Translating cumulative antibiogram to antibiotic policy

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	Enterobacteriaceae		NFGNB	
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
ESBLs	72% *SHV, TEM, CTX-M-15*	61% *SHV, TEM, CTX-M-15*	25% *VEB*	70 % TEM, PER
Carbapenemase	9 % NDM, Oxa-48 like	40% Oxa-48 like, NDM	25% VIM, NDM, IMP, GES	70% Oxa-23, 24, 51, 58 NDM
Colistin	8 %	37 % *mgrB, PhoP/Q, PmrA/B*	<5 % *PhoP/Q, PmrA/B, ParR/S*	<5 % *PmrA/B, Lpx genes*
Hyper virulent		+++		

Among carbapenem resistant organisms

Deciding empirical therapy is "Challenging"
as the mechanisms of resistance are highly diverse
Rapid microbial identification and AST profile may help for appropriate therapy

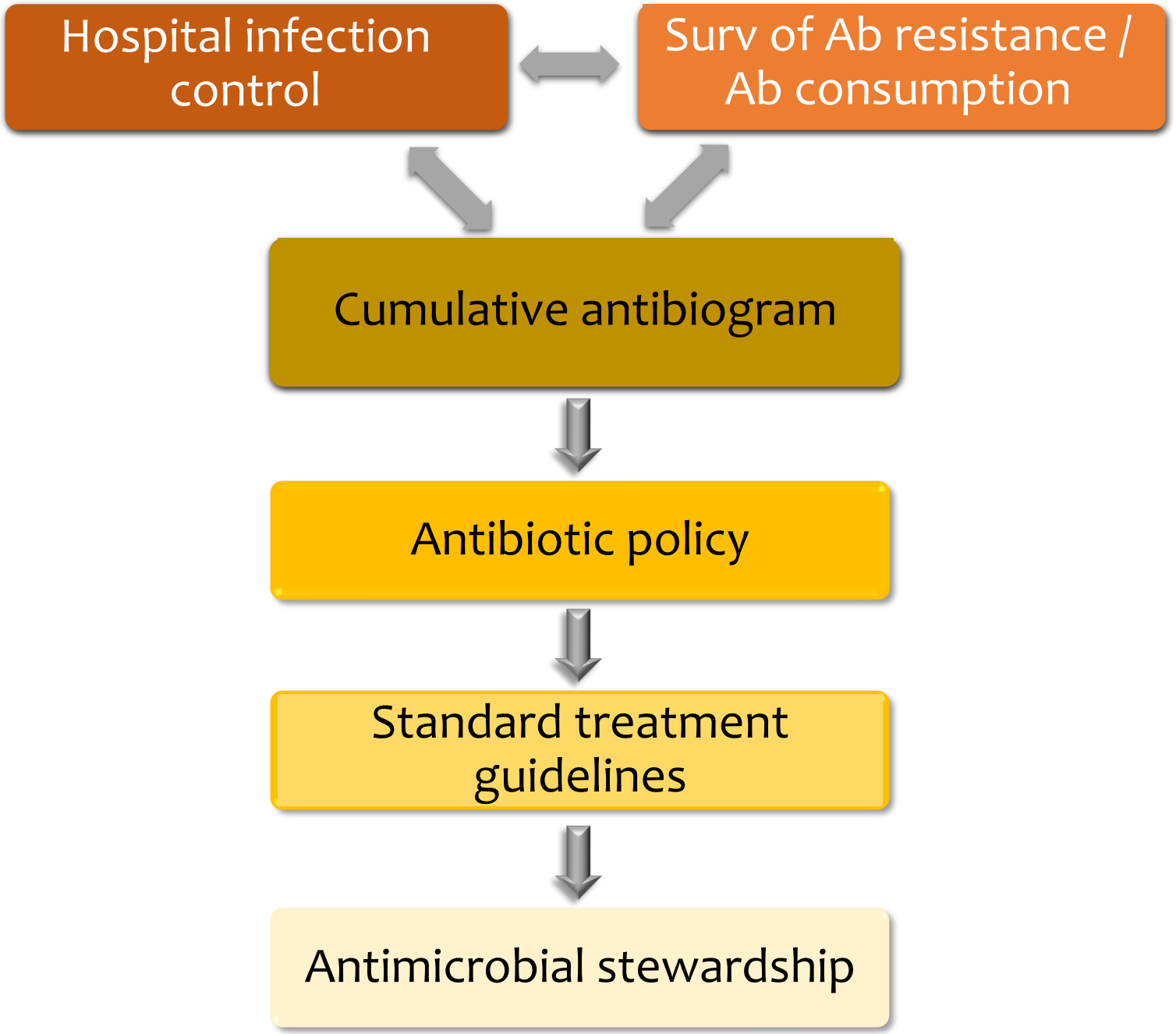
Antimicrobials in the pipeline : Will this benefit India ?

