

When to use restricted items (Be AWaRe of stewardship)



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Make today matter



Wits UpTo Speed 2020

CONTENTS



Superbugs - are all of them equal?

Do you know YOUR unit's "superbug" profile?

BUGS – DRUGS – PATIENTS

Treatment options

NO culture = NO data = NO recommendation

"New" Reserve drugs to be AWaRe of

Two short cases

Superbugs in Paediatrics:

Superbugs in paediatrics are resistant bacteria, viruses, parasites, and fungi that can cause severe infection in infants and children. They are especially important in hospitalized children, including those in neonatal units, paediatric wards, and PICU, where limited treatment options may increase the risk of complications, prolonged admission, and death.



MODERN DAY SUPERBUGS

URGENT THREATS

- *Clostridioides difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

PRIORITY 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

SERIOUS THREATS

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida*
- Extended-spectrum Beta-lactamase producing *Enterobacteriaceae*
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

PRIORITY 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

CONCERNING THREATS

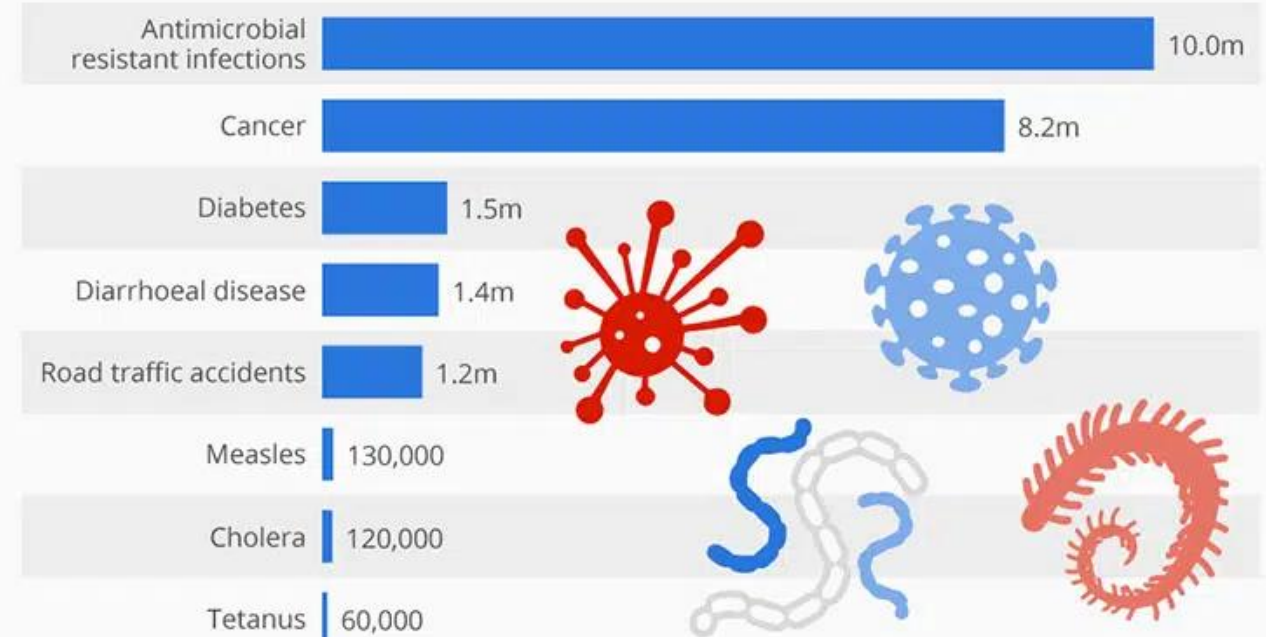
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-Resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

PRIORITY 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



@StatistaCharts

Source: Review on Antimicrobial Resistance

statista

The CDC (left column) and WHO (right column) have both published lists of the drug-resistant infections that pose the biggest threat to humanity.

Credit: Nanalyze

Incidence of Multidrug-Resistant Organism Among Children Admitted to Pediatric Intensive Care Unit in a Developing Country

Ahmed El-Nawawy,¹ Galal A. Ashraf,² Manal A.M. Antonios,¹
Marwa A. Meheissen,³ and Marwa M.R. El-Alfy¹

Aim: Multidrug-resistant infections are an increasingly common condition particularly in critical care units. This study aimed to determine the incidence and types of resistant bacteria acquired in a pediatric intensive care unit (PICU) of a university hospital.

Subject and Methods: A prospective study was conducted during the year 2016. All children aged below 16 years were studied for infection development and pattern of susceptibility to various groups of antibiotics.

Results: A total of 264 patients were admitted to the PICU: 16 patients had community-acquired infection (CAI), 23 had hospital-acquired infection, and 24 patients had PICU-acquired infection (with 36 episodes) which is equivalent to 14.75 case/1,000 patient days. The study revealed high incidence of resistant organisms in the PICU but more important is the appearance of multi- and extreme drug-resistant bacteria in CAI. The study revealed that gram-negative bacteria were more prevalent in PICU, especially *Klebsiella* (30.5%), *Acinetobacter baumannii* (22.22%), and *Pseudomonas* (16.67%). Infection with resistant organisms in the PICU caused initial treatment failure and increased fourfold risk of mortality.

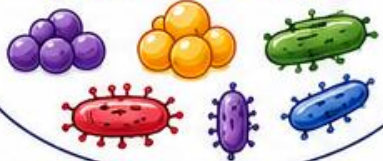
Conclusion: The incidence of resistant bacteria especially gram-negative pathogens was very high in the PICU. The top three resistant organisms of concern were *Klebsiella*, *Acinetobacter*, and *Pseudomonas*. This is a global concern that necessitates new strategies.

Keywords: antimicrobial, bacteria, microbial drug resistance, nosocomial infections, resistance

Developing countries/South Africa:

1. Unique mixture of infection types
 1. CAI including OI's (CLWH/TB)
 2. HAI including children with chronic needs (ex-preterm)
 3. PICU-acquired including medical & surgical paediatric patients (CLABSI / VAP)
2. TWO different population characteristics
 1. Private vs public health sector
 - Risk factors
 - Diagnostic capacity
 - Therapeutic availability
3. Antimicrobial choices should always be pediatric specific!
4. Paediatrician's focus should NOT BE on just treatment strategies, but prevention through breastfeeding, immunisation, nutrition, and ensuring maternal health is paramount.

ESKAPE



ESKAPE PATHOGENS

Six opportunistic pathogens that “**escape**” the effect of many antibiotics

MAJOR CAUSES OF HEALTHCARE-ASSOCIATED INFECTIONS IN THE PICU



E Enterococcus faecium

GRAM-POSITIVE COCCI



COMMON INFECTIONS

- Bloodstream infections
- Endocarditis
- Urinary tract infections

KEY RESISTANCE

- Vancomycin resistance (VRE)
- High-level aminoglycoside resistance

FIRST-LINE OPTIONS (if susceptible)

- Ampicillin
- Vancomycin

ALTERNATIVE / RESERVE

- Linezolid
- Daptomycin*

*Not for pneumonia

S Staphylococcus aureus (MRSA)

GRAM-POSITIVE COCCI



COMMON INFECTIONS

- Pneumonia
- Bloodstream infections
- Skin and soft tissue infections

KEY RESISTANCE

- mecA (PBP2a) → methicillin resistance
- Multi-drug resistance

FIRST-LINE OPTION (if susceptible)

- Vancomycin

ALTERNATIVE / RESERVE

- Linezolid
- Ceftaroline
- Clindamycin (if susceptible)

K Klebsiella pneumoniae

GRAM-NEGATIVE ROD



COMMON INFECTIONS

- Pneumonia (VAP)
- Bloodstream infections
- Urinary tract infections
- Intra-abdominal infections

KEY RESISTANCE

- ESBLs
- Carbapenemases (OXA-48, NDM, KPC)
- AmpC β-lactamases

FIRST-LINE OPTION (if susceptible)

- Meropenem (ESBL producers)

ALTERNATIVE / RESERVE

- Ceftazidime-avibactam (OXA-48, KPC)
- Aztreonam + CAZ-AVI (NDM)
- Cefiderocol (limited access)

A Acinetobacter baumannii

GRAM-NEGATIVE COCCOBACILLUS



COMMON INFECTIONS

- Ventilator-associated pneumonia
- Bloodstream infections
- Wound infections

KEY RESISTANCE

- Carbapenem resistance
- OXA-type carbapenemases
- Efflux pumps, porin loss

FIRST-LINE OPTION (if susceptible)

- Colistin (polymyxin E)

ALTERNATIVE / RESERVE

- Colistin + high-dose sulbactam
- Cefiderocol**

**Limited paediatric experience

P Pseudomonas aeruginosa

GRAM-NEGATIVE BACILLUS



COMMON INFECTIONS

- Ventilator-associated pneumonia
- Bloodstream infections
- Burn and wound infections

KEY RESISTANCE

- AmpC β-lactamase
- Efflux pumps
- Porin loss
- Metallo-β-lactamases (MBLs)

FIRST-LINE OPTIONS (if susceptible)

- Piperacillin-tazobactam
- Ceftazidime / Cefepime
- Meropenem

ALTERNATIVE / RESERVE

- Ceftolozane-tazobactam
- Ceftazidime-avibactam
- Cefiderocol (limited access)

E Enterobacter spp.

GRAM-NEGATIVE ROD



COMMON INFECTIONS

- Bloodstream infections
- Pneumonia
- Urinary tract infections
- Intra-abdominal infections

KEY RESISTANCE

- AmpC β-lactamases
- ESBLs
- Carbapenemases

FIRST-LINE OPTION (if susceptible)

- Cefepime (if AmpC low risk)
- Meropenem

ALTERNATIVE / RESERVE

- Ceftazidime-avibactam
- Cefiderocol (limited access)



From ESKAPE to ESCAPE, From KPC to CCC

Expanded opportunistic pathogens that 'escape' the effect of many antibiotics

MAJOR HEALTHCARE-ASSOCIATED AND OPPORTUNISTIC PATHOGENS IN THE PICU

Adapted from De Rosa FG et al. Clin Infect Dis 2015;60:1289–1290.



