is a plasmid-borne, horizontally transferable colistin resistance gene first reported in *E. coli* from pigs and meat in China in November 2015 - a global concern because it moves between species. [2][3]

Overview

1. Polymyxins are cationic polypeptide antibiotics of which two members are used in clinical practice: polymyxin B and polymyxin E, better known as colistin. They are approved for serious infections caused by multidrug-resistant gram-negative bacteria, particularly Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and are often the only effective agent left against carbapenem-resistant Enterobacteriaceae. [1]
2. The mechanism is physical rather than biochemical. The positively charged drug is drawn to the phosphate groups of the negatively charged lipid A of lipopolysaccharide, displaces the calcium and magnesium that stabilise the outer membrane, and increases permeability until the cell leaks and dies. Because that target exists only in the gram-negative outer membrane, the class has no gram-positive activity. The same binding also neutralises free lipopolysaccharide released when bacteria die. [1]
3. Colistin was approved by the FDA in 1959 and then largely abandoned because of its nephrotoxicity; it returned to practice only because resistance closed off the safer alternatives. Nephrotoxicity still has the highest incidence of its adverse effects, and neurotoxicity affects around 7% of patients, ranging from paresthesia to neuromuscular blockade with respiratory failure. Prescribing a polymyxin is a decision made when the alternatives have run out. [1][3]
4. Resistance has followed the revival. The plasmid-borne mcr-1 gene, first reported in *Escherichia coli* from pigs and meat in China in November 2015, transfers horizontally between gram-negative species and has since been found worldwide alongside further variants. Because polymyxins sit at the end of the treatment line, their loss has no obvious successor. [2][3]

Classification and drug examples

Intro: A small class. The clinically meaningful split is between the two systemic agents - which differ in whether the drug arrives active or as a prodrug - and the topical and inhaled preparations used for local effect.

1. Name: Systemic agent given in active form

1. Note: Preferred for intravenous use because it delivers faster and more reliable drug levels with lower nephrotoxicity than the colistin prodrug.

Name: Polymyxin B

Polymyxin B sulfate

Route: IV

Note: Administered parenterally in its active form; also used intrathecally or intraventricularly in preservative-free formulations. [1] [1]

2. Name: Systemic agent given as a prodrug

2. Note: Colistimethate sodium is inactive until hydrolysed to colistin, which delays and complicates the achievement of active drug levels.

Name: Colistin

1. Polymyxin E

2. Colistimethate sodium (CMS)

Route: IV/inhaled

Note: Given parenterally as the inactive prodrug colistimethate sodium; hydrolysis releases active colistin. [1][3] [1][3]

3. Name: Topical and inhaled preparations

3. Note: Used where a local effect is wanted and systemic exposure - with its nephrotoxicity - is best avoided.

1. Name: Polymyxin B, topical

1. Route: Ophthalmic/otic/skin

1. Note: Used in otitis externa, bacterial conjunctivitis and minor skin infection, usually in combination preparations. [1]

2. Name: Colistimethate sodium, inhaled

1. Nebulised colistimethate

2. Colistimethate dry powder for inhalation

2. Route: Inhaled

2. Note: Used for chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis; a dry-powder inhaler formulation exists alongside nebulised delivery. [4][1] [1][4]

Mechanism of action

Summary: Positively charged polymyxin binds the phosphate groups of the negatively charged lipid A of gram-negative lipopolysaccharide, displaces stabilising calcium and magnesium, increases outer membrane permeability and kills the organism; it also binds free lipopolysaccharide released on cell death.

