MMed and DCH Lectures

Weekly by Zoom

Prof Trevor Duke

MMed and DCH Lectures

Antibiotics and antibiotic resistance

August 24, 2020

Prof Trevor Duke

Overview

- Steps in antibiotic prescribing
- Antibiotic mechanisms
- Common sepsis pathogens in neonates and children
- Resistance mechanisms
- ESBL
- MRSA
- Carbapenemase resistant Gram negatives

Steps in antibiotic prescribing

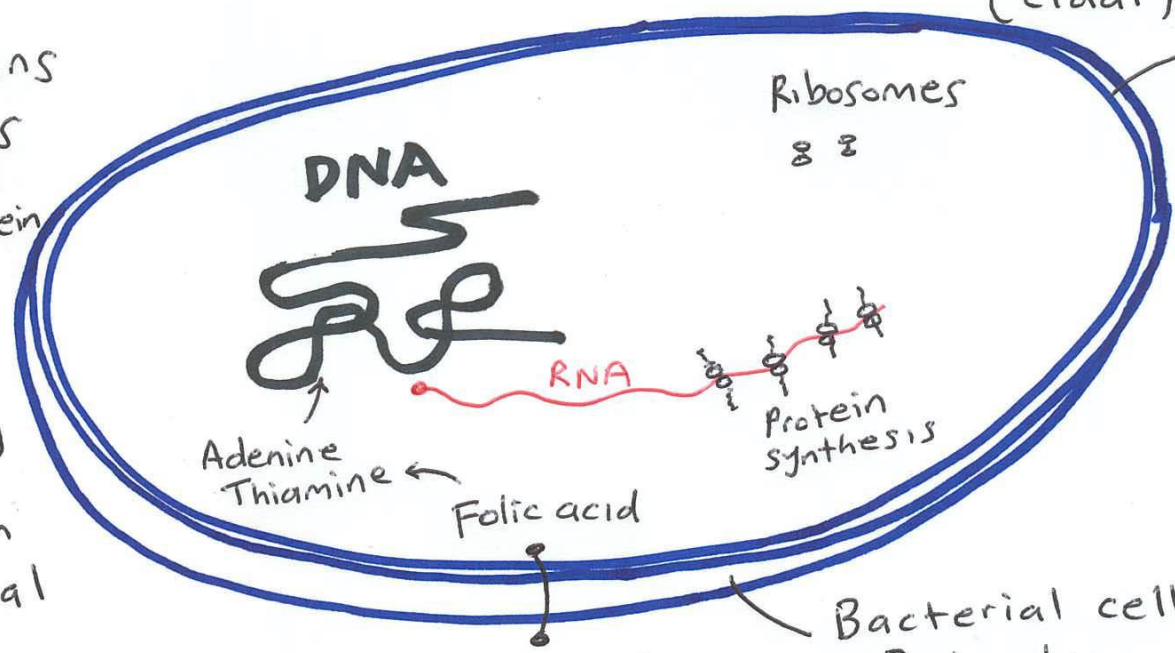
1. Is an antibiotic needed? Is the child likely to have a bacterial infection?
2. Take cultures before giving antibiotics
3. Choose an appropriate standard antibiotic
4. Assess likelihood of antibiotic resistance
5. Choose drug with adequate tissue penetration
6. Aim for single drug with desired spectrum of activity
7. Ensure correct dose and route of administration
8. Start antibiotic without delay in severe infections
9. Ensure early source control
10. Antibiotic stewardship

Inhibition of cell wall synthesis

Penicillins
Cephalosporins
Carbapenems
Bind Penicillin Binding Protein on Peptidoglycan Cell wall
↑ Permeability
→ cell destruction
∋ Bacteiacidal

Disruption of cell membrane function

Disrupt phospholipid bilayer
→ ↑water uptake → cell death (cidal) - Polymixin



Inhibition of Folic Acid synthesis

Cotrimoxazole

Inhibition of protein synthesis

50s RNA subunit Erythromycin Chloramphenicol

30s RNA subunit Tetracycline, Aminoglycosides Gentamicin.