1 *Enterococcus faecium*

GRAM-POSITIVE COCCUS



- Common infections: BSIs, endocarditis, urinary tract infections
- Key resistance: Vancomycin resistance (VRE)
- Treatment options: Linezolid, daptomycin
- Important in PICU BSIs and device-associated infections

2 *Staphylococcus aureus* (MRSA)

GRAM-POSITIVE COCCUS



- Common infections: BSIs, pneumonia, skin/soft tissue infections, device infections
- Key resistance: Methicillin resistance (MRSA)
- Treatment options: Vancomycin, linezolid, daptomycin

3 *Clostridioides difficile*

GRAM-POSITIVE ANAEROBE



- Common infections: Antibiotic-associated diarrhea, colitis, toxic megacolon
- Key resistance: Fluoroquinolone resistance
- Treatment options: Oral vancomycin, fidaxomicin

7 *Candida* spp.

FUNGUS (YEAST)



- Common infections: Candidemia, intra-abdominal, urinary tract infections
- Key risk factors: Broad-spectrum antibiotics, central lines, TPN, ICU stay
- Treatment options: Echinocandins, fluconazole

4 *Acinetobacter baumannii*

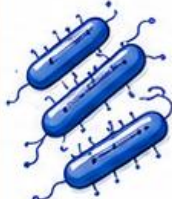
GRAM-NEGATIVE COCLOBACILLUS



- Common infections: VAP, BSIs, UTIs, wound infections
- Key resistance: Carbapenem resistance
- Treatment options: Polymyxins, tigecycline, cefiderocol
- Important in ventilator- and device-associated infections

5 *Pseudomonas aeruginosa*

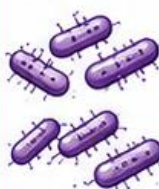
GRAM-NEGATIVE BACILLUS



- Common infections: VAP, BSIs, UTIs, wound infections
- Key resistance: Multidrug resistance (MDR) including carbapenem resistance
- Treatment options: Piperacillin-tazobactam, ceftazidime-avibactam, cefiderocol+aztreonam

6 *Enterobacterales* / *Enterobacteriaceae*

GRAM-NEGATIVE BACILLI



- Common infections: BSIs, UTIs, AIs, pneumonia
- Key resistance: ESBL, AmpC, carbapenemase (e.g., KPC, NDM)
- Treatment options: Carbapenems, β -lactam/ β -lactamase inhibitors, aminoglycosides

8 *CRE* Carbapenem-resistant *Enterobacterales*

GRAM-NEGATIVE BACILLI



- Common infections: BSIs, UTIs, pneumonia, intra-abdominal infections
- Key resistance: Carbapenem resistance; carbapenemases (KPC, NDM, OXA-48, VIM, IMP)
- Treatment options: Ceftazidime-avibactam for selected KPC/OXA-48 CRE; aztreonam + ceftazidime-avibactam for MBL producers where available; other therapy guided by susceptibility and site of infection

FROM ESKAPE TO ESCAPE



- MDR bacteria are major causes of nosocomial and healthcare-associated infections.
- The acronym shifted from ESKAPE to ESCAPE because *Klebsiella pneumoniae* / *Enterobacter* spp. were broadened to *Enterobacterales* / *Enterobacteriaceae*, and *Clostridioides difficile* was added.

RISK FACTORS IN PICU



Prolonged hospital stay



Broad-spectrum antibiotic exposure



Bowel colonization / gut dysbiosis



Contaminated environment



Healthcare worker hand transmission



Central venous catheters



Severe illness / ICU stay

KEY MESSAGE



Early recognition, infection prevention, antimicrobial stewardship, source control, and microbiology-guided targeted therapy are essential to improve outcomes in PICU patients.

FROM KPC TO CCC



- Gut dysbiosis during prolonged antibiotic exposure may favor colonization by KPC-producing (*Klebsiella pneumoniae*), *Clostridioides difficile*, and *Candida* spp.
- These organisms may coexist and contribute to invasive infection in vulnerable hospitalized patients.



KNOW THE PATHOGENS

Understand their behaviour, reservoirs, and transmission.



UNDERSTAND THE RESISTANCE

Identify mechanisms and monitor local resistance patterns.



CHOOSE WISELY

Use the right drug, right dose, right duration.



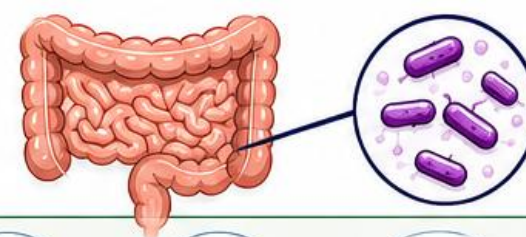
SAVE LIVES

Reduce resistance. Protect our patients.



ENTEROBACTERALES

THE GRAM-NEGATIVE FAMILY DRIVING PICU AMR



Enterobacterales (formerly Enterobacteriaceae) are a large family of **Gram-negative, rod-shaped bacteria**.

They are **normal residents** of the human and animal gut but can cause **severe infections** if they spread elsewhere.



BLOODSTREAM INFECTIONS



PNEUMONIA (VAP)



UTIs (CAUTI)



MENINGITIS (NEONATES)



HEALTHCARE-ASSOCIATED INFECTIONS



1. THE "BIG FOUR" LAB RULES

Every member of this family shares these four key biological traits.

GRAM-NEGATIVE



Stain pink/red under a microscope.

OXIDASE NEGATIVE



Do not produce the enzyme cytochrome oxidase.

CATALASE POSITIVE



Break down hydrogen peroxide into water and oxygen.

GLUCOSE FERMENTERS



Ferment glucose to produce acid, often with gas.

● ACID ○ GAS

2. THE MAIN PLAYERS

LACTOSE FERMENTERS ("PINK COLONIES" ON MACCONKEY AGAR)



Escherichia coli



Klebsiella pneumoniae



Enterobacter cloacae complex



Serratia marcescens

MAJOR CAUSES IN PICU:

- Sepsis / Bacteraemia
- Ventilator-associated pneumonia
- CAUTI / Urosepsis
- Healthcare-associated infections



NON-LACTOSE FERMENTERS ("COLOURLESS COLONIES")



Salmonella spp.



Shigella spp.



Proteus spp.



Yersinia spp.

MORE COMMONLY ASSOCIATED WITH:

- Gastroenteritis / Enteric fever
- Community-acquired infections
- Proteus-associated UTIs
- Dysentery (*Shigella*)



3. WHY PICU CLINICIANS SHOULD CARE

Most MDR Gram-negative infections in PICU arise from this family.



E. coli



Klebsiella pneumoniae



Enterobacter cloacae complex

These organisms may acquire:

- ESBLs
- AmpC β -lactamases
- Carbapenemases (OXA-48, NDM, KPC)

→ leading to **CRE** and difficult-to-treat infections.

4. THE AMR PROGRESSION



WILD-TYPE SUSCEPTIBLE

Usual gut coloniser



ESBL PRODUCERS

Reduced response to many β -lactams



AmpC PRODUCERS

Resistance to more β -lactams



CRE (CARBAPENEM-RESISTANT ENTEROBACTERIALES)

Limited treatment options



DTR (DIFFICULT-TO-TREAT RESISTANCE)

High mortality risk in PICU

5. KEY TAKE-HOME MESSAGE



Not all Enterobacterales are major PICU pathogens, but **most ESBL and CRE** infections encountered in **South African PICUs** originate from this family.

TOP DRIVERS OF MDR IN PICU

- 1 *Klebsiella pneumoniae*
- 2 *Escherichia coli*
- 3 *Enterobacter cloacae* complex



