

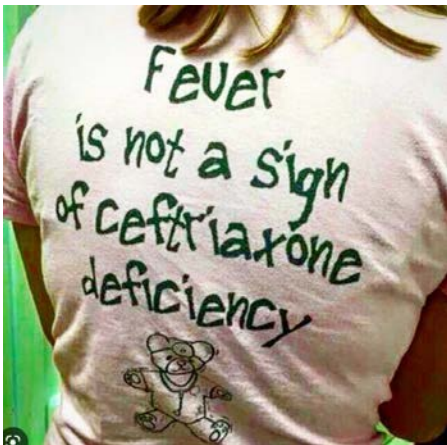
Choosing antibiotics wisely

*Who really needs ceftriaxone and
pip/tazobactam?*

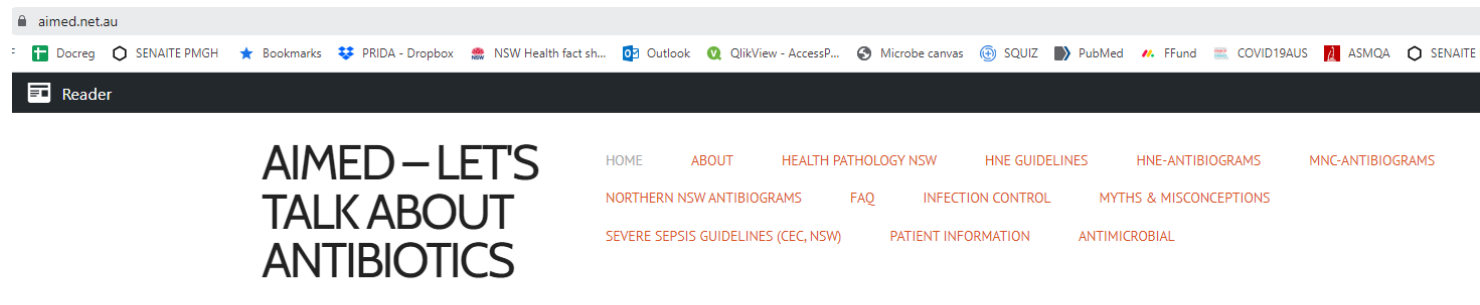
John Ferguson

Infectious Diseases & Microbiology

HNE Health, November 2022



<http://aimed.net.au>
District AMS resource



AMS website

<http://aimed.net.au>

- Subscribe email for weekly updates
- More than 100 searchable prior postings

CATEGORY CLOUD

Abdomen/GIT Allergy **AMS**
strategy Antibigrams
Antimicrobial Bloodstream CNS
Infections Dentistry **General**
Practice Guidelines Health
Pathology NSW HNE LHD
Hospital practice
Infection prevention **Journal**
paper Microbiology Myths &
Misconceptions News Patient
information Respiratory Salutory tale
SexuallyTxDis Skin/soft tissue
Uncategorized Urinary tract infections
Weird facts



Functions of antibiotic Rx

Function	Principles
Empirical Rx	Guided by local antibiogram TG: Antibiotic recommendations Local guidance – CAP, HAP, SABSI
Directed Rx	Based on microbiology results from the patient Rx to match the bug Route and duration dependent on site/bug
Prophylaxis	Single dose usually

HNELHD Cumulative Antibigrams 2021: John Hunter Hospital: Urine

Very moderate
levels of Gram
negative resistance

Strong AMS effort

Very moderate levels of Gram negative resistance strong AMS effort	Ampicillin		Benzylpenicillin		Cefazolin (Urine)		Flucloxacillin		Gentamicin		Nitrofurantoin		Trimethoprim		Amikacin		Cefepime		Ceftazidime		Ceftriaxone		Ciprofloxacin		Meropenem		Norfloxacin		Piperacillin and tazobactam		
	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	%S	n	
Organism																															
Gram-negative																															
Escherichia coli	59	1598			91	1346			94	1598	99	1598	80	1598	100	1540	97	1535	95	1595	94	1590	90	1592	100	NA	87	1597	95	1531	
Klebsiella pneumoniae	0	204			96	175			96	203			89	204	100	199	98	197	97	204	97	204	95	204	99	NA	93	202	91	199	
Pseudomonas aeruginosa									92	180					93	217	96	217	96	224			91	225	95	NA		91	217		
Proteus mirabilis	86	101			99	73			100	101			84	101	100	93	100	93	98	101	100	101	96	101	100	NA	96	101	100	92	
Enterobacter cloacae complex									83	83			75	83	96	80	94	80					81	83	95	NA	76	83			
Klebsiella oxytoca	0	57			58	50			98	57			91	57	100	54	98	54					100	56	97	NA	96	57	83	54	
Klebsiella (Enterobacter) aerogenes									100	38			97	38	100	38	100	38					100	38	100	NA	95	38			
Morganella morganii									85	34			88	34	100	33	97	34					97	34	100	NA	97	34			
Serratia marcescens									100	32			97	31	100	32	100	31					91	32	100	NA	84	32			
Gram-positive																															
Enterococcus faecalis	100	318									100	318																			
Enterococcus faecium	1	80																													
Staphylococcus aureus			30	33			88	52					100	44																	