Agents	FDA status	Active against genotypic markers	
Ceftolozane / tazobactam	Approved	ESBLs, AmpC	NO (Except for *P. aeruginosa*)
Ceftazidime / avibactam	Approved	ESBLs, AmpC, KPC and some class D β- lactamases	NO
Meropenem / vaborbactam	Approved	ESBLs, AmpC, KPC	NO
Aztreonam / avibactam	Phase 3 development	ESBLs, AmpC, KPC, MβLs,	Moderate activity
Imipenem / relebactam	Phase 3 development	ESBLs, AmpC, KPC	NO (Except for *P. aeruginosa*)
Cefiderocol	Phase 3 development	ESBLs, AmpC, KPC, MβLs, class D Oxa's (Oxa-48, 23, 24, 51, 58)	Only promising agent
Plazomicin	FDA approved	All AMEs (AAC, APH, ANT)	Moderate activity 5-20% against AMEs producing organisms

newer agents may work for ESBLs but not for carbapenemase

Goal……

- ✓To minimize the morbidity and mortality due to antimicrobial-resistant infection
- ✓To preserve the effectiveness of antimicrobial agents in the treatment
- ✓To prevent microbial infections


Hospital infection control
Surv of Ab resistance / Ab consumption
Cumulative antibiogram
Antibiotic policy
Standard treatment guidelines
Antimicrobial stewardship

Streptococcus pneumoniae

Cumulative antibiogram (Susceptibility)

Penicillin(%)		Cefotaxime(%)		Erythromycin(%)	Azithromycin (%)	Clindamycin (%)	Levofloxacin (%)	Moxifloxacin(%)	Co-amoxiclav(%)
M	NM	N	NM						
31	92	74	94	27	35	70	94	96	93

Antibiotic policy

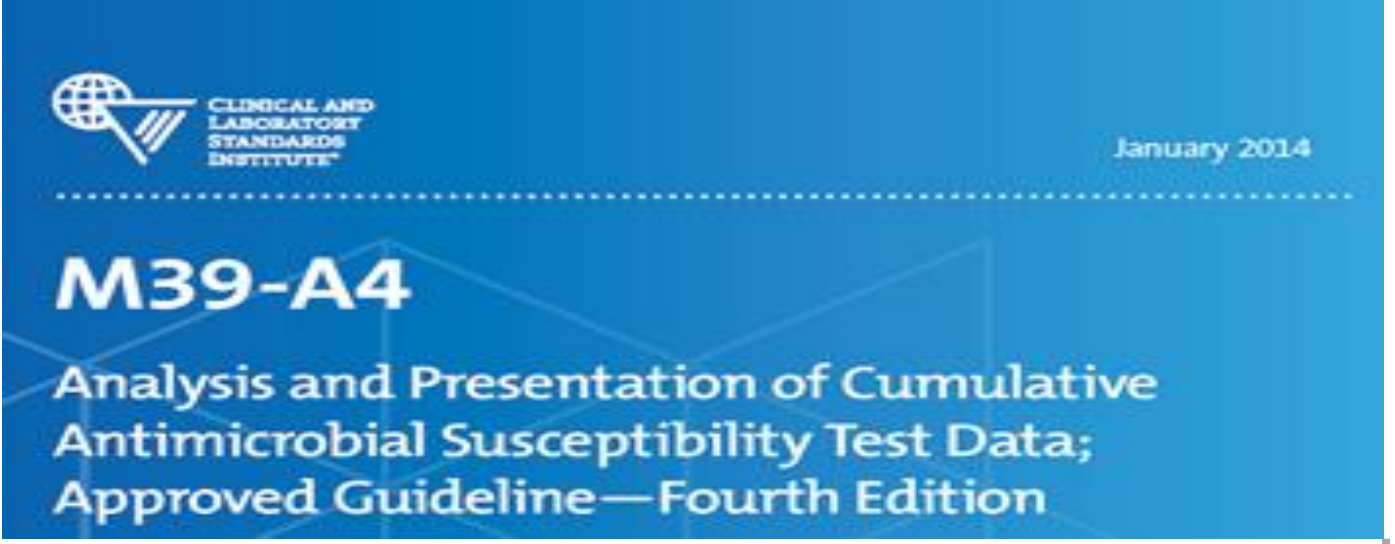
Meningitis: Penicillin/ Cefotaxime/ Vancomycin/ Meropenem
CAP: Amoxicillin/Co-amoxiclav or cephalosporin with macrolide or doxycycline / Ampicillin-Sulbactam/ respiratory fluoroquinolone/ vancomycin (MRSA) /Pip-Tazo, cefepime with Imipenem (Pseudomonas spp)
AOM: Amoxicillin/Co-amoxiclav, cefpodoxime, cefuroxime, ceftriaxone