ESBL infections



Carbapenem resistance

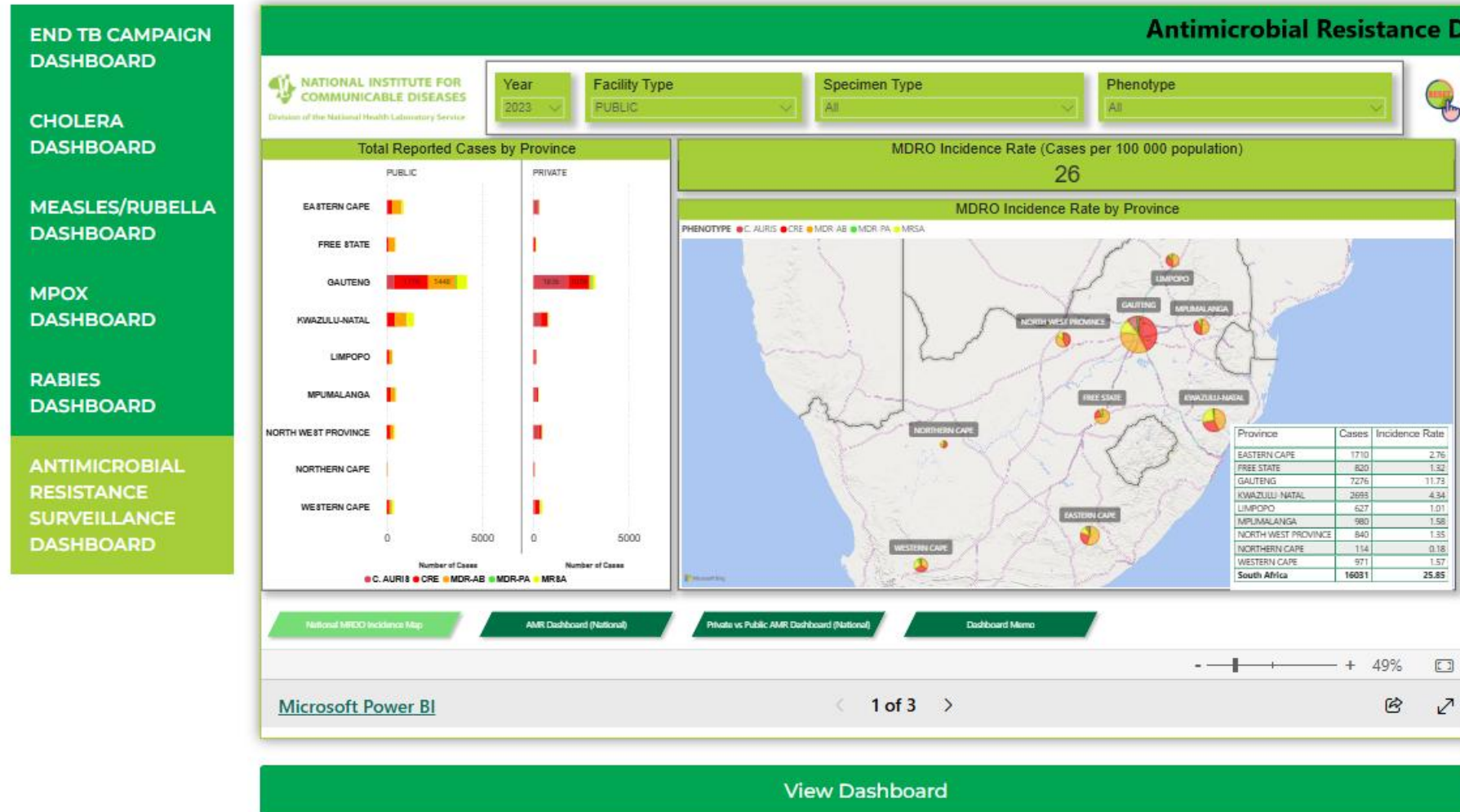


Healthcare-associated sepsis



PICU outbreaks

South African AMR data



<https://www.nicd.ac.za/anti-microbial-resistance-surveillance-dashboard/>

Wits Up To Speed 2026



Surveillance for Antimicrobial Resistance and Consumption of Antibiotics in South Africa 2018-2022

March 2024
National Department of Health



The acronym ESKAPE is used to describe the organisms that currently form part of the surveillance system and characterise an internationally accepted group of AMR-priority pathogens.

- *Enterococcus faecalis* and *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Escherichia coli*

Table 1: Antibiotics categorised into Access, Watch and Reserve groups

ACCESS	WATCH	RESERVE
<ul style="list-style-type: none"> • Amoxicillin • Amoxicillin and clavulanic acid • Ampicillin • Benzathine benzylpenicillin • Benzylpenicillin • Cefalexin, cefazolin • Chloramphenicol • Clindamycin • Cloxacillin • Doxycycline • Gentamicin, amikacin • Metronidazole • Nitrofurantoin • Phenoxymethylpenicillin • Procaine benzylpenicillin • Spectinomycin • Sulfamethoxazole and trimethoprim 	<ul style="list-style-type: none"> • Anti-pseudomonal penicillins with beta-lactamase inhibitor (e.g. piperacillin and tazobactam) • Carbapenems and penems (e.g. imipenem and cilastatin, meropenem) • Third generation cephalosporins with or without beta-lactamase inhibitor (e.g. cefixime, cefotaxime, ceftazidime, ceftioxaone) • Glycopeptides (e.g. teicoplanin, vancomycin) • Macrolides (e.g. azithromycin, clarithromycin, erythromycin) • Quinolones and fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin) 	<ul style="list-style-type: none"> • Aztreonam • Fourth generation cephalosporins (e.g. ceftazidime) • Fifth generation cephalosporins (e.g. ceftaroline) • Daptomycin • Fosfomycin (intravenous) • Oxazolidinones (e.g. linezolid) • Polymyxins (e.g. colistin) • Tigecycline



COMMON RESISTANCE MECHANISMS & PATTERNS of Gram-Negative Pathogens in the PICU



The enemy knows our antibiotics – understand how it escapes!

KEY RESISTANCE MECHANISMS

1 ENZYME PRODUCTION

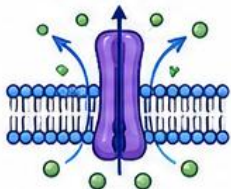
Destroy the antibiotic



- ESBLs (CTX-M, TEM, SHV)
- AmpC β -lactamases
- Carbapenemases (KPC, NDM, OXA-48, VIM, IMP)
- MBLs (NDM, VIM, IMP)

2 EFFLUX PUMPS

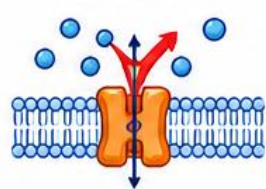
Expel antibiotic from the cell



- Overexpression of AcrAB-TolC, MexAB-OprM
- Contributes to MDR *Pseudomonas* & *Acinetobacter*

3 PORIN LOSS / ALTERATION

Decreased entry into the cell



- OmpK35/36 loss in *Klebsiella*
- OprD loss in *Pseudomonas* (carbapenem resistance)
- Reduced permeability

4 TARGET MODIFICATION

Change the target so drug can't bind



- Mutations in *gyrA*/*parC* (fluoroquinolone resistance)
- Altered PBP (β -lactam resistance)

5 BIOFILM FORMATION

Protects bacteria from antibiotics and host immunity



- On devices (ETT, CVC, urinary catheters)
- Increases persistence and recurrence

RESISTANCE PATTERNS IN PICU (TYPICAL)

	<i>Klebsiella pneumoniae</i> ESBL ($\approx 70\%$), CRE ($\uparrow\uparrow$), KPC, NDM, OXA-48	
	<i>Pseudomonas aeruginosa</i> MDR ($\uparrow$), Carbapenem-resistant ($\sim 20\text{--}25\%$) DTR strains, Efflux + Porin loss	
	<i>Acinetobacter baumannii</i> Carbapenem resistance $\sim 80\%$ OXA-type carbapenemases, Biofilm	
	<i>Escherichia coli</i> ESBL (CTX-M), AmpC, Emerging CRE	
	<i>Enterobacter spp.</i> AmpC, ESBL, Carbapenemases	

ANTIBIOTIC CLASSES MOST AFFECTED



β -LACTAMS
(Penicillins, Cephalosporins, Carbapenems)

ENZYME PRODUCTION

- ESBL, AmpC
- Carbapenemases (KPC, NDM, OXA-48, VIM, IMP)

AMINOGLYCOSIDES



EFFLUX PUMPS

- Aminoglycoside modifying enzymes

FLUOROQUINOLONES



TARGET MUTATIONS

- *gyrA*, *parC*
- plasmid-mediated genes

PIPERACILLIN/TAZOBACTAM



ESBLs, AmpC, Carbapenemases

COLISTIN



mcr-1 gene (plasmid-mediated resistance)

MECHANISM-PATTERN-IMPACT

MECHANISM	EXAMPLE GENES / TYPES	RESULT	CLINICAL IMPACT
Enzyme production	ESBL, AmpC, KPC, NDM, OXA-48, VIM, IMP	Drug destroyed	Treatment failure, limited options
Efflux pumps	AcrAB-TolC, MexAB-OprM	Drug pumped out	Reduced drug levels
Porin loss	OmpK35/36, OprD	Reduced entry	Carbapenem resistance
Target modification	<i>gyrA</i> , <i>parC</i> , PBP changes	Drug can't bind	Fluoroquinolone/ β -lactam resistance
Biofilm formation	Extracellular matrix, quorum sensing	Protected niche	Persistent infections, relapses

SOUTH AFRICA PICU TAKE-HOME



Know your local antibiogram



Prevent transmission & biofilm



Use antibiotics wisely



Culture before escalation



Strong stewardship saves lives

RED FLAGS FOR MDR GRAM-NEGATIVE INFECTION



Previous MDR colonisation



PICU stay > 7-10 days



Prior broad-spectrum antibiotics



Mechanical ventilation



Central line / urinary catheter



Multiple antibiotics

KEY RISK FACTORS FOR MULTIDRUG-RESISTANT GRAM-NEGATIVE INFECTIONS IN CRITICALLY ILL CHILDREN

Identify early. Act early. Prevent MDR.



MDR Gram-negative infections lead to treatment failure, prolonged PICU stay, high costs and increased mortality.

MODIFIABLE & NON-MODIFIABLE RISK FACTORS

1

PREVIOUS MDR COLONISATION



Strongest predictor

- ESBL-producing *Enterobacteriales*
- CRE
- MDR *Pseudomonas*
- MDR *Acinetobacter*

OR 5.15 in PICU study¹

2

PROLONGED PICU STAY



- Risk increases with increasing days
- PICU stay >9 days is an independent risk factor¹

3

PREVIOUS ANTIBIOTIC EXPOSURE



- Especially broad-spectrum agents (3rd gen cephalosporins, piperacillin-tazobactam, carbapenems)
- Selects resistant organisms

4

MULTIPLE ANTIBIOTICS (≥2)



- Use of ≥2 antibiotics independently increases risk of MDRI²

5

MECHANICAL VENTILATION



- Ventilation >5 days is an independent risk factor²
- Major risk for VAP with MDR organisms

6

INVASIVE DEVICES



- Central venous catheter
- Urinary catheter
- Endotracheal tube
- Dialysis catheter

Bypass natural barriers & promote biofilm formation

7

COMORBIDITY / IMMUNOCOMPROMISE



- Oncology, HIV
- Primary immunodeficiency
- Chronic lung/neurologic disease
- Congenital heart disease

Independent risk factor¹

8

RECENT SURGERY



- Especially abdominal or cardiac surgery
- Significantly associated with MDRI¹

9

PARENTERAL NUTRITION



- Requires central access
- Associated with longer PICU stay & severity
- Independent predictor of MDRI²

10

SEVERE CRITICAL ILLNESS



- High PELOD/PIM score
- Multi-organ dysfunction
- Septic shock

Drives more exposures & selects resistant organisms

THE STRONGEST PREDICTORS



1 Previous MDR colonisation



2 Prolonged PICU stay (>9 days)



3 Prior antibiotic exposure



4 Mechanical ventilation (>5 days)

COMMON MDR GRAM-NEGATIVE PATHOGENS IN PICU



Klebsiella pneumoniae
ESBL, CRE (NDM, OXA-48, KPC)



Pseudomonas aeruginosa
MDR / XDR (carbapenem resistance)



Acinetobacter baumannii
MDR / XDR (carbapenem resistance ~80%)



Enterobacteriales (*E. coli*, *Enterobacter* spp.)
ESBL, CRE

THE TYPICAL HIGH-RISK PICU PATIENT



Previous MDR colonisation

+



PICU stay >7-10 days

+



Mechanical ventilation >5 days

+



Central line / Urinary catheter

+



Broad-spectrum antibiotics (multiple courses)

+



Surgery / Comorbidity

=



HIGH RISK FOR MDR GRAM-NEGATIVE INFECTION



TAKE-HOME MESSAGE

Recognize these risk factors early, optimise antibiotic use, minimise device days, and strengthen infection prevention to reduce MDR Gram-negative infections in the PICU.