<https://aimed.net.au/2022/11/22/antibiograms-and-commentaries-2021-data-hunter-new-england-lhd/>

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LMIC comparison; excessive ab use driving high community and healthcare Gram neg resistance

Port Moresby General Hospital Cumulative Antibigram, 2018 data

Table 1 - Urinary isolate antibiogram (adults and children)

Organism type			Isolates	% total	Ampicillin / Amoxycillin	Amoxycillin+ clavulanate	Cefaclor	Nitrofurantoin	Co-trimoxazole (Septrim)	Gentamicin (aminoglycoside)	Amikacin	Ceftriaxone	Ciprofloxacin / Norfloxacin
All isolates			998	70 miscellaneous/contaminant species excluded.									
Gram negative isolates	<i>Escherichia coli</i>		402	40%	10%	28%	n/a	79%	21%	65%	79%	68%	70%
											155		
	<i>Klebsiella</i> species		327	33%	R	15%	n/a	40%	20%	36%	86%	32%	59%
											228		
	<i>Enterobacter</i> -like species*		53	5%	R	R	R	42%	28%	60%	82%	59% **	62%
							31	36	35	17	37	37	
Gram negative isolates	<i>Proteus</i> species		63	6%	20%	39%	n/a	R	19%	42%	91%	48%	52%
											34		
	<i>Pseudomonas aeruginosa</i>		36	4%	R	R	R	R	R	29%	52%	R	36%
Gram positives											23		
	<i>Staphylococcus saprophyticus</i>		16	2%	S	S	S	S	n/a	n/a	n/a	S	n/a
Gram positives	<i>Streptococcus agalactiae</i> (group B strep)		0	0%	S	S	S	S	n/a	R	R	S	n/a
Gram positives	<i>Enterococcus</i> species		31	3%	S	S	R	S	R	R	R	R	R

High levels of R

-augmentin

-bactrim

-ceftriaxone

-cipro/norflo

-gentamicin

Emerging R

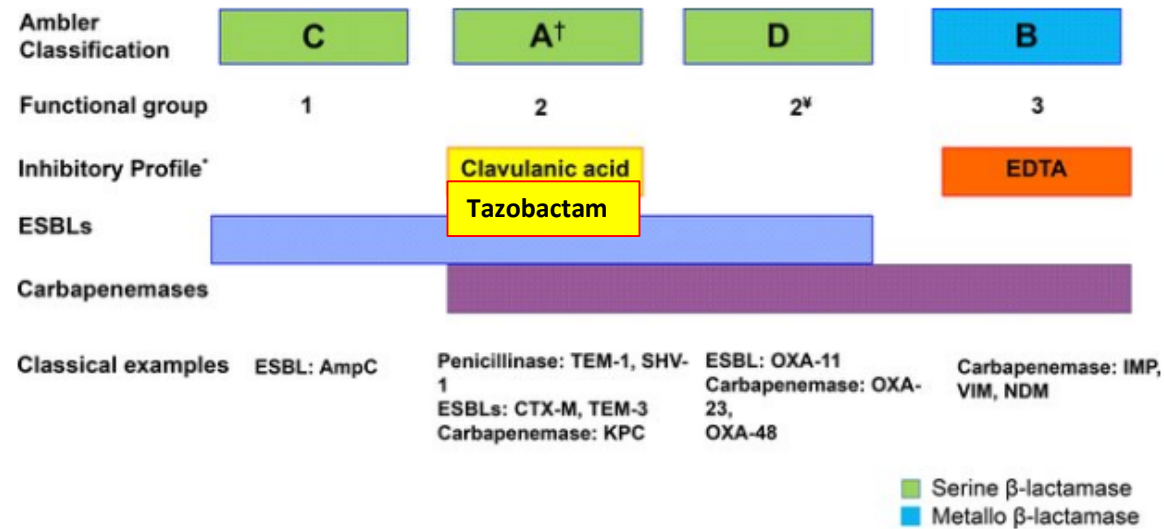
-meropenem

Gram negatives and betalactams

Species/Family	Intrinsic resistance (other)	Acquired R to TGC (ESBL)	Emerging resistance
<i>Enterobacterales</i> - <i>E. coli</i> - <i>Klebsiella</i>	Benzylpen (LPS wall) Ampicillin (<i>TEM</i> - class A BL)	<i>CtxM</i> (class A BL) <i>AmpC</i> BL (class C)	<i>IMP</i> / <i>GES</i> / <i>NDM</i> etc (CP-classes A, C or D) FQ R
“ <i>ESCPMM</i> ” - <i>Enterobacter</i> - <i>Serratia</i> etc	Amp/cefazolin/aug/ ce FOX itin (<i>AmpC</i> BL)	<i>CtxM</i> , <i>TEM</i> <i>AmpC</i> BL++	CP FQ R Aminoglycoside R
<i>Pseudomonas aeruginosa</i>	Amp/cefaz/aug/ CRO / FOX (<i>AmpC</i> and other BLs)	n/a	CP OM porin changes Efflux pumps FQ R Aminoglycoside R
<i>Acinetobacter baumannii</i>	Amp/cefaz/augm/ CRO / FOX	n/a	
<i>Bacteroides</i> , <i>Prevotella</i> species (anaerobes)	Amp / cefaz /CRO (chromosomal BLs)	n/a	Metronidazole Cefoxitin Pip/tazobactam