Standard treatment Guidelines

Respiratory infections: Amoxicillin -500-1000mg thrice daily(PO or IV), Co-amoxiclav- 1gm twice daily/ 625 mg thrice daily oral or 1.2gm IV q8h, Doxycycline-100mg twice daily, Levofloxacin – 750 mg twice daily PO or IV, Moxifloxacin-400mg once daily PO or IV, Ceftriaxone(CTR)-2gm once daily, Cefotaxime-2gm thrice daily Cefepime-2gm twice daily, cefuroxime-500mg twice daily, cefpodoxime-200mg twice daily, Pip/Tazo-4.5gm thrice daily
CNS: CTR- 2gm 12 hourly, Ceftazidime -2GM q 6-8 hourly, Cefotaxime- 2gm 6 hourly, Meropenem- 2gm 8 hourly, Vancomycin-15mg/Kg (max 2gm) eight hourly
Vaccine recommendations: PCV and PPSV for risk group (elderly, smokers and with co-morbidities)

Antimicrobial stewardship

Meningitis : cefotaxime alone , if cefotaxime MIC ≤ 1.0µg/ml; add vancomycin if cefotaxime MIC ≥ 1.0µg/ml
Non-meningeal, invasive:
Perform both penicillin and cefotaxime MIC / increase the dosage of penicillin if MIC is ≥0.06 to ≤2.0 µg/ml and increase dosage of cefotaxime, if cefotaxime MIC ≥ 1.0 and penicillin MIC is >2.0
Respiratory infections : De-escalation or step-down therapy after the culture and AST results



Cumulative hospital antibiogram

Cumulative susceptibility of bacterial isolates

- ✓ Strategy that help in choosing the right empirical antibiotic
- ✓ Track local antibiotic resistance trends
- ✓ Drug-bug combinations, to be reported
- ✓ Next level antibiogram
  - specimen type or infection site
  - organism resistance characteristics
  - Clinical service or patient population

Key Reporting strategies

- ✓ Always report
  - narrow spectrum agents
  - at least one oral and one IV agent
  - at least one agent for patients with penicillin allergy

Staphylococcus aureus

Staphylococcus aureus (% of susceptibility)

Organism	Cefoxitin	Gentamicin	Erythromycin	Clindamycin	Co-trimoxazole	Minocycline	Chloramphenicol	Rifampicin	Vancomycin	Linezolid
MSSA (n=203)	100% (203/203)	95% (192/203)	50% (97/193)	75% (139/186)	79% (157/199)	100% (191/191)	99% (131/132)	99.5% (199/200)	Not reported	100% (202/202)
MRSA (n=157)	0% (0/157)	57% (90/157)	32% (49/155)	59% (91/153)	72% (107/148)	99% (153/154)	97% (119/123)	95% (149/157)	100% (21/21)	100% (157/157)