¹ González-Anleo C, et al. Eur J Pediatr. 2024;183:5255–5265.

² Wang Z, Xia Z. Ital J Pediatr. 2020;46:17.



WHY IS PAEDIATRIC AMR DIFFERENT IN THE SOUTH AFRICAN PUBLIC SECTOR?

Challenges that make Gram-negative infections harder to diagnose and treat in PICUs



1 OVERBURDENED PUBLIC SECTOR



- Majority of children depend on the state sector
- High patient volumes and overcrowding
- Inequalities between public and private healthcare



Increased transmission of MDR Gram-negative organisms

2 LIMITED PICU CAPACITY



- Prolonged admissions
- High use of invasive devices (ETT, CVC, urinary catheters, dialysis, etc.)
- High rates of healthcare-associated infections



Greater risk of colonisation and infection with MDR organisms

3 MULTIPLE INTER-HOSPITAL TRANSFERS



- District → Regional → Tertiary → PICU
- Each transfer increases antibiotic exposure and healthcare contact



Higher likelihood of colonisation with MDR Gram-negatives

4 HIGH EMPIRIC ANTIBIOTIC EXPOSURE



- Frequent use of broad-spectrum antibiotics before cultures
- Drives selection of ESBL, CRE and MDR non-fermenters



Increases emergence of resistance and treatment failure

5 DIAGNOSTIC CHALLENGES

DELAYED MICROBIOLOGY



- Conventional culture based
- Identification in 24–72 h
- Full susceptibility in 3–5 days
- Resistance confirmed often after clinical deterioration

LIMITED RAPID DIAGNOSTICS



- Limited access to PCR panels, carbapenemase testing, WGS
- High cost of molecular technologies



Treatment decisions often made 'blind' with consequences for outcomes

6 FEW THERAPEUTIC OPTIONS



- Rising CRE and CRAB
- Heavy reliance on carbapenems and colistin
- Newer β -lactam/ β -lactamase inhibitor combinations largely unavailable in public sector (due to cost)



Limited options = older, more toxic drugs and combination regimens

7 LIMITED PAEDIATRIC EXPERTISE



- Scarcity of paediatric infectious diseases specialists
- Difficult to provide specialist review for every MDR infection



Evidence often extrapolated from adult data – children are not small adults

8 INFECTION PREVENTION CHALLENGES



- Shortage of soap, water, alcohol hand rubs, gloves, masks, sterile gowns/aprons
- Re-use of equipment intended for single use
- Limited isolation facilities
- Staff shortages affect IPC compliance



High burden of HAIs and rapid spread of MDR organisms

9 SOUTH AFRICAN DISEASE BURDEN INCREASES AMR RISK

HIV



- Increased healthcare exposure
- Higher MDR colonisation rates
- More frequent and prolonged antibiotic use
- Immune suppression increases infection risk



TUBERCULOSIS

- Prolonged hospitalisation
- Frequent HIV co-infection
- Increased antimicrobial exposure
- Difficulty isolating infectious patients in crowded facilities

10 SURVEILLANCE CHALLENGES



- Limited paediatric AMR surveillance data
- Under-reporting common in LMICs
- Few national datasets focused on critically ill children (PICU/NICU)
- Heterogeneous laboratory capacity across provinces

11

THE BOTTOM LINE



The South African paediatric AMR challenge is not simply resistant bacteria.

It is the intersection of:

- ✓ Vulnerable children
- ✓ Overstretched healthcare systems
- ✓ Delayed diagnostics
- ✓ Limited treatment options
- ✓ High infection pressure from HIV, TB and HAIs



OUR MOST POWERFUL INTERVENTIONS: STRONG INFECTION PREVENTION & CONTROL • EFFECTIVE ANTIMICROBIAL STEWARDSHIP • ROBUST SURVEILLANCE

These are achievable today and save lives tomorrow.



MDR: multidrug-resistant ESBL: extended-spectrum β -lactamase CRE: carbapenem-resistant Enterobacteriales CRAB: carbapenem-resistant Acinetobacter baumannii ICU: intensive care unit PICU: paediatric ICU HAIs: healthcare-associated infections

Adapted from Siggers RT, Mothibi LM, Irwin AD, Naidoo KD. Challenges Facing PICUs in Low- and Middle-Income Countries in the Treatment of Emerging Multidrug-Resistant Organisms: a Review and Perspective from a South African PICU. Curr Infect Dis Rep. 2023;25:233–242. doi:10.1007/s11008-023-00817-5



TREATMENT PRINCIPLES

GUIDE YOUR ANTIBIOTIC DECISIONS. OPTIMISE OUTCOMES.



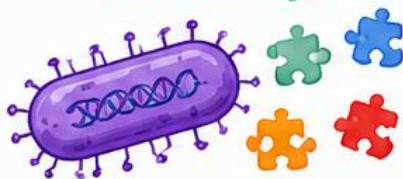
FOUR QUESTIONS BEFORE CHOOSING ANTIBIOTICS

1 What organism is most likely?



- Site of infection
- Patient history & exposures
- Local epidemiology and antibiogram

2 What resistance mechanism is most likely?



- Prior colonisation or infection
- Previous antibiotic exposure
- Local resistance patterns
- Consider ESBL, CRE, MBL, AmpC, carbapenemase, etc.

3 How sick is the child?



- Severity of illness
- Organ dysfunction
- Risk of deterioration
- Need for immediate broad coverage?

4 Can source control be achieved?



- Identify and control the focus
- Remove or drain when possible
- De-escalate once controlled
- Essential for cure



REMEMBER

“Antibiotics do not compensate for inadequate source control.”

ACHIEVE SOURCE CONTROL



Remove
Infected
lines



Drain
Abscesses



Debride
Necrotic
tissue

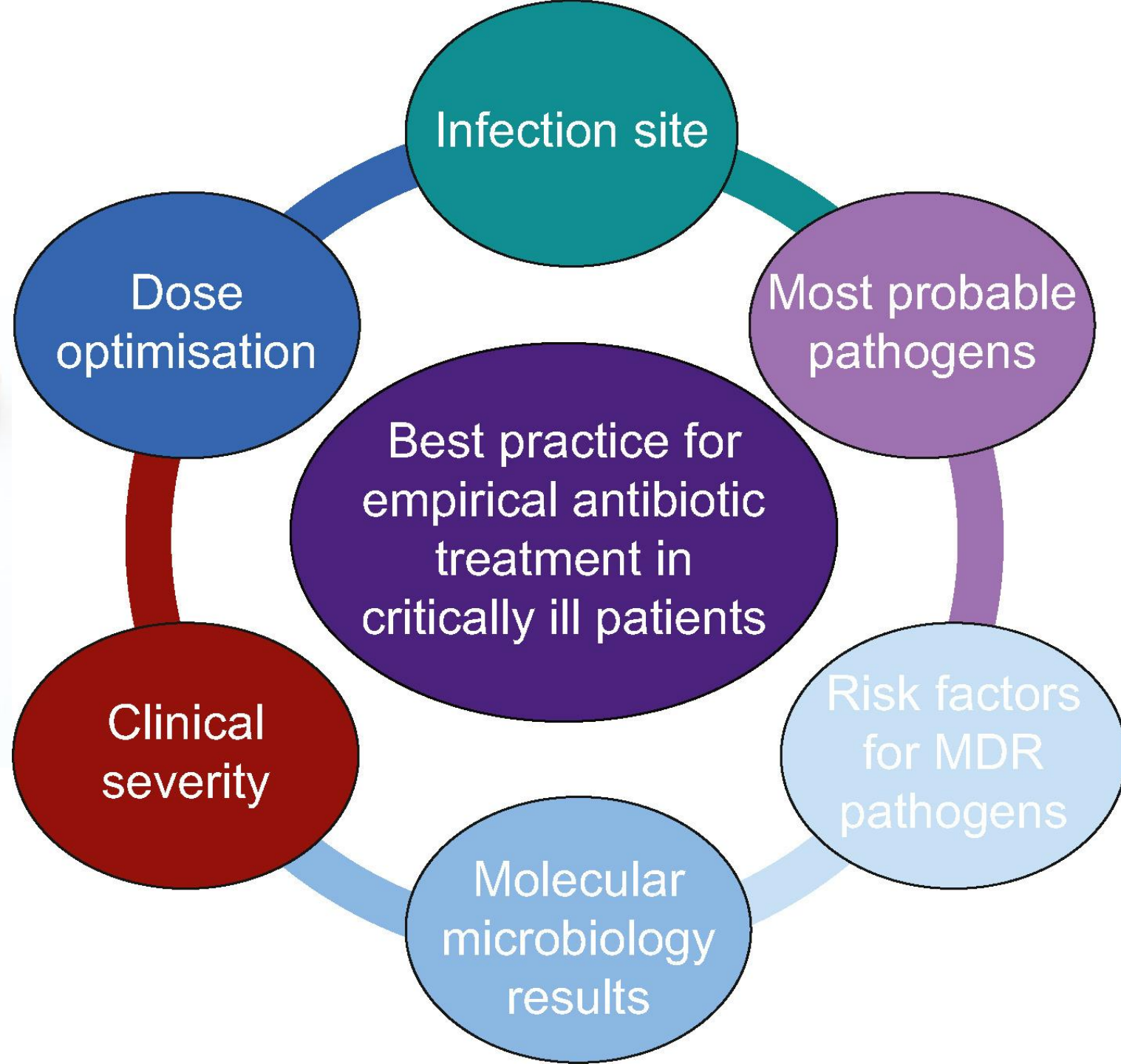


Remove
Infected
devices



GOOD CLINICAL JUDGMENT + TIMELY ANTIBIOTICS + EFFECTIVE SOURCE CONTROL = **BETTER OUTCOMES**







RISK-STRATIFIED EMPIRIC THERAPY — IN THE PICU —



MATCH EMPIRIC THERAPY TO THE CHILD'S RISK OF MDR INFECTION



LOW MDR RISK



NO:

- ✓ Previous MDR colonisation
- ✓ Recent PICU admission
- ✓ Recent carbapenem exposure



LIKELY ORGANISMS

Standard Enterobacterales
(e.g., *E. coli*, *Klebsiella*, *Enterobacter* spp.)



WHAT TO DO

Use local empiric protocols
based on local antibiogram
and severity of illness



**TARGET: ADEQUATE COVERAGE WITHOUT
UNNECESSARY BROAD-SPECTRUM THERAPY**

WHAT IS THE
CHILD'S RISK OF
MDR INFECTION?



Review history



Check local
antibiogram



Reassess
frequently (48–72 h)



De-escalate
when possible



HIGH MDR RISK



PREVIOUS / RISK FACTORS:

-  ESBL colonisation
-  CRE colonisation
-  Prolonged PICU stay
(>7–10 days)
-  Multiple antibiotic courses
/ recent broad-spectrum use



WHAT TO CONSIDER

Escalate empiric therapy based on
local antibiogram and patient factors
(consider coverage for ESBL, CRE,
MDR *Pseudomonas*, CRAB)



**TARGET: PREVENT UNDERTREATMENT
IN HIGH-RISK CHILDREN**



KEY MESSAGE

**“NOT EVERY
SEPTIC CHILD
NEEDS A CARBAPENEM.”**



RIGHT DRUG



RIGHT CHILD



RIGHT TIME



FROM ESKAPE TO ESCAPE...CCC: ANTIMICROBIAL OPTIONS AT A GLANCE



Match the drug to the resistance mechanism. De-escalate when culture and sensitivities are available.

PATHOGEN (ESCAPE...CCC)	COMMON RESISTANCE MECHANISMS	FIRST-LINE / ACTIVE OPTIONS (if susceptible)	NEWER / RESERVE AGENTS (where available)	KEY NOTES FOR PICU
E <i>Enterococcus faecium</i> (VRE) 	<ul style="list-style-type: none"> Ampicillin resistance Vancomycin resistance (VRE) High-level aminoglycoside resistance 	<ul style="list-style-type: none"> Ampicillin (if susceptible) Vancomycin (if susceptible) Linezolid 	<ul style="list-style-type: none"> Daptomycin* (*Not for pneumonia) Tigecycline (not for bacteremia) Oritavancin / Dalbavancin** 	 <ul style="list-style-type: none"> High-level aminoglycoside resistance is common Check VRE status Source control essential
S <i>Staphylococcus aureus</i> (MRSA) 	<ul style="list-style-type: none"> mecA / PBP2a (MRSA) Multi-drug resistance 	<ul style="list-style-type: none"> Vancomycin Linezolid Clindamycin (if susceptible) Daptomycin 	<ul style="list-style-type: none"> Ceftaroline Dalbavancin / Oritavancin** Daptomycin (high dose for complicated infections) 	 <ul style="list-style-type: none"> Confirm MRSA with PCR / rapid test Monitor for nephrotoxicity with vancomycin Consider lung penetration for pneumonia
C <i>Clostridioides difficile</i> (<i>C. difficile</i>) 	<ul style="list-style-type: none"> Broad-spectrum antibiotic exposure Fluoroquinolone resistance Recurrent disease 	<ul style="list-style-type: none"> Oral vancomycin Fidaxomicin 	<ul style="list-style-type: none"> Bezlotoxumab (for recurrent disease) Fecal microbiota-based therapy*** Tigecycline (rarely for fulminant/complicated cases in combination) 	 <ul style="list-style-type: none"> Stop unnecessary antibiotics Prioritise contact precautions and environmental cleaning Recurrence risk is high in PICU
A <i>Acinetobacter baumannii</i> 	<ul style="list-style-type: none"> OXA carbapenemases Efflux pumps Porin loss Biofilm production 	<ul style="list-style-type: none"> Colistin (polymyxin E) Tigecycline (adjunct) Sulbactam-durlobactam**** Minocycline / Doxycycline (if susceptible) 	<ul style="list-style-type: none"> Cefiderocol** High-dose sulbactam Combination therapy (e.g., colistin + tigecycline + sulbactam-based regimen) 	 <ul style="list-style-type: none"> High rates of MDR / XDR Ensure infection control Combination therapy often required in severe disease
P <i>Pseudomonas aeruginosa</i> 	<ul style="list-style-type: none"> AmpC overexpression Efflux pumps Porin loss Metallo-β-lactamases (MBLs) 	<ul style="list-style-type: none"> Piperacillin-tazobactam (if susceptible) Ceftazidime (if susceptible) Cefepime (if susceptible) Meropenem (if susceptible) 	<ul style="list-style-type: none"> Ceftolozane-tazobactam** Ceftazidime-avibactam Cefiderocol** Imipenem-relebactam 	 <ul style="list-style-type: none"> Adjust doses for renal function Use mechanism-guided therapy Source control and airway clearance are essential
E <i>Enterobacterales / Enterobacteriaceae</i> (ESBL, AmpC, KPC, NDM, OXA-48) 	<ul style="list-style-type: none"> ESBL, AmpC overproduction Carbapenemases: KPC, OXA-48, NDM, IMP, VIM Porin loss, efflux pumps 	<ul style="list-style-type: none"> Ceftriaxone / Ceftaxime (if susceptible) Piperacillin-tazobactam (selected cases) Carbapenem (if susceptible and no carbapenemase) Cefepime (selected cases) 	<ul style="list-style-type: none"> Cefepime-enmetazobactam** Ceftazidime-avibactam (KPC, OXA-48) Aztreonam + Ceftazidime-avibactam (for NDM / MBL producers) Eravacycline / Tigecycline (limited role) Fosfomycin (combination / urinary) 	 <ul style="list-style-type: none"> OXA-48 common in South Africa Seek ID / microbiology input De-escalate to targeted therapy as soon as possible
C <i>Candida spp.</i> (including non-albicans) 	<ul style="list-style-type: none"> Azole resistance (e.g., <i>C. auris</i>, <i>C. glabrata</i>) Biofilm formation on devices 	<ul style="list-style-type: none"> Echinocandin (e.g., caspofungin, micafungin, anidulafungin) 	<ul style="list-style-type: none"> Fluconazole (if susceptible and stable) Liposomal amphotericin B Isavuconazole / Posaconazole (selected refractory cases) 	 <ul style="list-style-type: none"> Remove infected lines where possible Follow antifungal stewardship Check susceptibility
CRE Carbapenem-resistant Enterobacterales (CRE) 	<ul style="list-style-type: none"> Carbapenemases: KPC, OXA-48, NDM, VIM, IMP Porin loss, efflux pumps 	NO SINGLE EMPIRIC OPTION – USE SUSCEPTIBILITY & MECHANISM-GUIDED THERAPY	<ul style="list-style-type: none"> Ceftazidime-avibactam (KPC, OXA-48) Aztreonam + Ceftazidime-avibactam (for NDM / MBL producers) Cefiderocol (broad-spectrum) Eravacycline, Tigecycline (adjunct) Fosfomycin (combination / urinary) 	 <ul style="list-style-type: none"> Determine the carbapenemase before choosing therapy Combination therapy usually required in severe disease Source control remains critical

KEY PICU PRINCIPLES

 Obtain cultures before antibiotics

 Review daily and de-escalate when possible

 Use the narrowest effective therapy for the shortest appropriate duration

 Ensure source control and remove infected devices

RESISTANCE MECHANISM → PREFERRED AGENT EXAMPLES

ESBL	→ Ceftriaxone / Tazobactam combinations / Carbapenem (if susceptible)
AmpC	→ Cefepime / Carbapenem
KPC	→ Ceftazidime-avibactam / Meropenem-vaborbactam
OXA-48	→ Ceftazidime-relebactam
NDM / MBL	→ Aztreonam + Ceftazidime-avibactam / Cefiderocol
MRSA	→ Vancomycin / Linezolid / Daptomycin
VRE	→ Linezolid / Daptomycin
<i>C. difficile</i>	→ Oral vancomycin / Fidaxomicin

TAKE-HOME MESSAGE

From ESCAPE to ESCAPE...CCC,
the challenge is evolving from KPC to CCC.

The modern management of these pathogens
is no longer organism-driven—
it is **resistance mechanism-driven**.



Antibiotics do not replace adequate source control.



Infected lines



Abscesses



Necrotic tissue



Infected devices



Consult Infectious Diseases and Clinical Pharmacology teams early in complex cases.