BL – betalactamase CP- carbapenemase (meropenem R) OM- outer membrane (LPS layer) CRO- ceftriaxone FQ – fluoroquinolone ESBL – extended spectrum betalactamase

Ambler molecular classes of betalactamase



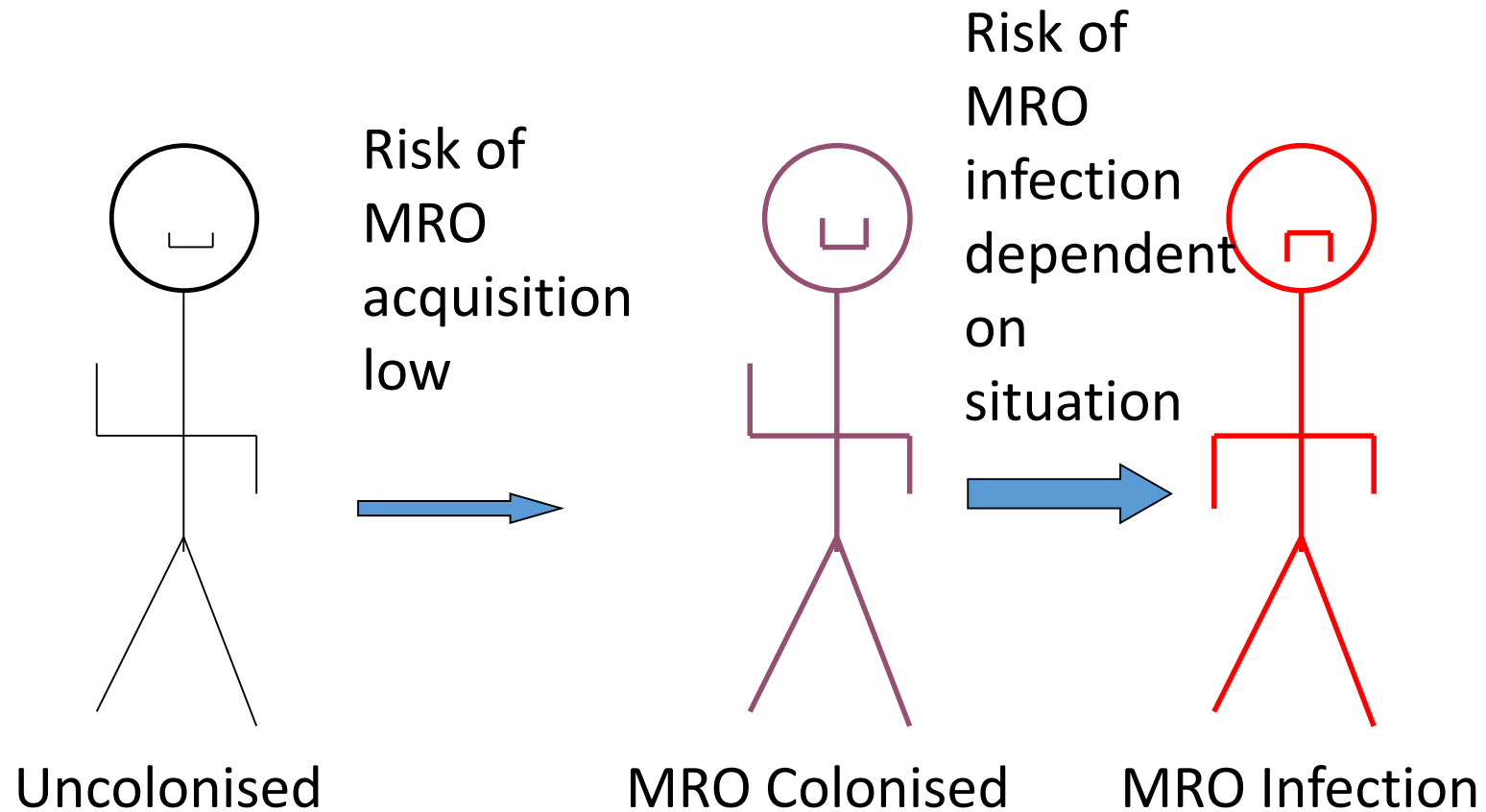
Figure

Caption

FIGURE 2 Schematic representation of β -lactamases. Molecular classification of β -lactamases follows the Ambler classification. Correlation with the main functional group of the Bush and Jacobi classification is also shown. Of note, the latter classification has several subgroups that are not shown. Representative examples of each group of enzymes are provided. † Class A enzymes are the most diverse and include penicillinases, ESBLs, and carbapenemases. * Ambler class D enzymes belong to the functional group/subgroup 2d. *Class A enzymes belonging to the subgroup 2br are resistant to clavulanic acid inhibition. EDTA, ethylenediaminetetraacetic acid; ESBLs, extended-spectrum β -lactamases.