Target: Lipid A of lipopolysaccharide in the gram-negative outer membrane

Cidal Static: bactericidal

Kill Kinetics: concentration-dependent

1. Step: 1

1. Title: Electrostatic attraction to lipid A

1. Detail: The positively charged polymyxin molecule is drawn to the phosphate groups of the negatively charged lipid A component of lipopolysaccharide in the gram-negative outer membrane. [1]

2. Step: 2

2. Title: Divalent cations are displaced

2. Detail: Binding displaces the calcium and magnesium ions that bridge and stabilise adjacent lipopolysaccharide molecules. [1]

3. Step: 3

3. Title: The outer membrane becomes permeable

3. Detail: Loss of those stabilising cations disrupts the outer membrane and increases its permeability - the detergent-like action that defines the class. [1]

4. Step: 4

4. Title: Cell contents leak and the organism dies

4. Detail: Cellular contents escape through the disrupted membrane and the bacterium is killed. The effect is bactericidal and does not depend on bacterial growth or protein synthesis. [1]

5. Step: 5

5. Title: Released endotoxin is neutralised

5. Detail: Polymyxins also bind lipopolysaccharide released as a result of cellular death, neutralising its endotoxin effects. [1]

6. Step: 6

6. Title: Gram-positives are unaffected throughout

6. Detail: Every step depends on lipopolysaccharide in an outer membrane. Organisms without one present no target, which is why the spectrum is gram-negative only. [1]

Spectrum of activity

Intro: A narrow, strictly gram-negative spectrum whose value lies in what it retains against multidrug-resistant organisms rather than in its breadth.

Subclass Id: class-wide

1. Enterobacteriaceae, including carbapenem-resistant strains
2. *Pseudomonas aeruginosa*, including multidrug-resistant strains
3. *Acinetobacter baumannii*

4. *Klebsiella pneumoniae*

1. All gram-positive organisms - no outer membrane, no target
2. *Proteus mirabilis* and *Proteus vulgaris* (intrinsic resistance)
3. *Serratia marcescens* (intrinsic resistance)
4. *Morganella morganii* and *Providencia* species (intrinsic resistance)
5. *Burkholderia* species (intrinsic resistance) [1][2][3]

Major clinical uses

1. Drug: Polymyxins as a class

1. Organism: Carbapenem-resistant Enterobacteriaceae

1. Indication: Serious infection where the organism is resistant to other available antibiotics

1. Line: reserve

1. Note: Often the only effective agent remaining, which is the whole basis of the class's continued use. [1]

2. Drug: Polymyxins as a class

2. Organism: Multidrug-resistant *Pseudomonas aeruginosa*

2. Indication: Systemic infection caused by susceptible multidrug-resistant strains

2. Line: reserve

2. Note: Susceptibility must be confirmed; intrinsic resistance elsewhere in the gram-negatives makes empiric assumptions unsafe. [1]

3. Drug: Polymyxins as a class

3. Organism: *Acinetobacter baumannii*

3. Indication: Serious multidrug-resistant infection

3. Line: reserve

3. Note: One of the three organism groups named in the approved indications. [1]
4. Drug: Polymyxin B
4. Organism: Multidrug-resistant gram-negative bacteria
4. Indication: Intravenous therapy where a polymyxin is indicated
4. Line: reserve
4. Note: Preferred over colistimethate intravenously for faster, more reliable drug levels and lower nephrotoxicity. [1]
5. Drug: Colistimethate sodium, inhaled
5. Organism: Pseudomonas aeruginosa
5. Indication: Chronic Pseudomonas lung infection in cystic fibrosis
5. Line: targeted
5. Note: Delivered by nebuliser or dry-powder inhaler; dry-powder colistimethate was found non-inferior to nebulised tobramycin on lung function measures. [4]
6. Drug: Polymyxin B, topical
6. Organism: Susceptible gram-negative organisms
6. Indication: Otitis externa, bacterial conjunctivitis and minor skin infection
6. Line: adjunct
6. Note: Local application avoids the systemic toxicity that constrains the class. [1]

