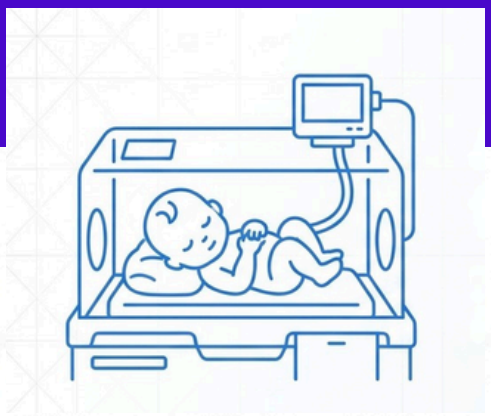
Antibiotic Strategies for Neonatal Sepsis

Navigating Efficacy, Emerging Resistance, and Practical Regimens

Source Meta-Analysis: Soni P., Matoria R., Nagalli M.M. "Antibiotic strategies for neonatal sepsis: navigating efficacy and emerging resistance patterns.' European Journal of Pediatrics (2025) 184:439.

The Dual Challenge of Neonatal Sepsis



37 Studies | 8,954 Neonates

Comprehensive assessment of empiric regimens across global NICUs (2005–2024).

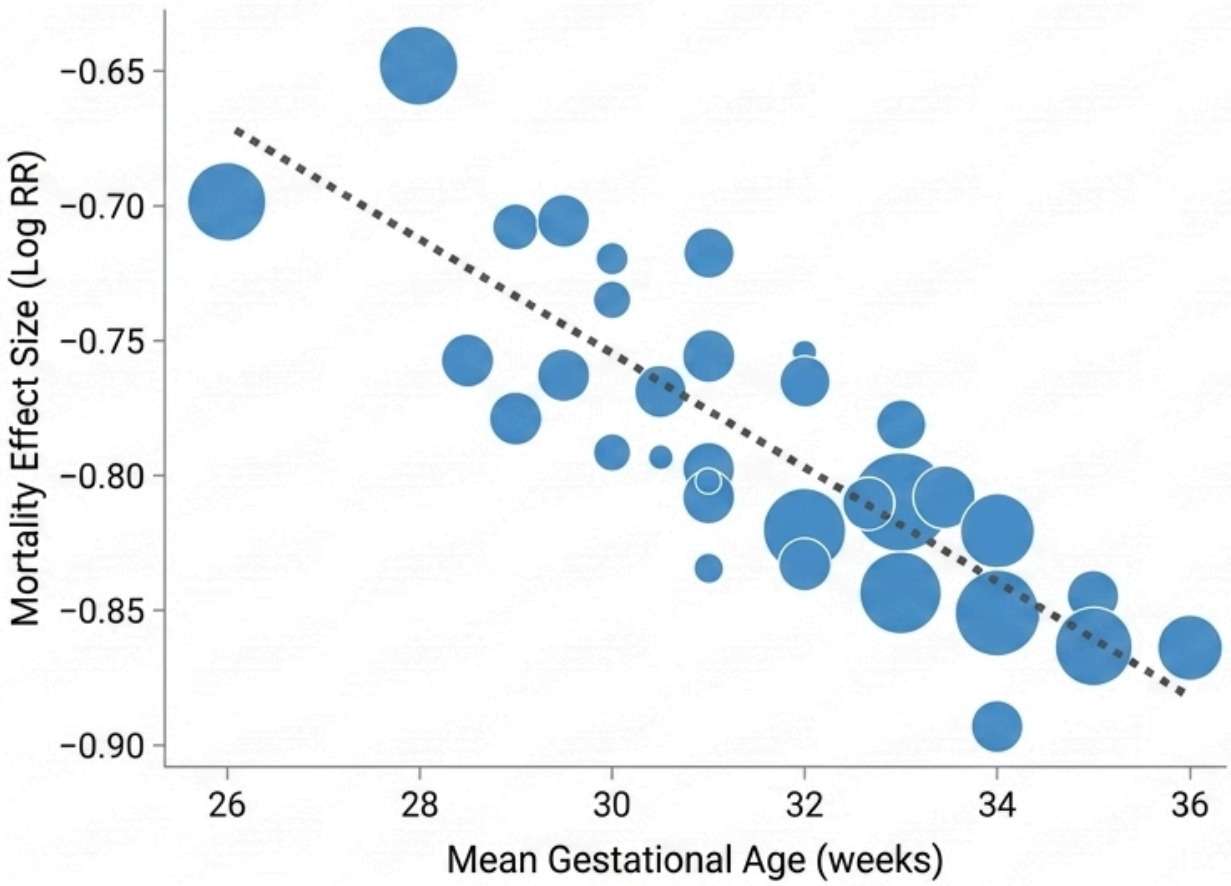
10% to 30% Mortality

Baseline neonatal sepsis mortality rates, highly dependent on appropriate empiric antibiotic selection.