Antibiotic choices

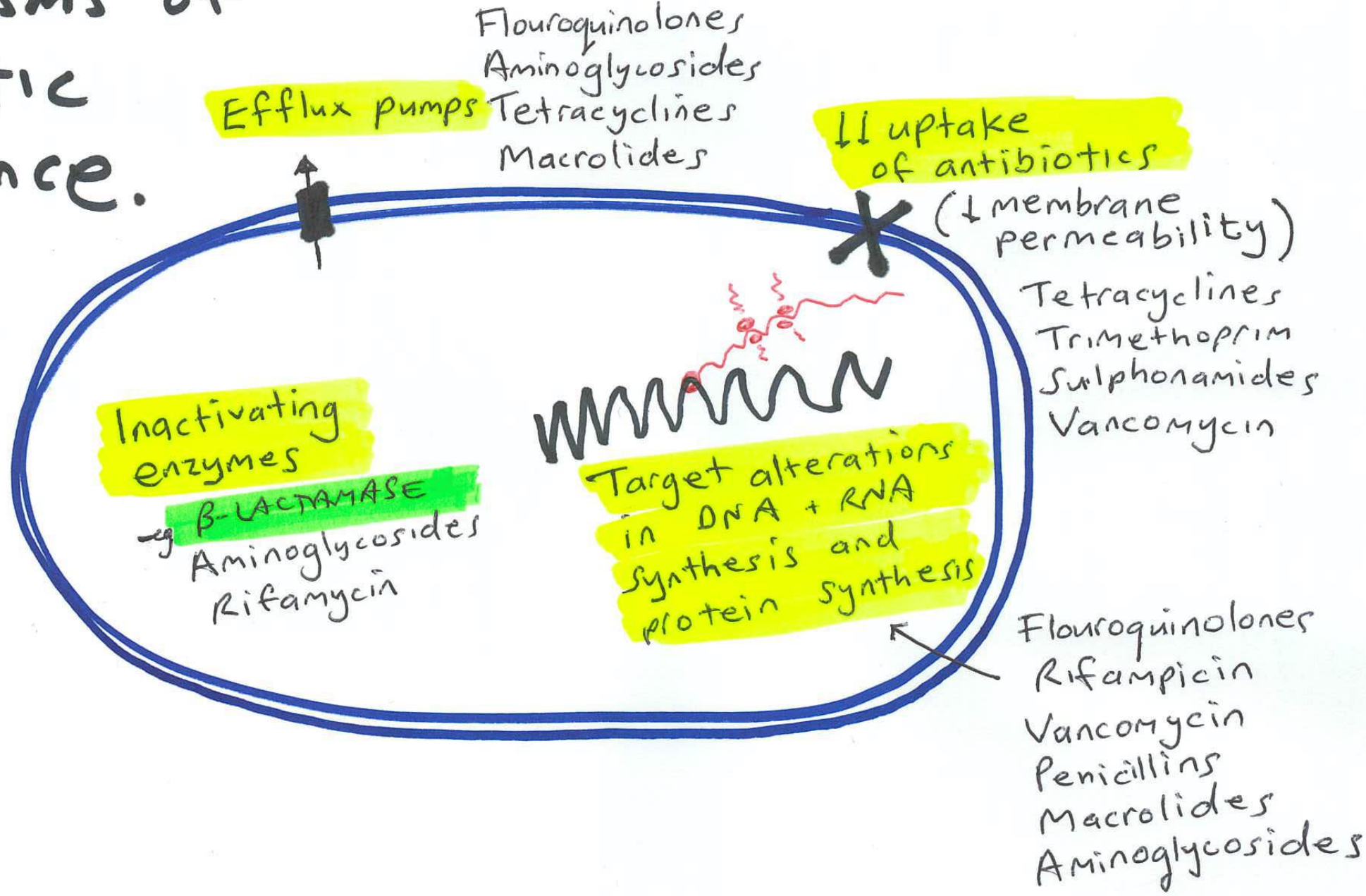
Gram positive

- Penicillin
- Amoxicillin
- Flucloxacillin
- Macrolides
- Cotrimoxazole
- Ciprofloxacin
- Glycopeptides - vancomycin

Gram negative

- Aminoglycosides
- Ceftriaxone / cefotaxime
- Meropenem
- Ciprofloxacin
- Cotrimoxazole

Mechanisms of Antibiotic Resistance.