Pharmacokinetics

1. Drug: Polymyxin B
1. Route: IV
1. Absorption: Not absorbed orally; given parenterally in active form
1. Csf Penetration: Poor - intrathecal or intraventricular preservative-free administration is used when CNS therapy is needed
1. Metabolism: Not a significant hepatic substrate
1. Elimination: See prescribing reference
1. Half Life: See prescribing reference
1. Dose Adjust: Renal function monitoring required; therapeutic drug monitoring is used [1]
2. Drug: Colistin (as colistimethate sodium)
2. Route: IV
2. Absorption: Not absorbed orally; given parenterally as an inactive prodrug requiring hydrolysis to active colistin
2. Csf Penetration: Poor - intraventricular or intrathecal routes used for CNS infection
2. Metabolism: Colistimethate is hydrolysed to active colistin
2. Elimination: See prescribing reference
2. Half Life: See prescribing reference
2. Dose Adjust: Renal function monitoring required [1][3]
3. Drug: Colistimethate sodium, inhaled
3. Route: Inhaled
3. Absorption: Delivered directly to the airway; systemic exposure limited compared with intravenous use
3. Csf Penetration: Not applicable
3. Metabolism: Hydrolysis to active colistin
3. Elimination: Not clinically framed by this route
3. Half Life: Not clinically relevant by this route
3. Dose Adjust: See prescribing reference [4][1]
1. The prodrug distinction is the pharmacokinetic headline of this class. Polymyxin B arrives active; colistimethate sodium must hydrolyse first, and that conversion is why intravenous polymyxin B achieves faster and more reliable drug levels with lower nephrotoxicity. [1][3]

2. Therapeutic drug monitoring is used alongside renal function monitoring - BUN, creatinine and urine output - because nephrotoxicity has the highest incidence of the class's adverse effects. [1]
3. Aerosolised administration is given with bronchodilator pre-treatment because of the risk of bronchospasm, and only preservative-free formulations may be used intrathecally or intraventricularly. [1]
4. This page gives no dose regimens by design. Doses depend on indication, organism, renal function, formulation and the unit of measurement used for the particular preparation, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Nephrotoxicity
 1. Detail: The adverse effect with the highest incidence and the factor that historically limited clinical use of the class. Presents with haematuria, proteinuria, oliguria and, at its worst, acute renal failure. [1][3]
2. Effect: Paresthesia and other mild neurological symptoms
 2. Detail: Paresthesia is the most common neurotoxic manifestation; dizziness, numbness, tingling and vertigo also occur. Mild neurological symptoms typically resolve after the drug is stopped. [1]
3. Effect: Hypersensitivity reactions
 3. Detail: Rash, urticaria and fever. [1]
4. Effect: Skin hyperpigmentation
 4. Detail: A recognised effect of the class. [1]
1. Effect: Neuromuscular blockade with respiratory failure
 1. Detail: Part of the neurotoxicity spectrum, which affects around 7% of patients overall. Blockade can progress to respiratory failure and apnoea.
 1. Action: Stop the drug and support ventilation mechanically if apnoea develops. Cholinesterase inhibitors such as neostigmine are of no benefit for the resulting respiratory depression. [1]
2. Effect: Acute renal failure
 2. Detail: The severe end of the nephrotoxicity spectrum, which is why renal parameters are monitored throughout therapy.
 2. Action: Discontinue therapy if renal impairment develops and give supportive care with fluid and electrolyte monitoring. [1]
3. Effect: Bronchospasm
 3. Detail: Associated with aerosolised administration.
 3. Action: Bronchodilator pre-treatment before nebulised therapy, and monitor for signs of bronchospasm. [1]
4. Effect: Superinfection
 4. Detail: A recognised consequence of therapy, since the drug leaves gram-positive and intrinsically resistant gram-negative organisms untouched.
 4. Action: Surveillance for superinfection is part of routine monitoring. [1]
1. Drug: Colistin (colistimethate sodium), intravenous
 1. Effect: Higher nephrotoxicity than intravenous polymyxin B, which is one reason polymyxin B is preferred for the intravenous route. [1]
 2. Drug: Colistimethate sodium, inhaled
 2. Effect: Bronchospasm on aerosolisation, mitigated by bronchodilator pre-treatment. [1]

Contraindications, precautions and interactions

- Hypersensitivity to polymyxin B, colistimethate sodium, colistin or any component of the formulation. [1]
1. Existing renal impairment, given that nephrotoxicity is the adverse effect with the highest incidence and therapy is discontinued if renal impairment develops. [1]
 2. Myasthenia gravis and other disorders of neuromuscular transmission, because the class causes neuromuscular

blockade that can progress to respiratory failure - and because cholinesterase inhibitors do not reverse it. [1]