Methicillin susceptible *S. aureus*
Susceptibility reporting

	First line antibiotics							Second line antibiotics			
Syndromes	Cefoxitin/ Oxacillin	Gentamicin	Erythromycin	Clindamycin	Tetracycline	Co-trimoxazole	Chloramphenicol	Rifampicin	Vancomycin	Linezolid	Daptomycin	Minocycline
Blood	✓	✓	X	X	X	X	✓	✓	X	X	X	X
SSTIs	✓	✓	✓	✓	✓	✓	X	✓	X	✓	X	X
Pneumonia	✓	X	X	X	X	X	X	X	X	✓	X	X
Bone and joint infections	✓	✓	X	X	✓	✓	X	✓	X	✓	X	✓
CSF/sterile site	✓	X	X	X	X	X	✓	✓	X	✓	X	✓

MSSA management
Recommendations

- ✓ Cefoxitin/oxacillin susceptible staphylococci can be considered susceptible to penicillinase stable penicillin, beta-lactam combination, cephalosporins, carbapenem and monobactams
- ✓ Cefazolin is better tolerated than anti-staphylocccal penicillins
- ✓ No vancomycin, only beta lactams
- ✓ Persistent bacteremia - addition of etrapenem gives dramatic recovery

Methicillin resistant *S. aureus*
Susceptibility reporting

	First line antibiotics							Second line antibiotics				
Syndromes	Cefoxitin/ Oxacillin	Gentamicin	Erythromycin	Clindamycin	Tetracycline	Co-trimoxazole	Chloramphenicol	Rifampicin	Vancomycin	Linezolid	Daptomycin	Minocycline
Blood	✓	✓	X	X	X	X	✓	✓	✓	✓	✓	X
SSTIs	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	X
Pneumonia	✓	X	X	X	X	X	X	X	✓	✓	✓	X
Bone and joint infections	✓	✓	X	X	✓	✓	X	✓	✓	✓	✓	✓
CSF/sterile site	✓	X	X	X	X	X	✓	✓	✓	✓	✓	✓

Gram negative

Percent Susceptible

Gram-Negative Organisms	No. Strains	Beta-lactams						Aminoglycosides			FQs[†]	Other	
		ampicillin	cefazolin	cefotaxime	ceftazidime	imipenem	piperacillin-tazobactam	amikacin	gentamicin	tobramycin	ciprofloxacin	nitrofurantoin[‡‡]	trimethoprim-sulfamethoxazole
Acinetobacter baumannii	32	7	-	34	52	80	46	80	60	59	51	-	58
Citrobacter freundii	49	-	-	72	67	99	67	100	100	100	90	78	67
Enterobacter aerogenes	31	-	-	68	69	99	74	100	91	91	92	85	95
Enterobacter cloacae	76	-	-	61	62	99	77	99	90	90	92	81	84
Escherichia coli	1433	36	74	96	94	99	51	99	91	92	72	98	65
Klebsiella pneumoniae	543	-	72	91	92	99	86	99	94	94	84	74	81
Morganella morganii	44	-	-	85	81	99	64	100	100	100	99	-	75
Proteus mirabilis	88	87	80	99	99	100	70	100	90	93	89	-	73
Pseudomonas aeruginosa	397	-	-	-	76	80	85	97	80	83	75	-	-
Salmonella spp.	32	88	-	97	97	100	91	-	-	-	90	-	86
Serratia marcescens	5												
Shigella spp.	3												
Stenotrophomonas maltophilia	7												

[*]%S for each organism/antimicrobial combination wa
[†]FQ = fluoroquinolones
[‡]Nitrofurantoin, data from testing urine isolates only;

Cumulative antibiogram
Generally…one big report, but…
increasing emphasis on segregating data to answer specific questions

Escherichia coli (% susceptibility)

Organism	Cefotaxime	Ceftazidime	Cefepime	Piperacillin/ Tazobactam	Cefoperazone/ Sulbactam	Imipenem	Meropenem	Amikacin	Gentamicin
E. coli (*n*=985)	27% (254/956)	26% (245/959)	33% (298/890)	64% (624/978)	71% (487/686)	88% (186/209)	88% (853/971)	87% (855/980)	64% (622/975)

Organism	Ciprofloxacin	Chloramphenicol	Tetracycline	Minocycline	Tigecycline	Ertapenem
E. coli (*n*=985)	32% (310/964)	76% (737/970)	39% (351/899)	75% (734/973)	83% (733/885)	89% (611/681)