β-lactamases

- Enzymes that can hydrolyse the β-lactam ring of penicillins and cephalosporins making them inactive
- Now many different β-lactamases,
  - Penicillinases (1940s)
  - Cephalosporinases (ESBL: 1980s)
  - Carbapenemases (2000s)
- How to overcome β-lactamases: **Initially**
  - Antibiotics with new structures that are more resistant to β-lactamases, such as "3rd generation" cephalosporins: ceftriaxone, cefotaxime, and ceftazidime.
  - Inhibitors of beta-lactamase – e.g. clavulanic acid (with amoxicillin); tazobactam (with piperacillin)

Then ESBL (1983)

- ESBL plasmid-coded, and the plasmids carry genes that confer resistance to aminoglycosides also
- Treatment options for ESBL:
  - Carbapenems: e.g. meropenem
  - Amikacin
  - Tazobactam (ESBL inhibitor) plus piperacillin

Other bacteria

- Pseudomonas resistance mediated by other mechanisms:
  - Production of **metallo-proteinases (enzymes)**
  - **Lack of drug penetration** due to mutations in the porins
  - Loss of outer membrane proteins and **efflux pumps**

- MRSA
  - **mecA gene** encodes penicillin binding protein 2a with low affinity for all β-lactam antibiotics
  - Treatment options: Vancomycin, Clindamycin, Rifampicin

Increase in sepsis due to multi-resistant enteric gram-negative bacilli in Papua New Guinea

Trevor Duke, Audrey Michael

THE LANCET • Vol 353 • June 26, 1999

Between April 1998 and March 2000, multi-resistant enteric gram negative sepsis occurred in 106 of 5331 paediatric admissions (2%), but caused 87 (25%) of 353 deaths

Bacteria	Nosocomial	Community acquired	Chloramphenicol sensitivity	Gentamicin sensitivity
Klebsiella sp*	12	2	0	3
*Pseudomonas aeruginosa**	7	4	0	2
*Escherichia coli**	1	7	1	5
Citrobacter freundii	1	2	1	0
Enterobacter sp	3	4	0	3
Morganella morganii	0	2	2	2
Burkholderia capacia	2	1	1	0
Proteus mirabilis	2	1	0	2
Acinetobacter sp	1	0	0	1
Serratia sp	0	2	0	1
Providentia sp	0	1	1	1
Aeromonas sp	0	1	0	1
Alcaligenes sp	0	1	0	1

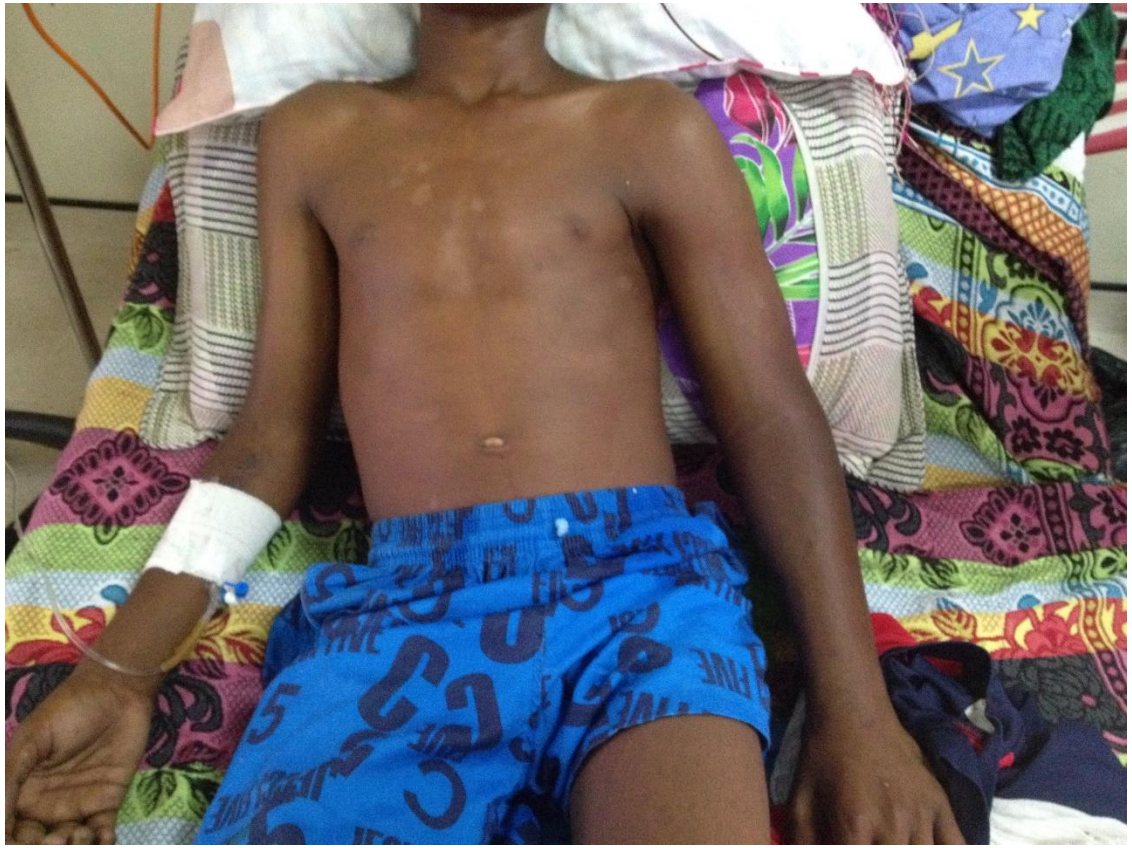
*We could not be certain of the origin of one additional isolate of each of these three bacteria.