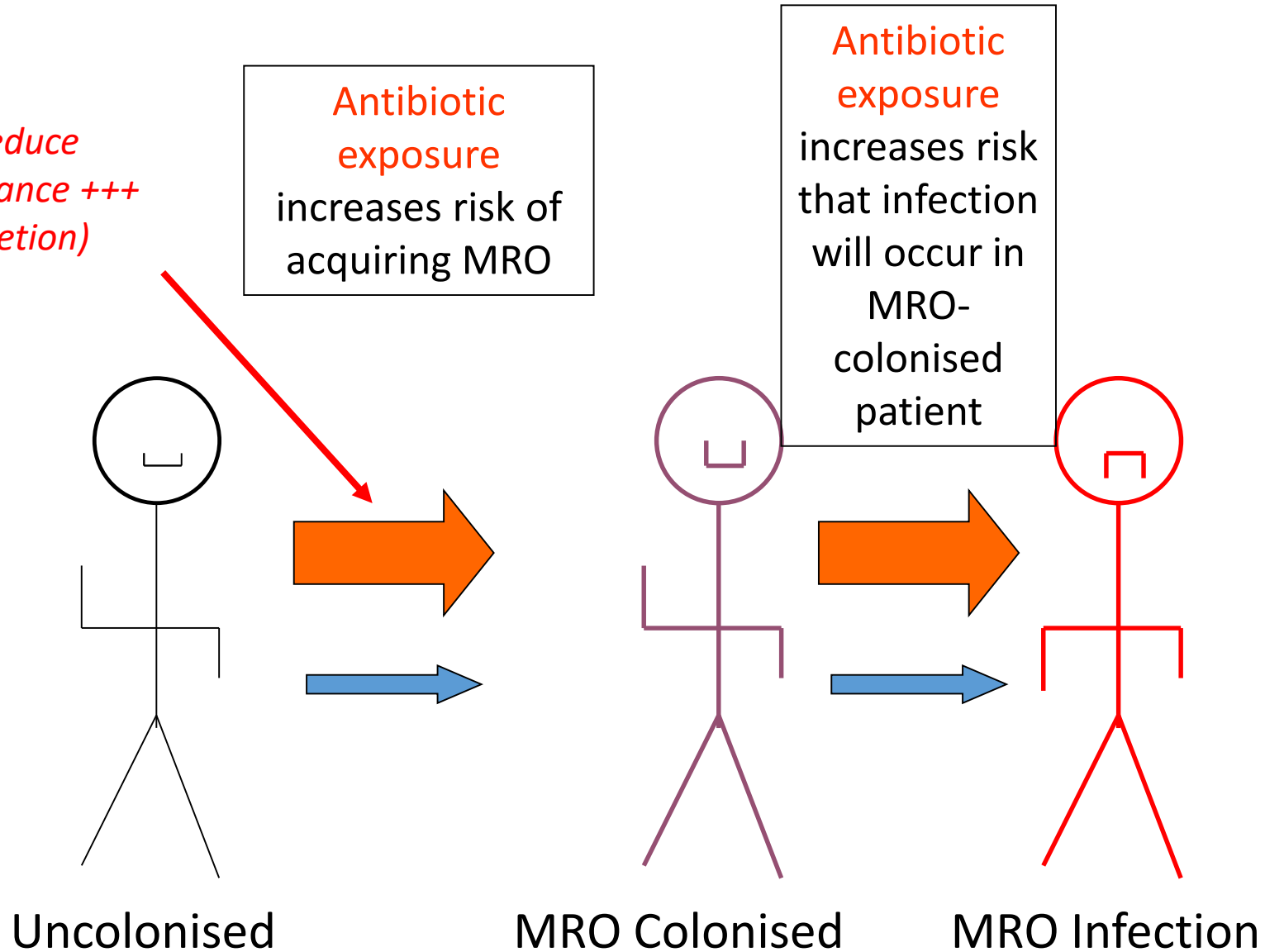
Multi-resistant organism (MRO) colonisation/infection sequence

Situation without antibiotic exposure



MRO colonisation/infection sequence

*Ceftriaxone and
Pip/tazobactam reduce
colonisation resistance +++
(heavy biliary excretion)*



JHH: a natural AMS experiment ...