Product names currently not registered in South Africa – Aztreonam, Sulbactam-durlobactam, Imipenem-relebactam

*Not for pneumonia

***Limited paediatric experience

***FMT – Faecal microbiota transplantation

****Not widely available in SA

What Most South African PICUs Actually Use

ESBL Enterobacterales

-  Meropenem

MDR Pseudomonas

-  Piperacillin-tazobactam (if susceptible)
-  Cefepime
-  Meropenem

CRE (Carbapenem-resistant Enterobacterales)

-  Ceftazidime-avibactam (where available and approved)
-  Colistin-based regimens

CRAB (Carbapenem-resistant *Acinetobacter baumannii*)

-  Colistin

Practical SA *Reserve-Use* Antimicrobial Availability (2026)

Agent	Registered in SA	Paediatric Experience	Public Sector Access
Meropenem	✓ Yes	✓ Extensive	✓ Widely available
Piperacillin-tazobactam	✓ Yes	✓ Extensive	✓ Widely available
Cefepime	✓ Yes	✓ Extensive	✓ Widely available
Colistin	✓ Yes	✓ Extensive (last-line)	✓ Widely available
Amikacin	✓ Yes	✓ Extensive	✓ Widely available
Linezolid	✓ Yes	✓ Extensive	✓ Widely available
Vancomycin	✓ Yes	✓ Extensive	✓ Widely available
Tigecycline	✓ Yes	⚠ Limited paediatric use	⚠ Restricted / motivation required
Ceftazidime-avibactam	✓ Yes	⚠ Growing experience	⚠ Restricted / motivation required
Ceftolozane-tazobactam	✓ Yes	⚠ Limited experience	✗ Rarely available in public sector
Cefiderocol	✗ Product names are currently not registered in South Africa	Minimal	✗ No routine access
Aztreonam			
Meropenem-vaborbactam			
Imipenem-relebactam			
Sulbactam-durlobactam			

PROLONGED MEROPENEM INFUSIONS IN CHILDREN

MAXIMISING EXPOSURE. OPTIMISING OUTCOMES IN THE PICU

WHY PROLONG THE INFUSION?

Meropenem is a **TIME-DEPENDENT** antibiotic. The key driver of efficacy is the time that **FREE** drug concentrations remain **ABOVE THE MIC (fT>MIC)**.

Time above MIC
 Better bacterial killing
 Improved clinical success

It's not the peak concentration that matters—it's the time above the MIC.

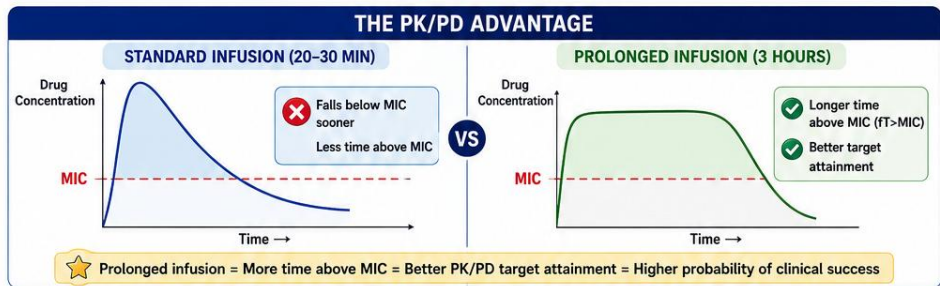
WHO BENEFITS MOST?

HIGH-RISK INFECTIONS

- ESBL infections (*Klebsiella*, *E. coli*, *Enterobacter* spp.)
- MDR Gram-negative sepsis
- Ventilator-associated pneumonia (VAP)
- Pseudomonas aeruginosa*
- High MIC organisms (MIC 1–4 mg/L)

COMPLEX PICU PHYSIOLOGY

- Augmented renal clearance (ARC)
- ECMO
- CRRT
- Burns
- Post-operative cardiac patients



WHEN SHOULD I USE PROLONGED MEROPENEM INFUSIONS?

CLINICAL SCENARIO	✓ CONSIDER EXTENDED	✗ NOT USUALLY NEEDED
Septic shock / severe sepsis	✓ YES	Low-risk infections <ul style="list-style-type: none"> Simple UTI Mild infections Rapid clinical response Organisms with very low MIC ✗ Usually NOT required
ESBL infections	✓ YES	
MDR Gram-negative infections (including <i>Pseudomonas</i> , <i>Acinetobacter</i>)	✓ YES	
Ventilator-associated pneumonia	✓ YES	
High MIC organisms (MIC 1–4 mg/L)	✓ YES	
Augmented renal clearance (ARC)	✓ YES	
ECMO / CRRT	✓ YES	

PRACTICAL PICU APPROACH

STANDARD

20–30 min infusion

EXTENDED

3-hour infusion

RESULT

- ✓ Better fT>MIC
- ✓ Better bacterial killing
- ✓ PK/PD optimisation without increasing dose

Individualise based on patient severity, MIC, organ function and clinical response

KEY TAKE-HOME MESSAGE

If you are worried enough to prescribe meropenem for a critically ill child with severe Gram-negative infection, **you should also ask whether that child would benefit from an extended infusion strategy.**

Meropenem

Paediatric Dosage

Paed. forms avail. in SA and covered in this monograph: inj

Paed. dosages below include:

- General dosing range
- Indications and dosages registered in other jurisdictions

Infections caused by: Most aerobic and anaerobic organisms (excluding Methicillin resistant *Staphylococcus* spp.)

General dosing range

Younger than 3 months

- Not established for use

Between 3 months - 11 years or <50kg

- IV: 10-40mg/kg, 8hrly

Older than 12 years or > 50kg

- See adult dosage

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria

Colistin prescribing in PICU



Gauteng Provincial Antimicrobial Stewardship Committee

GUIDELINE FOR THE USE OF COLISTIN January 2026

The Guideline is modelled on the COLISTIN adult and paediatric guideline for South Africa, 2016 for adults and the Colistin Guideline: Appropriate use of colistin in neonates, infants and children: Interim Guidance, 2023 for paediatric use.

Table 1: Expected colistin activity against currently prevalent mechanisms of resistance

<u>Antibiotic</u>	<u>Amp-C</u>	<u>ESBLs</u>	<u>KPC</u>	<u>MBLs</u> <u>(NDM, VIM</u> <u>and IMP)</u>	<u>OXA-</u> <u>48</u>	<u>CRPA</u>	<u>CRAB</u>
Colistin	✓	✓	✓	✓	✓	✓	✓

ESBLs extended spectrum β -lactamases; KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-beta-lactamases; NDM, New Delhi metallo-beta-lactamase; VIM, Verona integron-encoded metallo-beta-lactamase; IMP, imipenemase; AmpC, ampicillinase C; OXA-48, Oxacillinase-48; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, Carbapenem-resistant *Acinetobacter baumannii*.

NB! Colistin is active against ESBLs, however it should be reserved for hospital acquired invasive infections, caused by carbapenemase producing enterobacterales (CPEs), carbapenem resistant enterobacterales (CREs), CRPA, and CRAB.

Colistin prescribing in PICU



Gauteng Provincial Antimicrobial Stewardship Committee

GUIDELINE FOR THE USE OF COLISTIN January 2026

The Guideline is modelled on the COLISTIN adult and paediatric guideline for South Africa, 2016 for adults and the Colistin Guideline: Appropriate use of colistin in neonates, infants and children: Interim Guidance, 2023 for paediatric use.

Table 2: Recommendation on polymyxin combination therapy versus monotherapy for invasive infections caused by CREs, CRAB, or CRPA

Organism	Invasive infection	Susceptible agent(s) available†	Non-susceptible agent(s) available only	Polymyxin/colistin combination therapy recommended	Polymyxin/colistin monotherapy recommended
CREs	✓	✓		✓	
			✓‡	✓	
CRAB	✓	✓		✓	
			✓		✓
CRPA	✓	✓		✓	
			✓‡	✓	

Key: †, 2nd and/or 3rd agent(s) display a susceptible minimum inhibitory concentration.

‡, Preference to be given to the 2nd and/or 3rd non-susceptible agent with the lowest MIC relative to the respective susceptibility breakpoint.

Chibabhai, et al. provides similar recommendations in the paediatric population with regard to colistin combination therapy versus monotherapy.⁴ Combination therapy with a second active antibiotic (meropenem, tigecycline, aminoglycoside etc.) is recommended in the treatment of severe sepsis or septic shock, BSI with a non-urinary/non-biliary source of infection or severe underlying disease, caused by (CPE)/CRE, (MDR)/XDR *A. baumannii*, or (MDR)/XDR *P. aeruginosa*.⁴ When choosing the second active agent, factors such as site of infection, antibiotic MICs and patient renal function should be considered.⁴ In the case of (MDR)/XDR *A. baumannii*, if a second active agent is not available then colistin monotherapy is acceptable.⁴

NB! When considering colistin monotherapy, it is advised that a clinical microbiologist, infectious disease specialist, or other appropriate specialist be consulted.

BLICs (β -Lactam/ β -Lactamase Inhibitor Combinations)

Combination	Main Role
Amoxicillin-Clavulanate	Community infections
Piperacillin-Tazobactam	Severe hospital-acquired infections
Ampicillin-Sulbactam 	Mixed infections, <i>Acinetobacter</i> activity
Ticarcillin-Clavulanate 	Largely historical



Products name is currently not registered in South Africa

New-Generation BLICs

Combination	Main Role
Ceftazidime-Avibactam (CEFTAZ-AVI)	ESBL, KPC, OXA-48, some MDR <i>Pseudomonas</i> *
Ceftolozane-Tazobactam	MDR <i>Pseudomonas aeruginosa</i>
Meropenem-Vaborbactam 	KPC-producing CRE
Imipenem-Relebactam 	KPC, MDR <i>Pseudomonas</i>
Sulbactam-Durlobactam 	<i>Acinetobacter baumannii</i>

*Not active against: NDM, VIM, IMP, *Acinetobacter*

 Product names currently not registered in South Africa



Ceftazidime–Avibactam (CEFTAZ-AVI)

Overview, spectrum and stewardship in paediatric and neonatal care



1 What is CEFTAZ-AVI?

CEFTAZIDIME

Third-generation cephalosporin



AVIBACTAM

Non-beta-lactam beta-lactamase inhibitor



- Avibactam inhibits certain beta-lactamases.
- It protects ceftazidime from degradation and allows it to work against resistant bacteria.