Sensitivity of bacterial isolates and place of acquisition

Risk factors

- Village births
- Prolonged hospital stay
- Kwashiorkor in adopted children
- Previous treatment with broad-spectrum antibiotics

- 12 year old boy
- Home tattoo with a friend
- 2 days later fever, swollen left arm
- Lethargy, difficult breathing
- What could be the diagnosis?



- 2 year old boy
- Fever, swollen eye

Methicillin-Resistant Staphylococcus Aureus in Melanesian Children with Haematogenous Osteomyelitis from the Central Highlands of Papua New Guinea

*Izzard Aglua[1], Jan Jaworski[2], Jimmy Drekore[3], Bohu Urakoko[2], Harry Poka[4], Audrey Michael[5], Andrew Greenhill[6]

70 children with osteomyelitis
Staphylococcus aureus (S. aureus) grown in 47 (67%)
Much community-acquired MRSA

- Resistance
  - Penicillin: 91.5%
  - Methicillin: 85.1%
  - Oxacillin 89.4%
  - Ampicillin: 93.6%
  - Ceftriaxone: 80.9%
- Sensitivity *
  - Gentamicin: 91.5%
  - Erythromycin: 93.6%
  - Clindamicin: 93.6%
  - Chloramphenicol: 93.6%
  - Cotrimoxazole: 95.7%

* Vancomycin, Linezolid, Rifampicin not tested

Resistance in dysentery in PNG

Shigella spp. Antimicrobial Drug Resistance, Papua New Guinea, 2000–2009

Table. Antimicrobial drug resistance of *Shigella* spp., Papua New Guinea, 2000–2009*

Drug	Total no. isolates tested	Sensitivity	*Shigella* sp., no. (%) isolates					Total
			S. boydi	*S. dysenteriae*	*S. flexneri*	*S. sonneii*	Unknown sp.	
Amoxicillin	98	S	0	1 (33)	2 (2)	0	1 (100)	4 (4)
		R	3 (100)	2 (67)	87 (98)	2 (100)	0	94 (96)
Cephalexin	46	S	2 (67)	2 (100)	38 (100)	2 (100)	1 (100)	45 (98)
		I	1 (33)	0	0	0	0	1 (2)
		R	0	0	0	0	0	0
Ciprofloxacin	41	S	2 (67)	NA	35 (100)	1 (100)	2 (100)	40 (98)
		I	1 (33)	NA	0	0	0	1 (2)
		R	0	0	0	0	0	0
Chloramphenicol	114	S	0	2 (50)	9 (9)	2 (100)	1 (50)	14 (12)
		I	0	2 (50)	28 (28)	0	1 (50)	31 (27)
		R	4 (100)	0	64 (63)	0	0	68 (60)
Naladixic acid	13	S	1 (100)	0	8 (100)	1 (100)	1 (50)	11 (85)
		R	0	1 (100)	0	0	1 (50)	2 (15)
Co-trimoxazole	76	S	1 (25)	1 (33)	9 (14)	0	0	11 (14)
		R	3 (75)	2 (67)	57 (86)	2 (100)	1 (100)	65 (86)