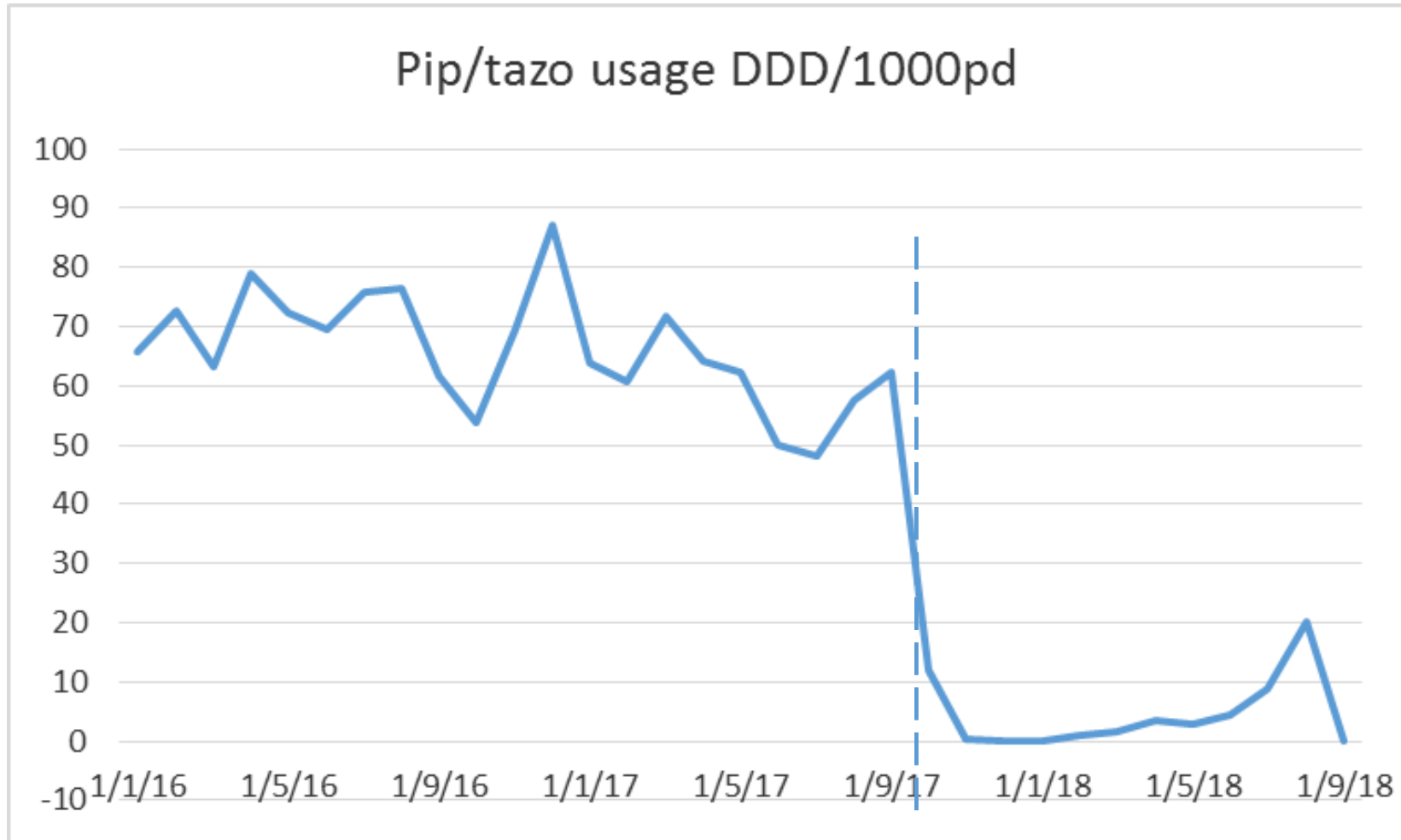
Explosion in Chinese factory in 2016 led to a global shortage of piperacillin+tazobactam (PT), affecting Australia from Sep 2017

John Hunter Hospital prepared for the PT shortage by:

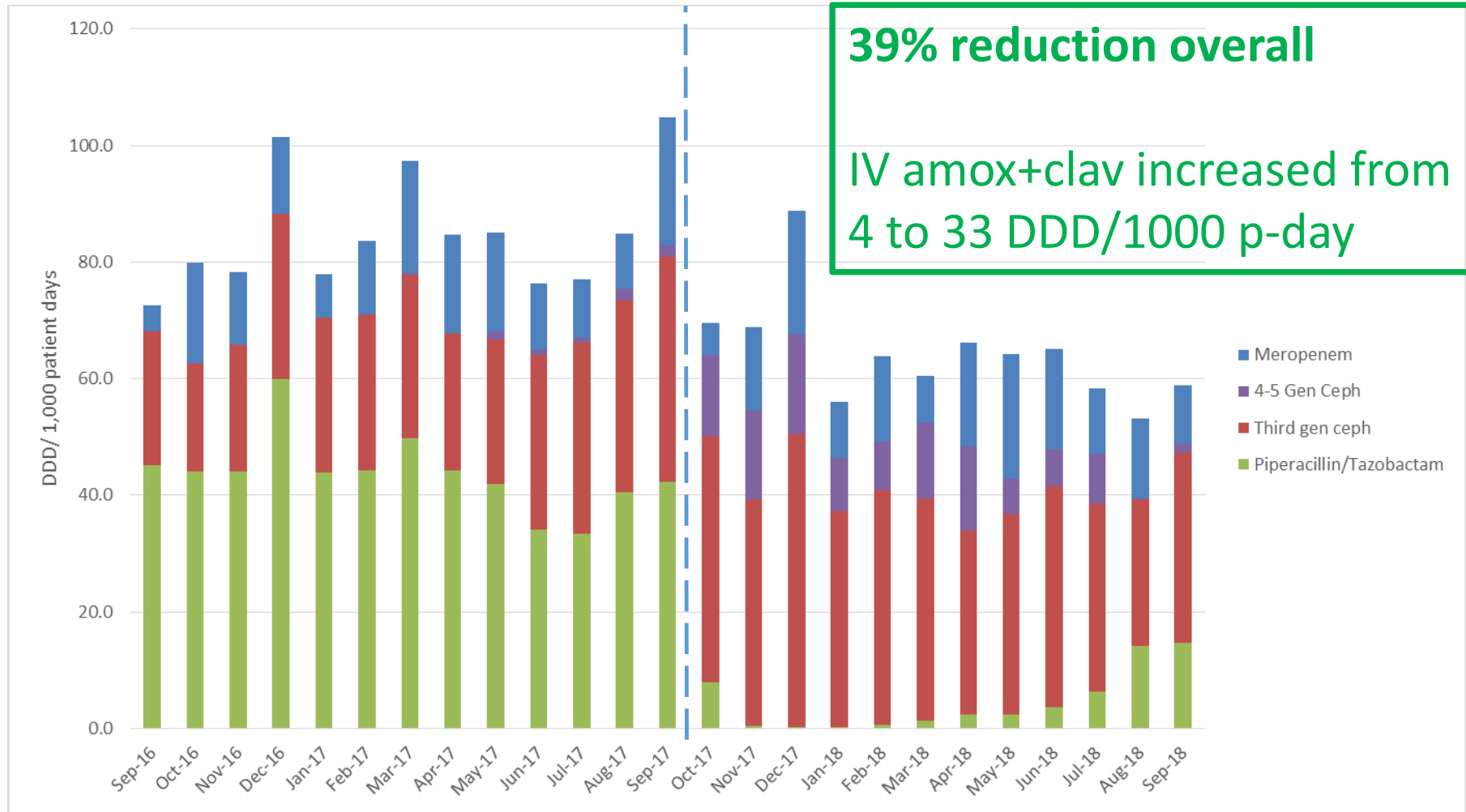
- Guidelines amended with inclusion of role for IV augmentin (available from 2017); avoidance of ceftriaxone or meropenem alternatives
 - Short course intra-abdominal sepsis guideline
 - Diabetic and vascular foot infection guideline
- Piperacillin+tazobactam access restricted
- General advice sheet provided to clinicians