E.coli Urine isolates % Susceptible *

4 patients populations

Category	n	Am	Cz	Cip	Fm	Sxt
All patient	3801	53	88	79	99	72
In patient	421	40	75	62	98	61
Out patient**	3411	54	89	80	99	73
18-40 yrs female out patient	998	60	92	92	99	77

* % Susceptible from first isolates/pt

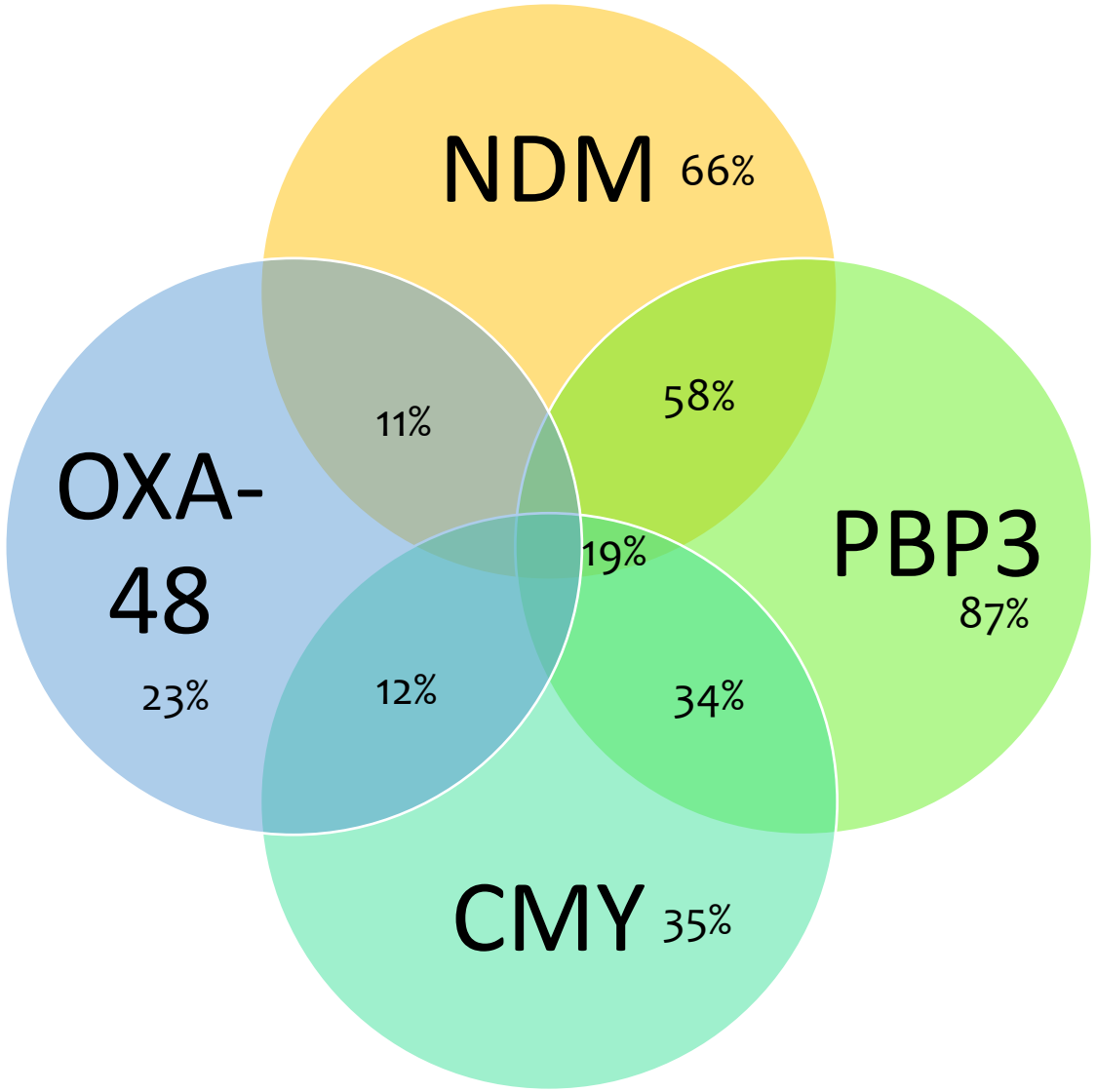
** Includes ER patients

Variability in urine culture & susceptibility ordering practices

Clinical Scenario	No (%) of general practitioners who said they would order C&S
Probable uncomplicated UTI	165/278 (59%)
Previous treatment failure in older women	262/291 (90%)