3. Airway disease when the inhaled route is used, because aerosolisation can provoke bronchospasm. [1]

4. Intrathecal or intraventricular administration requires preservative-free formulations only. [1]

1. With: Other nephrotoxic agents

1. Effect: Additive risk of renal injury on top of a drug whose principal toxicity is already nephrotoxicity. [1]

2. With: Neuromuscular blocking agents and other drugs impairing neuromuscular transmission

2. Effect: Compounded neuromuscular blockade, with the risk of respiratory failure. [1]

Resistance mechanisms

1. Mechanism: Intrinsic resistance through constitutive lipid A modification

1. Detail: Several gram-negative genera permanently modify their lipopolysaccharide with cationic substituents such as L-Ara4N and phosphoethanolamine, via the *arnBCADTEF* operon and *eptB* gene. This reduces the negative charge the cationic drug needs to bind, so these organisms are resistant before any exposure.

1. *Proteus mirabilis* and *Proteus vulgaris*

2. *Serratia marcescens*

3. *Morganella morganii*

4. *Providencia* species

5. *Burkholderia cepacia*

1. Countermeasure: Recognise the genus and choose a different class; do not treat these organisms empirically with a polymyxin. [2]

2. Mechanism: Chromosomal two-component system mutation

2. Detail: Mutations activating the *PmrAB* and *PhoPQ* regulatory systems switch on the same lipid A modifications in organisms that are normally susceptible. In *Klebsiella pneumoniae*, inactivation of the *mgrB* gene upregulates the *phoPQ* operon and produces resistance.

1. *Klebsiella pneumoniae* with *mgrB* inactivation

2. Enterobacteriaceae with *pmrAB* or *phoPQ* mutations

2. Countermeasure: Susceptibility testing on the individual isolate rather than assumption from species identity. [2]

3. Mechanism: Plasmid-mediated *mcr* genes

3. Detail: *mcr-1* was first reported in *Escherichia coli* isolated from pigs and meat in China in November 2015. Because it is plasmid-borne it transfers horizontally between gram-negative species and has since been identified across multiple continents, with variants now described through *mcr-10*; *mcr-1* accounts for the large majority of positive isolates globally.

1. *Escherichia coli*

2. Other Enterobacteriaceae acquiring *mcr*-carrying plasmids

3. Countermeasure: Surveillance, restriction of agricultural colistin use and stewardship of the remaining clinical supply. [2][3]

Stewardship Note: Polymyxins are what is left when carbapenems have failed, so resistance here has no obvious successor class. The pressure driving it is not mainly clinical: veterinary use in pig and poultry farming dominates global colistin consumption and sustains a livestock reservoir of *mcr*-carrying plasmids that can move into human pathogens.

Comparison tables

1. Title: Polymyxin B versus colistin

1. Caption: The two clinically used polymyxins differ chiefly in whether the administered drug is already active. Local susceptibility data and a prescribing reference govern actual therapy.

1. Key: feature

1. Label: Feature

1. Is Row Header: true
2. Key: polymyxin_b
2. Label: Polymyxin B
3. Key: colistin
3. Label: Colistin (polymyxin E)
1. Feature: Form administered parenterally
1. Polymyxin B: Active drug
1. Colistin: Inactive prodrug, colistimethate sodium [1][3]
2. Feature: Speed and reliability of drug levels
2. Polymyxin B: Faster and more reliable
2. Colistin: Delayed by the need for hydrolysis [1]
3. Feature: Nephrotoxicity by the IV route
3. Polymyxin B: Lower
3. Colistin: Higher [1]
4. Feature: Inhaled use
4. Polymyxin B: Not the usual inhaled agent
4. Colistin: Nebulised or dry-powder colistimethate in cystic fibrosis [4]
5. Feature: Preferred IV choice
5. Polymyxin B: Preferred
5. Colistin: Second choice intravenously [1]
2. Title: Three routes to colistin resistance
2. Caption: All three converge on the same endpoint - a less negatively charged lipid A that the cationic drug cannot bind.
1. Key: type
1. Label: Type
1. Is Row Header: true
2. Key: basis
2. Label: Genetic basis
3. Key: spread
3. Label: Can it spread between species?
4. Key: example
4. Label: Example
1. Type: Intrinsic
1. Basis: Constitutive arnBCADTEF / eptB lipid A modification
1. Spread: No - inherent to the genus
1. Example: Proteus, Serratia, Burkholderia [2]
2. Type: Acquired chromosomal
2. Basis: pmrAB, phoPQ, mgrB mutations
2. Spread: No - confined to the lineage
2. Example: Klebsiella pneumoniae with mgrB inactivation [2]
3. Type: Plasmid-mediated
3. Basis: mcr-1 and related mcr genes encoding phosphoethanolamine transferase
3. Spread: Yes - horizontal transfer, global spread
3. Example: Escherichia coli, first reported China 2015 [2][3]