<https://aimed.net.au/2017/06/09/piperacillintazobactam-shortage-recommended-alternatives-hnelhd/>

JHH: Sept 2017 - falling off a cliff...



JHH: sustained fall in broad spectrum beta-lactam use



Linear interrupted time series model

Hospital-onset VRE and MRSA acquisition as outcomes ,12 months pre and post pip-tazo shortage

40% reduction in VRE level ($p=0.004$) and trend ($p=0.002$) after October 2017
67% reduction in VRE sterile site infections ($n=24$ going to 8)
24% reduction in MRSA sterile site infections ($n=49$ going to 37)

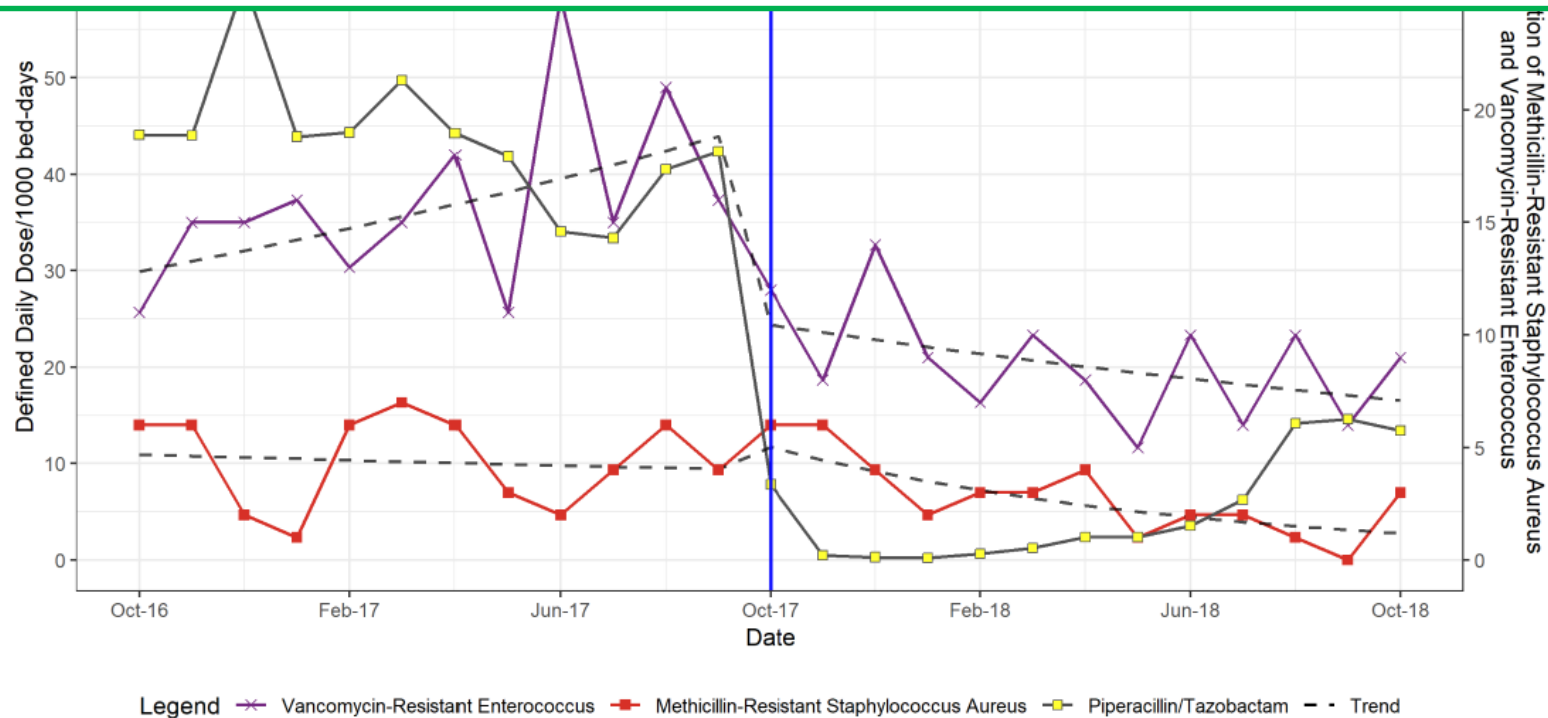
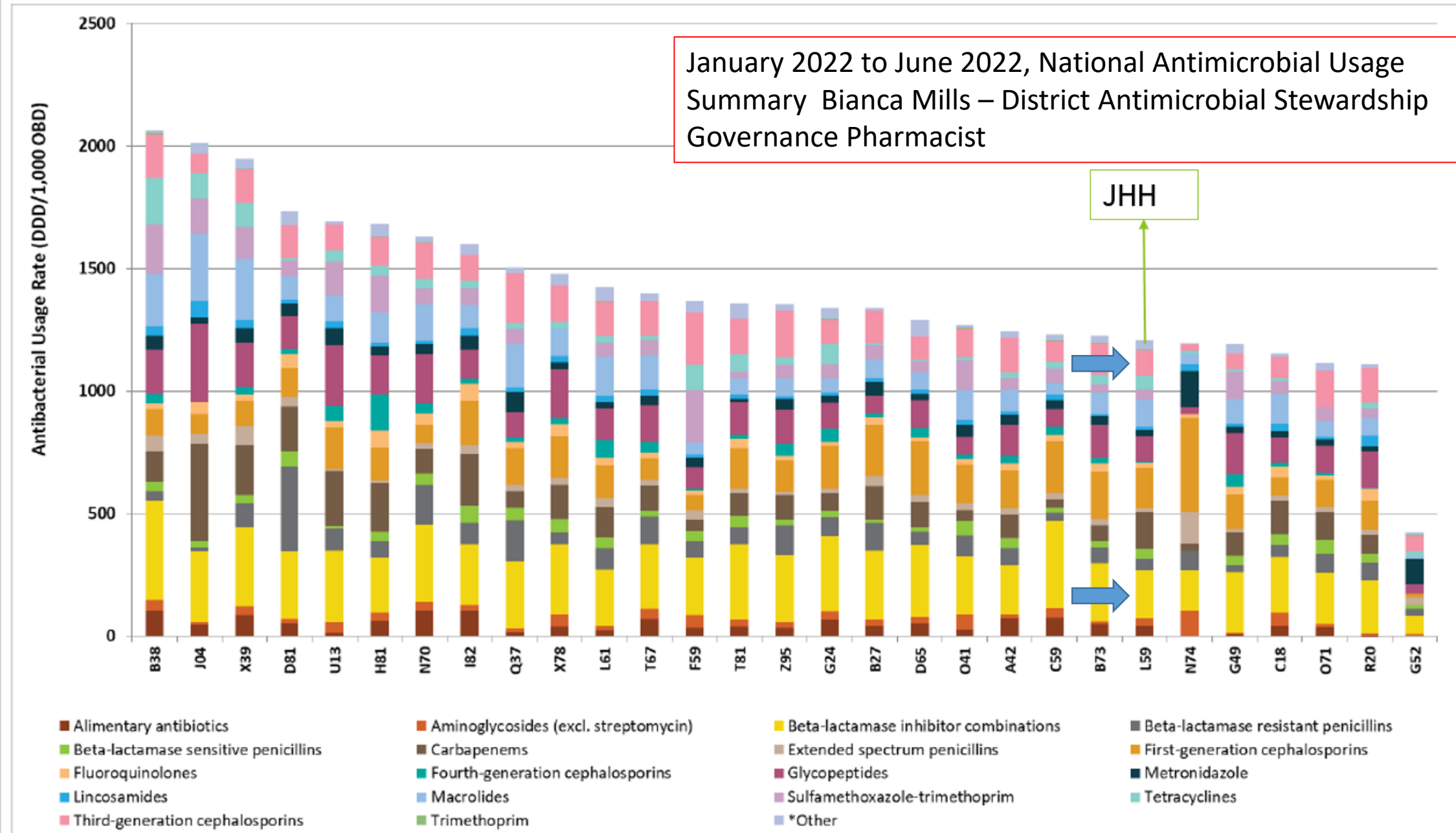


Chart 1: Critical Care antibacterial usage rates (DDD/1000 OBD) in 29 Principal Referral and Specialist Women's hospitals, Jan-Jun 2022



Alimentary antibiotics = rifaximin, fidaxomicin, paromomycin. Other* = antimycobacterial antibiotics, monobactams, nitrofurans, linezolid, daptomycin, other cephalosporins and penems, polymyxins, second-generation cephalosporins, steroids, streptogramins and streptomycin.