Up to 45% AMR

Surging aminoglycoside and cephalosporin resistance complicating traditional empiric regimens.

The Gestational Age Factor: Immaturity Drives Mortality



Inverse Relationship

As gestational age decreases, mortality risk sharply increases ($\beta = -0.024$, $p=0.012$).

ELBW Vulnerability

Extremely Low Birth Weight (ELBW) neonates suffer from underdeveloped adaptive and innate immune responses, making empiric accuracy critical.

Defining the Threat: Early vs. Late-Onset Sepsis

Early-Onset Sepsis (EOS)	
Onset	≤ 72 hours of life
Transmission	Vertical (Mother to infant)
Typical Pathogens	GBS, *E. coli*, *Listeria monocytogenes*
Immune Context	Directly impacted by maternal microbiota and immature innate immunity

Late-Onset Sepsis (LOS)	
Onset	> 72 hours of life
Transmission	Horizontal (Nosocomial or community-acquired)
Typical Pathogens	Coagulase-negative *Staphylococci*, *S. aureus*, *K. pneumoniae*, *Pseudomonas*
Immune Context	Altered microbiota due to NICU environment and prior interventions

Efficacy Insights: Combination vs. Monotherapy

Synergy Effect

Broad Coverage

Beta-lactam + Aminoglycoside provides broad-spectrum coverage and synergistic bacterial killing against initial Gram-positive and Gram-negative threats.

Overall Mortality

22% Risk Reduction

Combination therapy (Ampicillin + Gentamicin) yields a pooled Risk Ratio of 0.78 [95% CI: 0.66–0.93] for mortality vs. monotherapy.

ELBW Neonates

20% Risk Reduction

Combination therapy retains significant protective effects in highly vulnerable extremely low birth weight infants (RR = 0.80).

Practical Protocol: Early-Onset Sepsis (EOS)

Standard First-Line Empirical Regimen (Adjust per Local Guidelines)

Medication	Indication	Practical Dose (mg/kg)	Dilution / Prep	Administration
Ampicillin (Beta-lactam)	Gram-positive coverage (GBS, Listeria)	50–100 mg/kg/dose (Interval based on GA/Postnatal age)	Reconstitute with Sterile Water/NS; Final conc: 50-100 mg/mL	IV push over 3–5 minutes
Gentamicin (Aminoglycoside)	Gram-negative synergy (E. coli)	4–5 mg/kg/dose (Interval: q24h to q48h based on GA)	Dilute in NS or D5W to 2 mg/mL	IV infusion over 30 minutes

** Source efficacy proven (Soni et al., 2025). Dosing placeholders reflect standard neonatal protocols; always verify against local NICU guidelines and renal function.*

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Medicines

Neonatal infections, excluding meningitis

IM | Intermittent IV | Oral

125mg Powder | 250mg Powder | 500mg Powder | 1g Powder

Weight (kg)
2

Gestational age at birth - WEEKS
32

Gestational age at birth - DAYS
2

Postnatal age - DAYS
10

Desired dose (mg/kg/dose)

Suggested dose: 25 to 50 mg/kg/dose

Additional information
Bibliographical references

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Medicines

at birth - WEEKS

at birth - DAYS

DAYS

Desired dose (mg/kg/dose)
50

Suggested dose: 25 to 50 mg/kg/dose

Ampicillin
Intermittent IV - 500mg Powder

Postmenstrual age	33 weeks and 5 day(s)
Dose	100mg
Interval	12/12h

Reconstitution

Reconstitute with SWFI	5mL
Volume after reconstitution	5.2mL
Concentration after reconstitution	96mg/mL
Dose after reconstitution	1.04mL

Dilution

Dilute the reconstituted dose with NS	2.29mL
Final concentration after dilution	30mg/mL
Total volume to be administered	3.33mL
Infusion rate	10-15 min