High-yield exam pearls

1. Pearl: Polymyxins are detergents, not enzyme inhibitors.

1. Why: They work by electrostatic attraction between the cationic drug and the anionic phosphate groups of lipid A, displacing calcium and magnesium and physically increasing membrane permeability. Nothing about it depends on a bacterial enzyme, which is why resistance is about changing the membrane charge rather than destroying the drug. [1][2]
2. Pearl: Gram-positive organisms are untouchable by this class.
2. Why: The target is lipopolysaccharide in the gram-negative outer membrane. Gram-positives have no outer membrane and therefore no target at all. [1]
3. Pearl: Colistin is a prodrug when given systemically; polymyxin B is not.
3. Why: Colistimethate sodium is an inactive precursor that must hydrolyse to active colistin, which is why polymyxin B is preferred intravenously for faster and more reliable drug levels and lower nephrotoxicity. [1][3]
4. Pearl: Polymyxins also bind free LPS released by dying bacteria.
4. Why: This neutralises endotoxin as well as killing the organism - a mechanistic feature unique to this class among antibacterials. [1]
5. Pearl: Some gram-negatives are resistant before they ever meet the drug.
5. Why: *Proteus mirabilis*, *Serratia marcescens*, *Morganella morganii*, *Providencia* species and *Burkholderia cepacia* modify lipid A with L-Ara4N and phosphoethanolamine, reducing the negative charge the drug needs to bind. This is intrinsic resistance, not acquired. [2]
6. Pearl: mcr-1 changed the resistance picture because it sits on a plasmid.
6. Why: Chromosomal colistin resistance stays in one lineage; a plasmid gene can be transferred horizontally between gram-negative species and has been found on multiple continents. [2][3]
7. Pearl: Neostigmine does not reverse polymyxin neuromuscular blockade.
7. Why: Cholinesterase inhibitors provide no benefit for the resulting respiratory depression; management is mechanical ventilation if apnoea develops. This distinguishes it from blockade by competitive neuromuscular blocking drugs. [1]

Common exam traps

1. Trap: "Polymyxins are broad-spectrum because they are last-line agents."
1. Correction: Last-line and broad-spectrum are different things. Polymyxins act on the gram-negative outer membrane and have no gram-positive activity at all; they are reserved because few other options remain against MDR gram-negatives. [1]
2. Trap: "Colistin and colistimethate are the same drug."
2. Correction: Colistimethate sodium is an inactive prodrug that hydrolyses to active colistin. The distinction matters clinically: it is why IV polymyxin B reaches reliable levels faster than IV colistin. [1][3]
3. Trap: "A gram-negative isolate should respond to colistin."
3. Correction: Not if it is *Proteus*, *Serratia*, *Morganella*, *Providencia* or *Burkholderia* - these are intrinsically resistant through constitutive lipid A modification. [2]
4. Trap: "Polymyxin nephrotoxicity means the drug can never be restarted."
4. Correction: Nephrotoxicity is the dose-limiting toxicity and therapy is discontinued if renal impairment develops, but the injury is a tubular one that commonly recovers after withdrawal with supportive fluid and electrolyte care. It is a monitoring problem, not an automatic permanent contraindication. [1]
5. Trap: "Colistin resistance is a hospital problem only."
5. Correction: Veterinary use in pig and poultry farming dominates global colistin consumption and creates the selective pressure behind the mcr reservoir. The resistance story is an agricultural one as much as a clinical one. [3]