- ✓ More likely to have resistant organisms (Hillier et al.J antimicro Chemother.2006;58:1303)
- ✓ **Patient with uncomplicated UTI s often not cultured!**

Indian MDR *E. coli*



Antibiotic	Effect & Reason	
Amikacin	✗	RMTases
Pip/Taz	✗	CTX-M-15 and OXA-1
Meropenem	✗	NDM
Tigecycline	✓	
Minocycline	✓	
Colistin	✓	
CAZ/AVI	✗	NDM
AZT/AVI	✗	PBP3
Cefiderocol	✓	

Colistin after aerosol delivery and intravenous administration of CMS in critically ill patients

- ✓ IV colistin
  - Plasma (0.15 to 4.7 mg/L)
  - ELF (1.48 to 28.9 mg/L)
- ✓ Aerosol colistin
  - Plasma (0.15 – 0.73 mg/L)
  - ELF (9.53 to 1,137 mg/L)
  - 9% of CMS dose reaches ELF and only 1.4% presystemically converted to colistin

Tigecycline Pharmacokinetics in the Plasma, Epithelial Lining Fluid, and Alveolar Cells of Healthy Adult Subjects

- ✓ Tigecycline
  100 mg followed by 50mg q12h
- ✓ Plasma tigecycline level:
  0.11 – 0.98 mg/L
- ✓ ELF :
  1.49 - 2.33 mg/L

Boisson et al., Antimicrob agents chemother. 2014; 58:7331-9
Gotfried MH et al., Antimicrob Agents Chemother. 2017;61(9). pii: e01135-17.

Shigella spp – Recommendations

% susceptibility						
Organism	Ampicillin	Co-trimoxazole	Ciprofloxacin	Cefotaxime	Cefixime	Azithromycin
Shigella flexneri (n=52)	35% (18/52)	23% (12/52)	13% (7/52)	98% (51/52)	98% (51/52)	96% (50/52)
Shigella sonnei (n=44)	75% (33/44)	14% (6/44)	14% (6/44)	100% (44/44)	98% (43/44)	88% (37/42)

- ✓ Varying susceptibility was observed for ampicillin within species (*S. sonnei* are more susceptible than *S. flexneri*)
- ✓ *Shigella spp* are highly resistant to co-trimoxazole and fluroquinolones

- ✓ Current drug of choice will be third generation cephalosporins and azithromycin

P. aeruginosa (% susceptibility)

Organism	Ceftazidime	Cefepime	Aztreonam	Piperacillin/ Tazobactam	Cefaperazone/ Sulbactam	Meropenem	Levofloxacin	Amikacin	Tobramycin	Colistin
P. aeruginosa (*n*=985)	82% (226/274)	83% (226/272)	77% (210/273)	78% (213/273)	73% (161/220)	82% (222/272)	82% (226/272)	85% (231/272)	82% (221/269)	100% (71/71)

Anti-pseudomonal choice for empiric therapy

- ✓ Cumulative susceptibility may mislead at times – especially for *Pseudomonas*
- ✓ Susceptibility of isolates from hospital – ICUs differs from that of wards and community origin
- ✓ Discrepant profile of antibiotics within a same class – BEWARE…

Respiratory isolates with discrepant profile - common			
Ceftazidime	**Meropenem**	**Piperacillin/ Tazobactam**	**Phenotypes (n)**
S	**S**	**S**	**587**
R	**R**	**R**	**56**
R	**R**	**S**	**10**
S	**R**	**R**	**4***
S	**R**	**S**	**19***

**If empiric therapy is meropenem, its continuation for such phenotypes may cause clinical failures and the therapy must be narrowed down to a susceptible agents when in-vitro susceptibility report is available*

P aeruginosa % susceptible* (N=726) to 7 drugs and %S to either or both when 2 drugs are evaluated (% S 2 drugs does not imply synergy, antagonism or likely activity in vivo)