Antibiotic spectra comparison

	Ceftriaxone	Piperacillin/tazobactam
Strengths	Non-ESBL Gram negatives Neisseria gonorrhoeae [Streptococci (pneumococcus) [Haemophilus influenzae & related species [Gram positive anaerobes	Non-ESBL Gram negatives Pseudomonas aeruginosa Acinetobacter Gram negative and positive anaerobes Enterococcus faecalis [MSSA [Streptococci
Gaps	ESBL/CP Gram negatives Enterobacter cloacae and related species Pseudomonas Acinetobacter Gram negative anaerobes Staph. aureus (MSSA and MRSA) Enterococci Listeria	ESBL/CP Gram negatives Enterobacter cloacae and related species MRSA VRE

ESBL – extended spectrum betalactamase (ceftriaxone or ceftazidime R) CP – carbapenemase (mero R)

Selecting antibiotics for empiric therapy

Syndrome	Key empiric coverage required	Primary Rx
Sepsis (uncertain focus)	Gram negative aerobes – E. coli etc Staphylococcus aureus incl. MRSA	Gentamicin Flucloxacillin + vancomycin
Skin/soft tissue infection	Gram positives – S. aureus /Strep A, C, G Diabetic foot infection – add anaerobes DFI with sepsis	Flucloxacillin + vanc if known MRSA Amox/clavulanate Pip/tazobactam
Pneumonia (community)	Gram positives – Strep. pneumoniae Severe- Gram negative and Legionella cover	Benzylpenicillin Gentamicin + Azithromycin
Urinary tract infection (severe)	Gram negative aerobes – E. coli, Klebsiella etc Gram positives- Enterococcus, Strep	Gentamicin Ampicillin
Intra-abdominal sepsis	Gram negative aerobes Mixed anaerobes (Gram neg and pos) [+/-enterococci, +/- candida]	Gentamicin Metronidazole Ampicillin

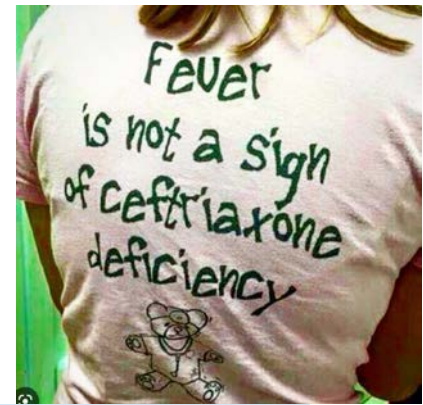
Bold indicates most important coverage required

2021 HNE MRSA BSI incidence 16%, 16%
(community and healthcare cases respectively)

Empiric indications for TGC or Pip/Tazo

TGC (ceftriaxone/ cefotaxime)	Piperacillin/Tazobactam
Community acquired meningitis	Diabetic foot / vascular foot infection with sepsis
Brain, lung or liver abscess [with added anaerobic cover]	Severe hospital-acquired pneumonia including VAP [cefepime for non-severe pen allergy]
Mastoiditis	Exacerbation of bronchiectasis (severe)
Suspected gonococcal infection (urethritis, PID, disseminated, epididymo-orchitis)	Febrile neutropenia [cefepime in paedts]
Orbital cellulitis	
Secondary indications – penicillin allergy	

TGC: avoiding unnecessary use



Syndrome	Preferred primary Rx [where relevant, TGC is for non severe pen allergy]
Surgical prophylaxis	Cefazolin
Community acquired pneumonia	Benzylopenicillin +/- gentamicin + azith
Hospital acquired pneumonia	Amoxycillin/clavulanate
Biliary sepsis/cholecystitis	Ampicillin + gentamicin OR amox/clav
Perforated intra-abdo viscus	Amp+gent+ metronidazole
Urinary tract infection (sepsis)	Amp+gentamicin
Skin/soft tissue infection	Flucloxacillin [no TGC indications]

Pip/tazobactam: common unnecessary use situations

- CAP, HAP –
 - Use up front (often prompted by past h/o pseudomonal colonisation)
 - Escalation from a first line agent after < 48 hrs rx
 - Empyema upfront usage (penicillin+mtz or augmentin appropriate)
- Intraabdominal infection-
 - Use up front (almost always NOT first line)
 - Premature escalation, esp if source control not adequate
- Diabetic or vascular foot infection in absence of sepsis – NOT first line
- Empiric / Directed rx of pseudomonal infection where anaerobe cover not required
 - Feb neutropenia – ceftazidime or cefepime preferred
 - Severe HAP – cefepime preferred

<https://aimed.net.au/2017/06/09/piperacillintazobactam-shortage-recommended-alternatives-hnelhd/>



Thank you!

<http://aimed.net.au> - Antimicrobial stewardship practical advice

<https://www.youtube.com/watch?v=GFfi5Ou4Kd8> The Pickup