Self-test questions

1. Question: Which sequence correctly describes how a polymyxin kills a gram-negative bacterium?
1. It inhibits lipopolysaccharide synthesis, so the outer membrane cannot be assembled

2. It is transported into the cytoplasm and inhibits ribosomal protein synthesis
3. The cationic drug binds the phosphate groups of anionic lipid A, displaces stabilising calcium and magnesium, and makes the outer membrane permeable
4. It cross-links peptidoglycan strands, leaving a rigid wall the cell cannot expand
1. Explanation: The action is physical rather than enzymatic. Electrostatic attraction pulls the positively charged molecule onto the negatively charged lipid A of lipopolysaccharide, and the divalent cations that bridge adjacent lipopolysaccharide molecules are pushed aside. The outer membrane then leaks its contents and the organism dies, a detergent-like effect that needs neither bacterial growth nor protein synthesis to work. [1]
2. Question: Why does the polymyxin class have no useful activity against gram-positive organisms?
1. Gram-positive bacteria have no outer membrane and therefore no lipopolysaccharide target
2. The thick peptidoglycan layer of gram-positives destroys the drug enzymatically
3. Gram-positive organisms pump the drug out through constitutive efflux systems
4. Gram-positive ribosomes differ too much for the drug to bind them
2. Explanation: Every step of the mechanism depends on lipid A sitting in an outer membrane. Organisms built without that membrane simply present nothing for a cationic detergent antibiotic to attack, so the gap is absolute rather than a matter of degree. Being reserved as a last-line agent says nothing about breadth of spectrum, and confusing the two is a common examination error. [1]
3. Question: Which statement about the two systemically used polymyxins is correct?
1. Both are administered as inactive prodrugs requiring hydrolysis
2. Colistin is given intravenously in active form, whereas polymyxin B is the prodrug
3. Colistimethate sodium is a different drug from colistin, with a different molecular target
4. Polymyxin B is given in active form, while colistin is administered parenterally as the inactive prodrug colistimethate sodium
3. Explanation: Colistimethate sodium has to hydrolyse in the body before any active colistin exists, and that conversion delays and blurs the achievement of useful drug concentrations. Polymyxin B needs no such conversion, which is why it is favoured for intravenous therapy: levels arrive sooner and more predictably, and nephrotoxicity by that route is lower. [1][3]
4. Question: Which adverse effect has the highest incidence with polymyxins and constrains their use most?
1. Skin hyperpigmentation
2. Nephrotoxicity
3. Bronchospasm
4. Hypersensitivity rash and urticaria
4. Explanation: Renal toxicity is the most frequent adverse effect of the class and the reason colistin was largely abandoned after its introduction, returning to practice only when resistance closed off gentler alternatives. It can present with blood or protein in the urine, reduced urine output and, at worst, renal failure, so urea, creatinine and urine output are followed throughout treatment. Therapy is stopped if renal impairment appears, though the tubular injury commonly recovers afterwards with supportive fluid and electrolyte care. [1][3]
5. Question: A patient on a polymyxin develops neuromuscular blockade progressing towards respiratory failure. Which statement is correct?
1. Neostigmine reliably reverses the blockade, as it does for competitive neuromuscular blocking drugs
2. Neurotoxicity from this class is confined to paresthesia and never threatens ventilation
3. Cholinesterase inhibitors are of no benefit; the drug is stopped and ventilation supported mechanically if apnoea develops
4. The blockade indicates an allergic reaction and is managed with adrenaline
5. Explanation: Neurological toxicity affects roughly seven in every hundred treated patients, most often as paresthesia, with dizziness, numbness, tingling and vertigo also described; mild symptoms usually settle once the drug is withdrawn. At the severe end the blockade can shut down respiration, and an anticholinesterase does nothing to

reverse it - mechanical ventilation is what supports the patient if apnoea occurs. This behaviour is what distinguishes it from blockade produced by competitive neuromuscular blocking agents. [1]

6. Question: A blood culture grows a gram-negative organism. Which group should not be assumed susceptible to colistin, because it is resistant before any exposure?