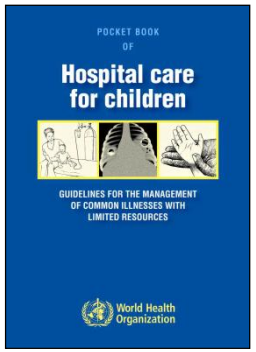
*S, sensitive; R, resistant, I, intermediate; NA, not applicable.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 11, November 2010

Effect of overuse of antibiotics on Multi-Resistant Organisms (MRO)

- Cephalosporins and other broad-spectrum β-lactams:
  - More resistant *Enterobacter, Serratia* spp
  - Extended spectrum β-lactamase producers (ESBL)
  - MRSA, VRE
  - *Clostridium difficile*
- Flouroquinolone
  - Foodborne pathogens: Campylobacter, *Salmonella typhi*
- Aminoglycosides
  - Acquisition of aminoglycoside-modifying enzymes by many strains of bacteria
  - *Stenotrophomonas maltophilia*

WHO recommendations on neonatal sepsis



Treatment

Antibiotic therapy

- Admit to hospital
- Where blood cultures are available, obtain blood cultures before starting antibiotics
- For any of these signs, give ampicillin (or penicillin) and gentamicin (for dosages see pages 62–66)
- Give cloxacillin (if available) instead of penicillin if extensive skin pustules or abscesses as these might be signs of Staphylococcus infecton
- Most serious bacterial infections in neonates should be treated with antibiotics for at least 10 days
- If not improving in 2–3 days the antibiotic treatment may need to be changed, or the baby referred

Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics—systematic review and meta-analysis

Lilian Downie,[1] Raffaela Armiento,[1] Rami Subhi,[1] Julian Kelly,[1,2] Vanessa Clifford,[2] Trevor Duke[1]