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Medicines

Ampicillin
Intermittent IV - 500mg Powder

Postmenstrual age	33 weeks 5 (s)
Dose	100mg
Interval	12/12h

Reconstitution

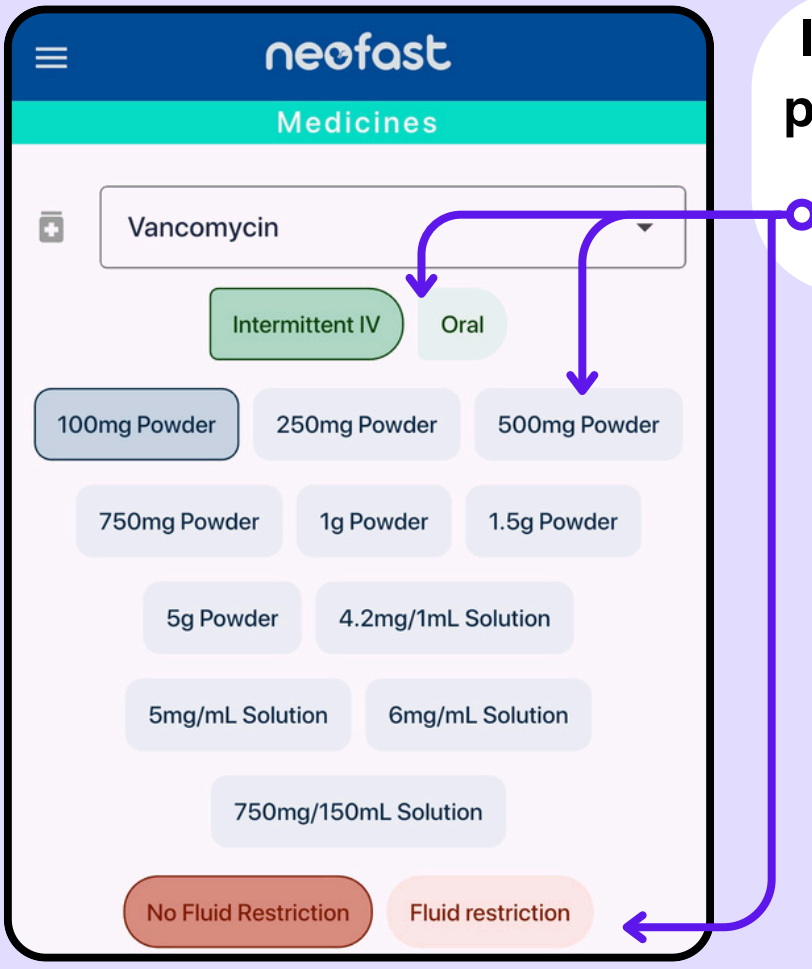
Reconstitute with

Practical Protocol: Late-Onset Sepsis (LOS)

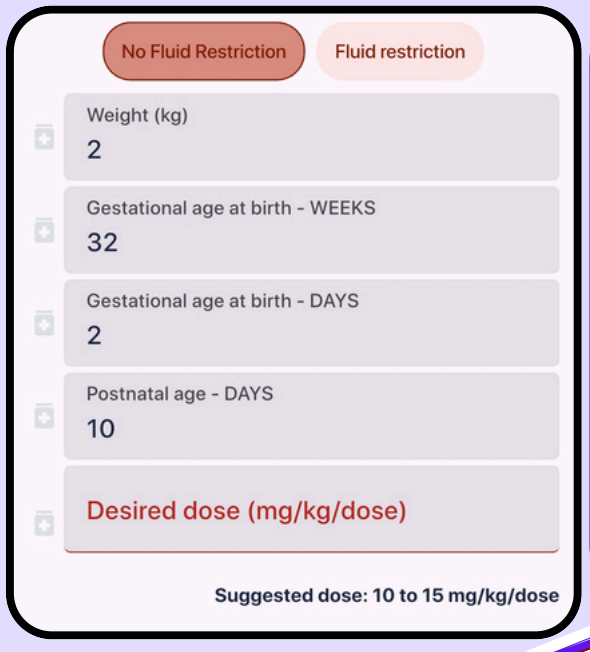
Escalated Empirical Regimen (Suspected Nosocomial / MDR Pathogens)

Medication	Indication	Practical Dose (mg/kg)	Dilution / Prep	Administration
Vancomycin	Gram-positive / MRSA coverage	10–15 mg/kg/dose (Interval based on GA/Serum Cr)	Dilute in NS or D5W to max 5 mg/mL	IV infusion over 60 minutes (Monitor trough levels)
Cefotaxime (or Aminoglycoside)	Broad Gram-negative / Meningitis risk	50 mg/kg/dose (q8h to q12h based on GA)	Dilute in NS or D5W to 20-40 mg/mL	IV infusion over 15–30 minutes

** Use restricted to cases of suspected Amp/Gent resistance. High risk of altering gut microbiota; rapid de-escalation required post-culture.*



In NeoFast, mark the route of administration, the presentation and whether there is fluid restriction (this influences the concentration of the medication).