1. *Klebsiella pneumoniae* and *Escherichia coli*
2. *Acinetobacter baumannii*
3. *Pseudomonas aeruginosa*
4. *Proteus*, *Serratia*, *Morganella*, *Providencia* and *Burkholderia*

6. Explanation: These genera constitutively decorate their lipid A with cationic substituents such as L-Ara4N and phosphoethanolamine, through the *arnBCADTEF* operon and the *eptB* gene. The resulting loss of negative charge leaves the cationic drug with nothing to bind, so resistance is built into the organism rather than acquired under pressure. Identifying the genus is therefore enough to rule the class out. [2]

7. Question: Why is *mcr-1* regarded as a more serious development than chromosomal colistin resistance?

1. It inactivates the drug enzymatically rather than altering the membrane target
2. It confers resistance to every antibiotic class simultaneously
3. It sits on a plasmid and so can move horizontally between gram-negative species
4. It arises only in organisms that are already carbapenem-resistant

7. Explanation: Mutations in regulatory systems such as *pmrAB*, *phoPQ* or *mgrB* stay locked inside the lineage that acquired them. A plasmid-carried gene travels laterally instead, and *mcr-1* has done so worldwide since it was first described in *Escherichia coli* from pigs and meat in China in November 2015, with further variants following.

Agricultural use in pig and poultry farming dominates global colistin consumption and sustains the reservoir, so this is an agricultural problem as much as a hospital one. [2][3]

Frequently asked questions

1. Question: Why do polymyxins only work against gram-negative bacteria?

1. Answer: Their target is lipid A, part of the lipopolysaccharide found in the gram-negative outer membrane.

Gram-positive organisms have no outer membrane and therefore nothing for the drug to bind, so the class is inactive against them entirely. [1]

2. Question: What is the difference between colistin and colistimethate sodium?

2. Answer: Colistimethate sodium is an inactive prodrug that must be hydrolysed in the body to release active colistin. Polymyxin B, by contrast, is given in its active form, which is why it is preferred intravenously for faster and more reliable drug levels and lower nephrotoxicity. [1][3]

3. Question: Why are polymyxins described as last-resort antibiotics?

3. Answer: Because they are often the only agent still effective against multidrug-resistant gram-negative organisms, particularly carbapenem-resistant Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Their nephrotoxicity had pushed them out of use until resistance removed the safer alternatives. [1][3]

4. Question: Which gram-negative organisms are naturally resistant to colistin?

4. Answer: *Proteus mirabilis* and *Proteus vulgaris*, *Serratia marcescens*, *Morganella morganii*, *Providencia* species and *Burkholderia* species. They constitutively modify lipid A with cationic sugars and phosphoethanolamine, reducing the negative charge the drug needs in order to bind. [2]

5. Question: Why is *mcr-1* such a concern?

5. Answer: Because it sits on a plasmid rather than the chromosome. First reported in *Escherichia coli* from pigs and meat in China in November 2015, it can transfer horizontally between gram-negative species and has since been found on multiple continents, with further variants described. Resistance that spreads laterally erodes a last-line class far faster than lineage-bound mutation does. [2][3]

6. Question: Can polymyxin-induced muscle weakness be reversed with neostigmine?

6. Answer: No. Cholinesterase inhibitors such as neostigmine provide no benefit for the respiratory depression caused

by polymyxin neuromuscular blockade. Management is to stop the drug and support ventilation mechanically if apnoea develops. [1]

7. Question: Why is colistin given by inhalation in cystic fibrosis?

7. Answer: Inhalation delivers the drug straight to the airway for chronic *Pseudomonas aeruginosa* lung infection, using nebulised or dry-powder colistimethate. Dry-powder colistimethate was found non-inferior to nebulised tobramycin on lung function measures. Bronchodilator pre-treatment is used because aerosolisation can cause bronchospasm. [4][1]

References

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