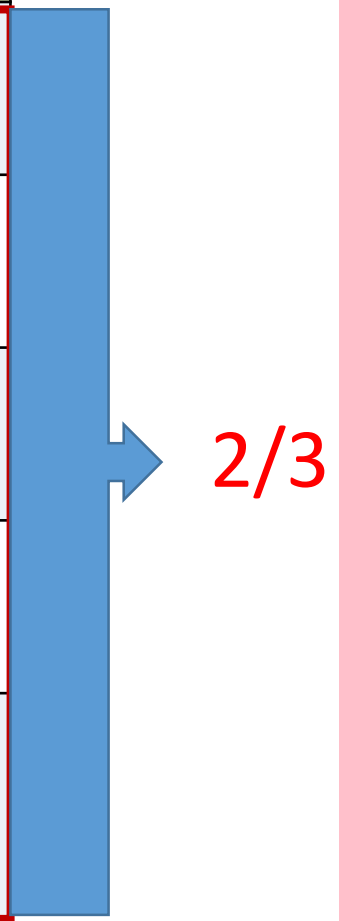
- 19 studies, 13 countries

Africa	9
Asia	8
Middle East	1
Multi-country	1

- 4049 isolates

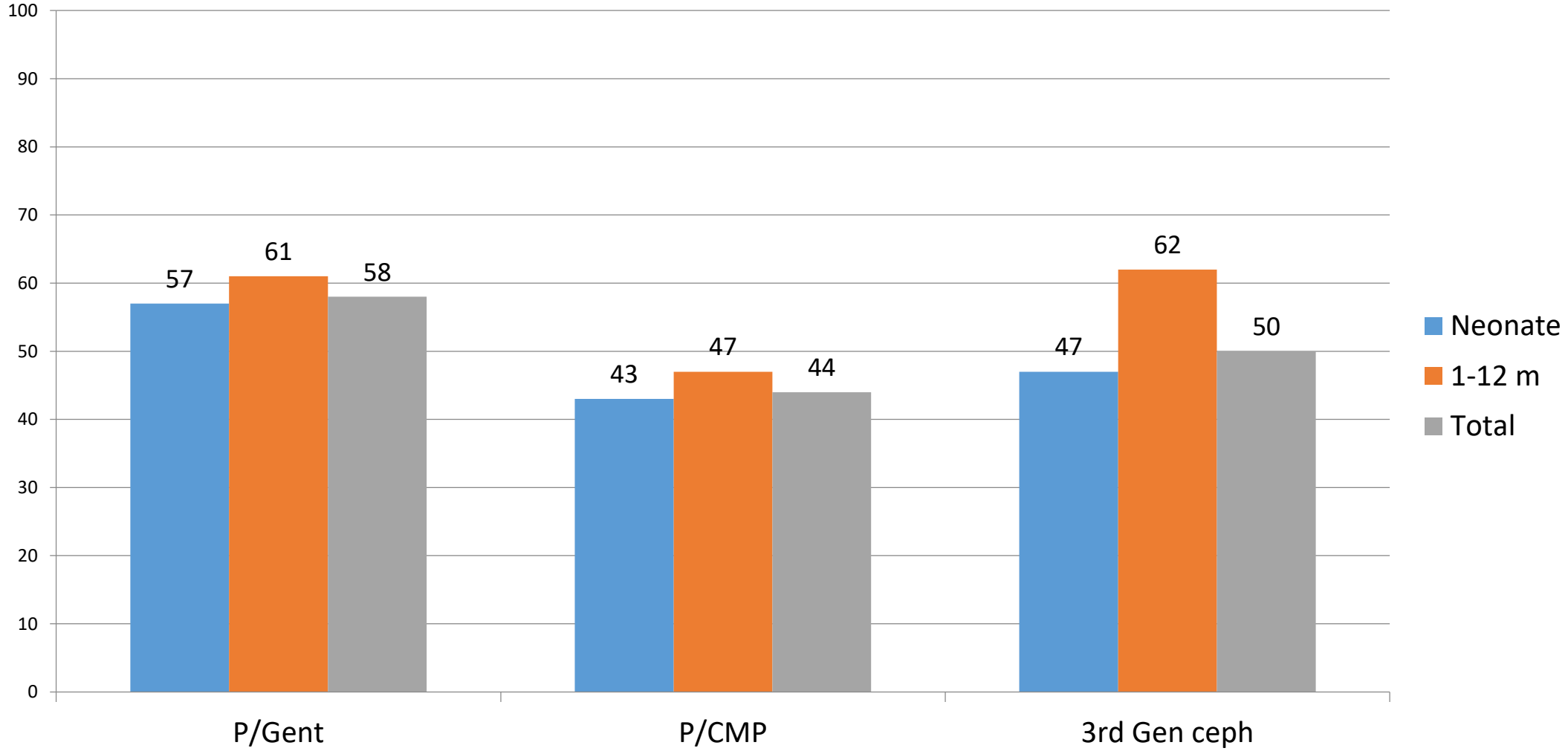
Neonates	76%
1-12 months	24%

Pathogen	Total number (% of total)	Number (% of total) neonates	Number (% of total) infants >1 month
Staphylococcus aureus	920 (23%)	772 (25%)	148 (15%)
Klebsiella spp	758 (19%)	655 (21%)	103 (11%)
E. coli	348 (9%)	244 (8%)	104 (11%)
Salmonella spp	297 (7%)	155 (5%)	142 (15%)
Streptococcus pneumoniae	256 (6%)	108 (4%)	148 (15%)
Streptococcus agalactiae	181 (5%)	179 (6%)	2 (0.2%)



Pathogen	Pen/ Amp	Gent	CMP	3-G Ceph	Cloxacillin
Staphylococcus aureus	12	83	54	51	50
Klebsiella spp	5	21	19	28	-
E. Coli	12	64	31		-
Salmonella spp	23	74	46	94	-
Streptococcus pneumoniae	90	7	92	90	-
Streptococcus agalactiae (GBS)	99	2	80	38	-

Antibiotic sensitivity



Antibiotic coverage of different combinations

- Neonates
  - Penicillin & gentamicin covered 58%
  - Third-generation cephalosporins covered 47%, $p<0.001$
- Older infants
  - Penicillin & gentamicin covered 61%
  - Third-generation cephalosoporins covered 63%

Antibiotic tissue penetration

Antibiotic	**CSF**	**Lung**	**Soft tissue / bone**	**Urinary tract**
Ampicillin	Good (high doses)	Good	Good	Good
Cloxacillin		Fair	Fair	No data
Clindamycin	Poor	No data	No data	No data
Aminoglycosides	Poor	Poor	Fair	Good (if normal GFR)
Ceftriaxone	Good (high doses)	Good	Good	Good
Ciprofloxacin	Good (high doses)	Good	Good	Good
Co-trimoxazole	Good	Good	Good	Good
Augmentin (amoxycillin-clavulinic acid)	Poor	Good	Good	Fair
Meropenem	Good (high doses)	Good	Good	Good
Vancomycin	Poor	Fair	Poor	Good
Linezolid	Good	Good	Good	Good