Then, fill in the newborn data. Note that the Suggestion of the dose will appear as soon as you fill in all of the above fields.

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Medicines

Intermittent IV | Oral

100mg Powder | 250mg Powder | 500mg Powder

750mg Powder | 1g Powder | 1.5g Powder

5g Powder | 4.2mg/1mL Solution

5mg/mL Solution | 6mg/mL Solution

750mg/150mL Solution

No Fluid Restriction | Fluid restriction

Weight (kg)
2

Gestational age at birth - WEEKS
32

Gestational age at birth - DAYS
2

Postnatal age - DAYS
10

Desired dose (mg/kg/dose)
15

Suggested dose: 10 to 15 mg/kg/dose

Vancomycin

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Medicines

Vancomycin
Intermittent IV - 100mg Powder

Postmenstrual age	33 weeks and 5 day(s)
Dose	30mg
Interval	12/12h

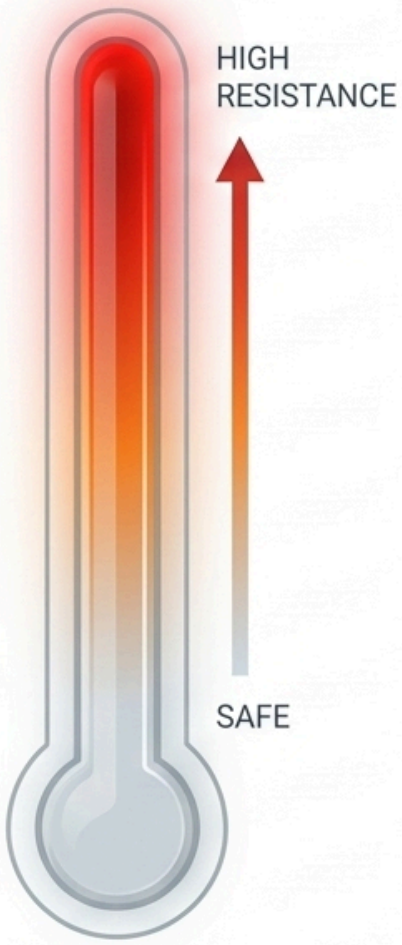
Reconstitution

Reconstitute with SWFI	2mL
Concentration after reconstitution	50mg/mL
Dose after reconstitution	0.6mL

Dilution

Dilute the reconstituted dose with NS , D5W, LR	5.4mL
Final concentration after dilution	5mg/mL
Total volume to be administered	6mL
Infusion rate	60 min

The AMR Escalation: Once-Reliable Agents Losing Efficacy



Aminoglycosides

20% to 45% Resistance

Severe threat to standard empiric combinations, particularly from Gram-negative bacilli.

3rd-Gen Cephalosporins

15% to 35% Resistance

Driven by the widespread emergence of Extended-Spectrum Beta-Lactamases (ESBLs).

Carbapenems

5% to 10% Resistance

Emerging global threat (especially in NICUs) largely due to carbapenemase-producing *K. pneumoniae*.

Resistance Matrix: Gram-Negative Pathogens

	Aminoglycosides	3rd-Gen Cephalosporins	Carbapenems	
Escherichia coli	20–35%	10–25%	3–8%	Rising ESBL producers.
Klebsiella pneumoniae	25–45%	20–35%	5–10%	Carbapenem-resistant strains emerging.
Acinetobacter baumannii	15–30%	10–20%	2–5%	Multidrug-resistant patterns in regional NICUs.

Resistance Profile: Gram-Positive Pathogens

Staphylococcus aureus

High Concern

10% to 25%
MRSA Prevalence

Impact: Necessitates Vancomycin consideration in Late-Onset Sepsis protocols where central line infections or nosocomial spread are suspected.

Streptococcus spp.