2 Spectrum of activity

ACTIVE AGAINST

- ✓ ESBL-producing *Enterobacterales*
- ✓ KPC-producing CRE
- ✓ OXA-48-producing *Enterobacterales*
- ✓ Some carbapenem-resistant *Pseudomonas aeruginosa* with proven susceptibility



NOT ACTIVE AGAINST

- ✗ NDM-, VIM-, and IMP-producing organisms (metallo-beta-lactamases)
- ✗ *Acinetobacter baumannii*
- ✗ *Enterococcus* spp.



If an MBL (NDM, VIM or IMP) is suspected, combine with **AZTREONAM** because avibactam does not inhibit metallo-beta-lactamases.



3 When should we use CEFTAZ-AVI?



- CEFTAZ-AVI is a **RESERVE** antibiotic.
- Use with microbiology guidance and antimicrobial stewardship approval.

INDICATED FOR:

- ✓ Susceptible carbapenem-resistant *Enterobacterales*
- ✓ Susceptible carbapenem-resistant *Pseudomonas aeruginosa*
- ✓ Severe, life-threatening difficult-to-treat Gram-negative infections when other options are limited

4 Key stewardship messages

- ✗ Not for routine empiric therapy.
- ✗ Not for routine ESBL infections.
- 🔬 Always confirm culture/susceptibility where possible.
- 📝 Document indication and review daily.
- ⬇️ De-escalate when possible.





Ceftazidime–Avibactam (CEFTAZ-AVI)

Paediatric and neonatal dosing, monitoring and safety



1 Paediatric IV dosing

Dosing is based on the **CEFTAZIDIME** component.

AGE GROUP	DOSE (Ceftazidime component)	FREQUENCY
< 3 months (postmenstrual or chronological age)	30 mg/kg/dose	Every 8 hours
3 to 6 months	40 mg/kg/dose	Every 8 hours
≥ 6 months to < 18 years	50 mg/kg/dose (maximum 2 g ceftazidime per dose)	Every 8 hours

Each 2.5 g vial contains 2 g ceftazidime + 0.5 g avibactam sodium (4:1 ratio).

2 Monitoring during therapy



Monitor renal function closely



Dose-adjust in renal impairment



Check liver function and full blood count during prolonged therapy



Review culture and susceptibility results regularly



Document indication and review daily (antimicrobial stewardship)

3 Adverse effects / safety profile



Generally similar to other beta-lactams



Nausea, diarrhoea, vomiting



Rash / hypersensitivity



Raised liver enzymes



Seizures reported rarely



Watch for superinfection / *C. difficile* with prolonged use

4 When extra caution is needed



Suspected or proven MBL producers (NDM, VIM, IMP): use with **AZTREONAM**



Do not use alone for complicated intra-abdominal infection — add **METRONIDAZOLE**



Not active against *Acinetobacter baumannii* or *Enterococcus* spp.



Avoid routine empiric use or routine ESBL use



Seek microbiology / stewardship approval

5 Main paediatric / neonatal uses



Complicated urinary tract infection (cUTI)



Complicated intra-abdominal infection (cIAI)*



Hospital-acquired pneumonia (HAP)



Ventilator-associated pneumonia (VAP)



Susceptible CRE infection



Selected susceptible resistant *Pseudomonas aeruginosa*

* For cIAI, use in combination with metronidazole because CEFTAZ-AVI has no anaerobic activity.

6 Practical take-home messages



Reserve antibiotic — not routine escalation



Best for susceptible CRE and selected resistant *Pseudomonas*



If MBL is suspected, think **AZTREONAM + CEFTAZ-AVI**



Use as stewardship-controlled, susceptibility-guided therapy

Tigecycline in Paediatrics

Key evidence and when to use it



1 What is it?



- A broad-spectrum glycylicycline antibiotic
- Usually bacteriostatic
- Used mainly as salvage therapy for severe MDR/XDR infection

2 Where it may help



- Complicated intra-abdominal infection
- Complicated skin and soft-tissue infection
- Selected MDR/XDR *Acinetobacter* infections
- Selected CRE / Enterobacterales infections when better options are unavailable
- Part of combination regimens for difficult polymicrobial infection

3 Key limitations



- ⚠ Do NOT rely on tigecycline for *Pseudomonas aeruginosa*
- ⚠ Not ideal as monotherapy for bacteraemia or septic shock
- ⚠ Poor urinary levels: not preferred for isolated UTI
- ⚠ Poor CSF penetration: standard IV therapy is inadequate for meningitis
- ⚠ Use only after culture review, source control, and expert input

4 Paediatric evidence snapshot



- Phase-2 paediatric study supports exposure-matched dosing in children
- Retrospective cohorts show variable but often favourable responses in severe MDR infection
- 36-child MDR bacteraemia series: microbiological eradication 75%, clinical response 83%
- Neonatal evidence is limited to small salvage case series

5 How it is usually used



- Usually in combination therapy, not alone
- Best considered when safer or better-supported agents are unsuitable
- Most useful for tissue-based infection rather than bloodstream infection
- Decision should be mechanism-, susceptibility-, and site-directed

6 Take-home message



Tigecycline is a restricted salvage antibiotic in paediatrics. It may be useful for selected severe MDR infections, but it should not be expected to cover *Pseudomonas* and is a poor stand-alone choice for bacteraemia, UTI, or meningitis.

Tigecycline in Paediatrics

Dosing, monitoring and safety



1 Standard dosing



- 8 to <12 years: 1.2 mg/kg IV every 12 hours
- Maximum dose: 50 mg per dose
- 12 to <18 years: 50 mg IV every 12 hours
- Usually infused over 30–60 minutes
- Typical duration: 5–14 days

2 Children <8 years



- No validated routine paediatric dose
- Published salvage regimens often use 1–2 mg/kg/dose IV every 12 hours
- Neonatal evidence is limited to small case series
- Use only with paediatric ID / microbiology / specialist oversight
- High-dose regimens are not standard care

3 When dosing needs caution



- ⚠ Severe sepsis or persistent bacteraemia may reduce target exposure
- ⚠ Consider whether the infection site is suitable
- ⚠ Poor serum and urinary concentrations limit use in bacteraemia and UTI
- ⚠ Poor CSF penetration limits use in meningitis
- ⚠ Do not expect activity against *Pseudomonas aeruginosa*

4 Monitor during therapy



- Full blood count and platelets
- ALT, AST, bilirubin and renal function
- PT/INR, aPTT and fibrinogen
- Electrolytes; amylase/lipase if indicated
- Repeat cultures, inflammatory markers and clinical response

5 Important adverse effects



- Nausea, vomiting and diarrhoea
- Raised transaminases or bilirubin
- Thrombocytopenia and occasional neutropenia
- Pancreatitis and coagulation abnormalities
- Tooth discolouration / effects on developing teeth and bone

6 Practical take-home



Use tigecycline as a restricted salvage antibiotic.
Best suited to selected tissue-based MDR infection.
Avoid relying on it as stand-alone therapy for bacteraemia, UTI, VAP or meningitis.
Always combine with source control and expert review.

MICROBIOLOGY

Tel: 012 319 2134

Specimen received: Tracheal aspirate

Tests requested: Resp Gram, Sterile site cult, Broth dil MIC, Communication

Gram Stain:

Neutrophils	Occasional
Gram negative bacilli	Numerous (3+)

Bacterial Culture:

A heavy growth of

1) *Acinetobacter baumannii* (ACIBA)

This is a multi-resistant organism. CONTACT PRECAUTIONS are necessary to ensure that this organism does not spread in the ward/unit.

Antibiotic/Culture:	ACIBA
-----	-----
Trimethoprim-sulfamethoxazole	R
Ciprofloxacin	R
Ceftazidime	R
Cefepime	R
Gentamicin	R
Piperacillin-tazobactam	R
Imipenem	R
Meropenem	R
Tigecycline	S

S - Sensitive ; I - Intermediate ; R - Resistant ; SDD - Sensitive Dose Dependant



Final choice depends on full clinical context, severity, organ function, and ID/microbiology review.



Case 1: XDR *Acinetobacter baumannii* from endotracheal aspirate

Suggested antibiotic approach based on microbiology only

1

What the report shows



- Tracheal aspirate / endotracheal aspirate culture.

- Heavy growth of *Acinetobacter baumannii*.
- Resistant to TMP-SMX, ciprofloxacin, ceftazidime, cefepime, gentamicin, piperacillin-tazobactam, imipenem and meropenem.
- Tigecycline: susceptible.
- Colistin MIC: 0.5 micrograms/mL.



2

First clinical question



- Treat only if this represents true VAP / lower respiratory infection.
- If this is colonisation only, **avoid targeted antibiotics** and maintain **contact precautions**.

3

If true infection



- Most practical available option: **IV colistin PLUS tigecycline**.
- Consider adjunct **nebulised colistin** for VAP if locally used.
- Consider **sulbactam-based therapy** only if locally available and supported by microbiology / ID.
- **Ceftazidime-avibactam** has **NO** role for *Acinetobacter baumannii*.

4

Key cautions



- Prefer **combination therapy** rather than tigecycline alone in severe ventilated infection.



- Monitor **renal function** closely with colistin.



- Ensure **source control** and VAP bundle review.