An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker *Lancet* 2000, **355:** 973–78

2 NNUs, cross-over trial, The Netherlands

A: Penicillin and Tobramycin
B: Amoxycillin and Cefotaxime

- Three neonates treated with the penicillin-tobramycin regimen became colonised with resistant bacilli versus 41 neonates on the amoxicillin-cefotaxime regimen ($p<0{\cdot}001$).
- The relative risk for colonisation with strains resistant to the empirical therapy per 1000 patient days at risk was 18 times higher for the amoxicillin-cefotaxime regimen compared with the penicillin-tobramycin regimen (95% CI 5·6–58·0)
- **Cephalosporins are not the answer** (except for meningitis, and proven Gram negative sepsis)

Infection control *and* Antibiotic stewardship

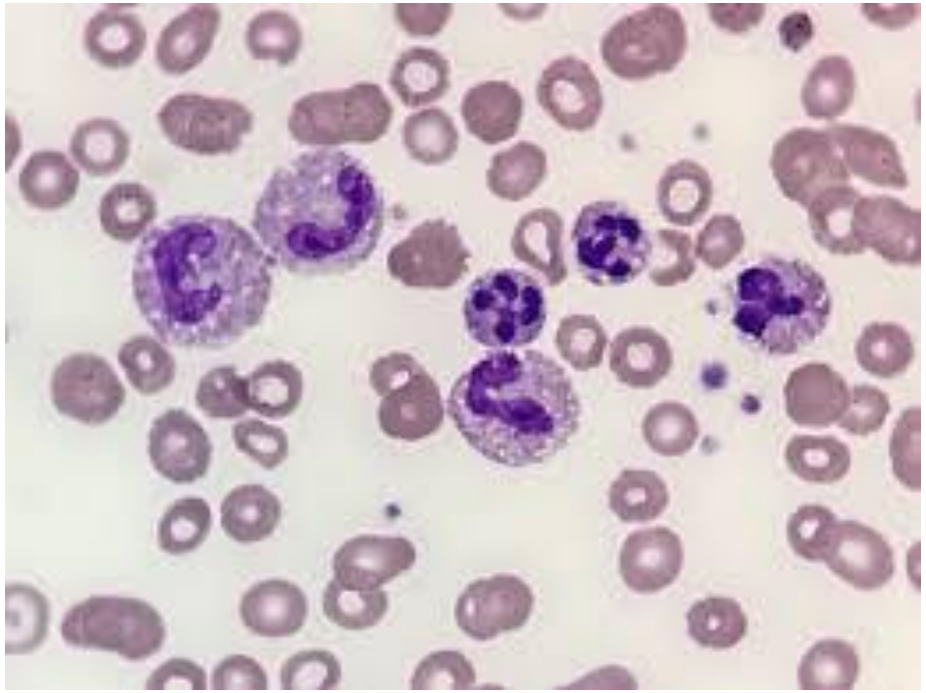
- Hand washing, face masks, gowns, gloves, isolation
- Reduce intravenous drip infections
- Enteral feeding, breast feeding
- Shorter courses of antibiotics to reduce exposure, and for patient safety
- Weekly antibiotic stewardship round

Weekly antibiotic stewardship round

1. Review all patients who are on antibiotics
2. Ensure there is a clear indication written, and a review date or a stop date
3. Check the doses are appropriate, and appropriately adjusted for renal function
4. Check for drug toxicity risk (such as several nephrotoxic drugs)
5. Review the clinical indication, microbiology and inflammatory markers (FBE markers, procalcitonin)
6. Check that the antibiotics prescribed are consistent with guidelines
7. Make recommendations about scaling back or ceasing antibiotics as appropriate, reducing the number of antibiotics, narrowing the spectrum, and duration of treatment

FBE markers of bacterial sepsis

- ↑↑ or ↓↓ WCC
- ↑↑ or ↓↓ Neutrophils
- ↑↑ Bands, myelocytes, metamyelocytes
- ↑↑ Platelets >800,000
- ↓ Platelets <100,000
- ↑↑ RDW
- “Toxic granulation of neutrophils”



- ↑↑ Procalcitonin
- ↑↑ESR