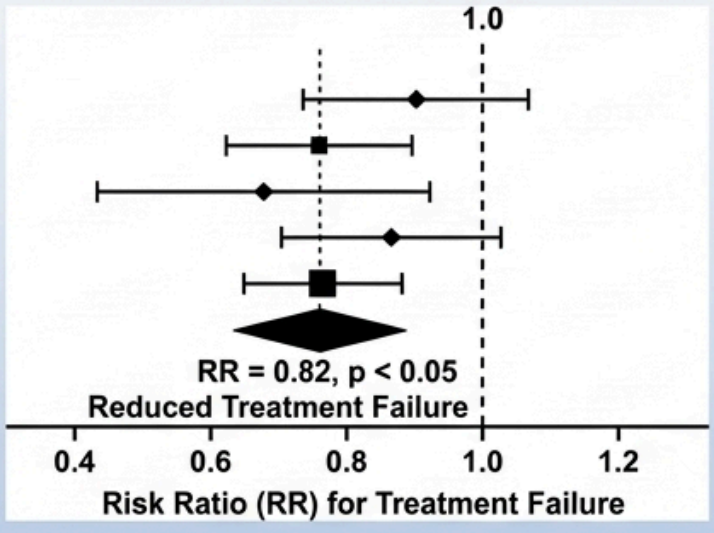
Stable Susceptibility

5% to 15%
Pen/Amp Resistance

Impact: Traditional beta-lactams remain highly viable and effective for Early-Onset Sepsis vertical transmission cases.

The Clinical Tightrope: Efficacy vs. Toxicity

Efficacy Factor



- Combination therapy significantly reduces the risk of treatment failure (RR = 0.82, $p < 0.05$).
- Prevents persistent bacteremia and reduces the need for emergency antibiotic escalation.

Toxicity Restraints

- **Nephrotoxicity & Ototoxicity**: Direct risks associated with Aminoglycoside use in premature kidneys.
- **Microbiota Disruption**: Broad-spectrum drugs foster further resistance and dysbiosis in the neonatal gut.
- **Action**: Mandates strict therapeutic drug monitoring (TDM) of serum trough levels.

Evaluating Adjunctive Therapies

Intravenous Immunoglobulin (IVIG)

Mechanism: Aims to supplement the underdeveloped adaptive immune system of ELBW neonates.

VERDICT: Mixed Results

Did not yield consistent mortality benefits across 7 evaluated studies.