BOTTOM LINE: ETA growth alone does not mandate treatment. If there is true VAP, a **colistin-based combination regimen** is the main option from this report, with **tigecycline** as the key additional active agent.

Specimen received: Blood culture

Tests requested: Blood cult, E-test MIC, Broth dil MIC, CRE, Communication

Bacterial Culture:

Bottle: Type FAN Paediatric Plus

Result Positive

Incubation time 3.8 hours

Gram Stain Gram negative bacilli

1) *Klebsiella pneumoniae* (KLEPN)

This is a multi-resistant organism. CONTACT PRECAUTIONS are necessary to ensure that this organism does not spread in the ward/unit.

Antibiotic/Culture:	KLEPN
-----	-----
Trimethoprim-sulfamethoxazole	R
Ampicillin / Amoxicillin	R
Amoxicillin-clavulanic acid	R
Ciprofloxacin	R
Cefuroxime (Parenteral)	R
Cefuroxime (Oral)	R
Cefoxitin	R
Cefotaxime / Ceftriaxone	R
Ceftazidime	R
Ceftazidime-avibactam	R
Gentamicin	R
Amikacin	R
Piperacillin-tazobactam	R
Imipenem	R
Meropenem	R

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Current CLSI guidelines have set colistin breakpoints for Enterobacterales, *P. aeruginosa* and *Acinetobacter* spp at ≤ 2 mg/L (intermediate) and ≥ 4 mg/L (resistant), with no susceptible category. Clinical and PK/PD data demonstrate this agent to be of limited clinical efficacy. If available, alternative agents to which the isolate is susceptible are strongly preferred. If these agents are not available, colistin monotherapy (for specific sites and uncomplicated infections) OR colistin in combination with one or more additional antibiotics with the lowest MIC should be used. Please consult a clinical microbiologist or infectious diseases physician if management advice is required.

Molecular Microbiology:

Confirmatory test for Carbapenemases:

Organism	<i>Klebsiella pneumoniae</i> (KLEPN)
OXA-48 (and variants)	Present
NDM	Absent
KPC	Absent
VIM	Absent

Comments:

This test confirms the presence of carbapenemase genes amongst Enterobacteriaceae (Enterobacterales). Detection of the carbapenemase by this test indicates the presence of the gene within the bacterium tested. For optimal management of patients colonised/infected with carbapenemase producing organisms, contact Pathologists in Microbiology or Infectious Diseases Physicians.



Case 2: OXA-48 CRE *Klebsiella pneumoniae* bacteraemia

Suggested antibiotic approach based on microbiology only



1

What the report shows



- Blood culture positive for *Klebsiella pneumoniae*.



- Carbapenemase detected: OXA-48 present.



- Resistant to carbapenems, aminoglycosides, piperacillin-tazobactam and multiple beta-lactams.



- Ceftazidime-avibactam: resistant.



- Tigecycline MIC: 1 micrograms/mL (susceptible).



- Colistin MIC: 0.5 micrograms/mL.

2

Immediate interpretation



- This is true invasive infection, not colonisation.



- Ceftazidime-avibactam is NOT useful here because the isolate is reported resistant.



- Aztreonam + ceftazidime-avibactam is not the main strategy from this report because OXA-48 is present and NDM, KPC and VIM are absent.

3

Most practical treatment option from this report



- Use IV colistin-based combination therapy.



- Add tigecycline as the main additional active agent.



- Do NOT rely on tigecycline alone for bloodstream infection.

4

Other key management steps



- Urgent ID / microbiology discussion.



- Repeat blood cultures.



- Remove or change infected intravascular line if relevant and obtain source control.



- Consider cefiderocol or another newer active agent only if locally accessible and susceptibility can be confirmed.

5

Key cautions



- Meropenem / imipenem are not useful with MICs greater than 32 micrograms/mL.



- Monitor renal function closely with colistin.



- Review daily for de-escalation if new susceptibility data emerge.



For this OXA-48 CRE bacteraemia, the lab report leaves a colistin-based combination as the practical option, with tigecycline as an adjunct rather than monotherapy.





SUPERBUGS IN THE PICU

EPIDEMIOLOGY & TREATMENT OF DIFFICULT PAEDIATRIC GRAM-NEGATIVE INFECTIONS

WHY CHILDREN ARE DIFFERENT



Immature immunity



Neonates & infants



HIV exposure/infection



Malnutrition



Frequent healthcare exposure

Higher risk of MDR infection

1 WHO IS AT HIGH RISK?

PATIENT FACTORS



Previous MDR colonisation



Neonate / Infant



Immunocompromised



Comorbid disease

HEALTHCARE FACTORS



Prior carbapenem exposure



Prolonged PICU stay (>9 days)



Mechanical ventilation



Central venous catheters



Previous hospitalisation



Multiple antibiotic courses

2 THE ESKAPE PATHOGENS



Enterococcus faecium
(Gram-positive cocci)



Staphylococcus aureus (MRSA)
(Gram-positive cocci)



Klebsiella pneumoniae
(Gram-negative rod)



Acinetobacter baumannii
(Gram-negative coccobacillus)



Pseudomonas aeruginosa
(Gram-negative bacillus)



Enterobacter spp.
(Gram-negative rod)



3 RESISTANCE EVOLUTION

Wild-type



ESBL



AmpC



CRE



DTR

KEY MECHANISMS

- ESBL
- AmpC
- OXA-48
- KPC
- NDM (MBL)
- VIM (MBL)
- IMP (MBL)

DTR = Difficult-to-Treat Resistance

4 DIAGNOSTIC & SYSTEM CHALLENGES



Overcrowded public sector hospitals



Multiple inter-hospital transfers



Delayed microbiology results



Limited paediatric AMR surveillance data



Limited molecular diagnostics



Restricted access to newer antibiotics



These challenges lead to delayed appropriate therapy and poorer outcomes.

5 TREATMENT PRINCIPLES

FOUR QUESTIONS BEFORE CHOOSING ANTIBIOTICS



What organism is likely?



What resistance mechanism is likely?



How sick is the child?



Can source control be achieved?

SOURCE CONTROL FIRST



Drain abscesses



Remove infected lines



Debride infected tissue



Remove infected devices



Antibiotics do not compensate for inadequate source control.

6 RISK-STRATIFIED EMPIRIC THERAPY

LOW MDR RISK

- ✓ No previous MDR colonisation
- ✓ No carbapenem exposure
- ✓ No recent PICU admission



Follow standard empiric guidelines

HIGH MDR RISK

- ✓ Previous ESBL / CRE colonisation
- ✓ Multiple antibiotic courses
- ✓ Prolonged PICU stay
- ✓ Invasive devices

- ◆ Escalate according to local antibiogram
- ◆ Obtain cultures early (before antibiotics)

7 MECHANISM-DIRECTED THERAPY

RESISTANCE MECHANISM	PREFERRED THERAPY	NOTES
ESBL	Meropenem	Consider prolonged infusion in critically ill
OXA-48 CRE	Ceftazidime-Avibactam (CEFTAZ-AVI)	Active against OXA-48 producers
KPC CRE	Ceftazidime-Avibactam (CEFTAZ-AVI)	Excellent activity against KPC
NDM / MBL	*	CAZ-AVI alone NOT active vs MBL
MDR Pseudomonas	Ceftolozane-Tazobactam	Best agent for MDR <i>Pseudomonas</i>
CRAB (<i>A. baumannii</i>)	Colistin-based regimens	Combination therapy preferred



CEFTAZ-AVI is active against ESBL, KPC and OXA-48 producers, but NOT against NDM-producing organisms unless combined with aztreonam.

8 PK/PD OPTIMISATION

CONSIDER PROLONGED MEROPENEM INFUSIONS

EXTENDED INFUSION
= BETTER OUTCOMES



Septic shock



Ventilator-associated pneumonia



ESBL infections



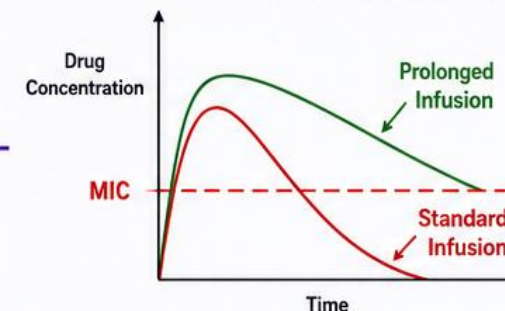
Augmented renal clearance



ECMO



CRRT



↑ Time
above MIC



↑ Target
attainment



↑ Clinical
success

9 THE 5 PILLARS OF PICU AMR CONTROL

PREVENT



Infection prevention
& control

- Hand hygiene
- Bundles
- Environmental cleaning
- Isolation when indicated

DETECT



Rapid diagnostics
& microbiology

- Early cultures
- Appropriate tests
- Rapid reporting
- Surveillance

TREAT



Appropriate
empiric therapy

- Assess risk factors
- Use local antibiogram
- Reassess at 48-72 hours

TARGET



Culture-guided
de-escalation

- Review results
- De-escalate / Stop
- Narrow spectrum where possible

PROTECT



Antimicrobial
stewardship

- Right drug
- Right dose
- Right duration
- Prevent resistance

10 TAKE-HOME MESSAGE



RIGHT PATIENT



RIGHT CULTURE



RIGHT DRUG



RIGHT DOSE



RIGHT DURATION

The future of paediatric AMR management is
MECHANISM-DIRECTED THERAPY
rather than
ORGANISM-DIRECTED THERAPY



Understand the
resistance
mechanism



Optimise
PK/PD



Preserve
new
antibiotics



Protect
children from
superbugs



KEY MESSAGE



Not every septic child
needs a carbapenem.



Not every MDR pathogen
needs a new antibiotic.



Every child needs the right
antibiotic, at the right dose,
for the right duration.



**BETTER STEWARDSHIP
BETTER OUTCOMES
BETTER FUTURE**