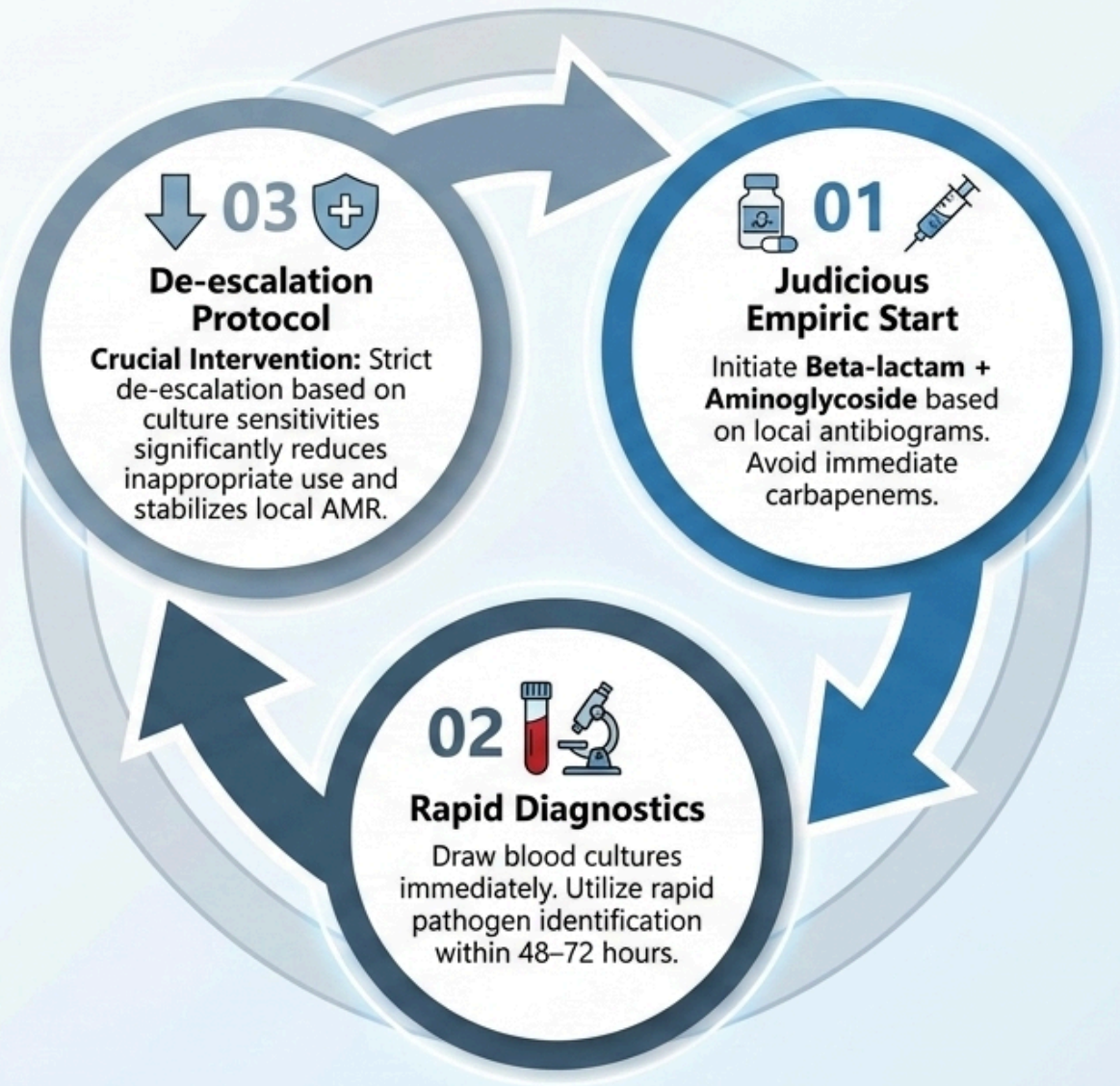
Prophylactic Fluconazole

Mechanism: Targets fungal pathogens and opportunistic infections in highly susceptible hospitalized neonates.

VERDICT: Needs Further Research

While fungal sepsis is a threat, broad prophylactic benefit remains context-dependent.

The Vital Role of Antibiotic Stewardship (ASP)



Synthesis: Neonatal Sepsis Clinical Pathway

Suspected Neonatal Sepsis
(Evaluate GA, Onset timing)

EOS (< 72h)

Empiric: Ampicillin + Gentamicin

LOS (> 72h / NICU)

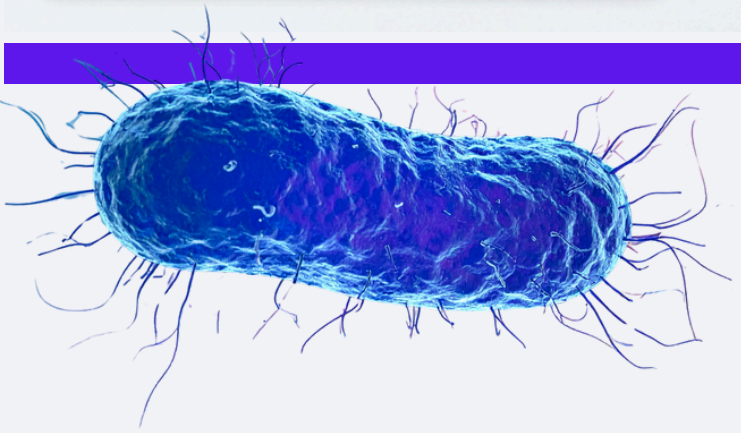
Empiric: Vancomycin + Aminoglycoside or **3rd-Gen Ceph**

48-72 Hour Check: Monitor clinical response & await culture results

Culture Negative + Clinically Stable → Discontinue antibiotics (Stewardship win)

Culture Positive
→ Tailor therapy to specific pathogen sensitivities

Culture Negative + Worsening
→ Re-evaluate, consider escalation or fungal coverage



Key Takeaways & Clinical Directives

Left Pillar

Combination Efficacy

Ampicillin plus gentamicin remains the most effective foundational regimen, offering significant mortality reduction (RR 0.78), even for highly vulnerable ELBW neonates.

Center Pillar

Regional Customization

With aminoglycoside resistance hitting 45% globally, empirical guidelines must be customized using local NICU antibiograms. Universal protocols are obsolete.

Right Pillar

Aggressive Stewardship

The fight against AMR requires rigid adherence to de-escalation. Rapid diagnostic integration and strict therapeutic monitoring are the only ways to preserve current antibiotic viability.

Reference: Soni P. et al., European Journal of Pediatrics (2025).