	Amik (94%)	Gent (80%)	Tob (85%)	Cip (64%)
Ceftaz (74%)	98	93	94	89
Mero (79%)	98	93	93	87
PiP/Taz (69%)	98	91	92	85
Cip (64%)	97	88	89	-

- ✓ Analysis included the most R result for each drug if patient had >1 isolate
- ✓ %S for either or both drugs (eg.% S to amik and/or Ceftaz)
- ✓ Used ≤ 16 µg/ml break point for S

Quantitative antibiogram linked
Empirical therapy

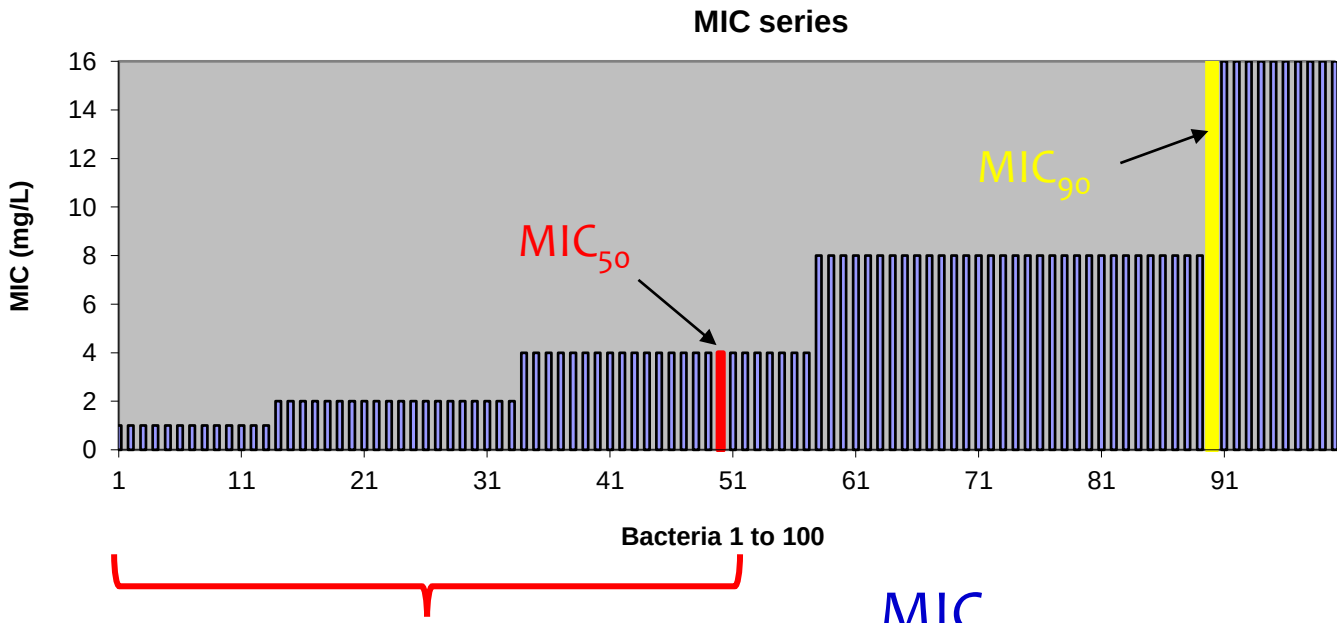
Clinical relevance of MIC_{50}, MIC_{90}

MIC_{50}

- ✓ More than susceptible breakpoint
- ✓ "Not suitable" for empiric therapy

MIC_{90}

- ✓ More than susceptible breakpoint
- ✓ Differs for Drug-bug combination
- ✓ Clinical success can be expected (60-70%)



MIC_{50}
Intrinsic activity of the drug

MIC_{90}
Indicates emergence of resistance

MIC50 and MIC 90 < Susceptible breakpoint

Rationale to treat ESBL infection

	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Recommendation	Probability of success
3GC (≤4 suscep bp)	> 32	>128	Not to be used	0%
Pip/Taz (≤16/4 Susc bp)	16/4	>128/4	ESBL producing *E.coli/Klebsiella* sp	50- 70 %
Cefto/Tazo (≤ 2/4 Sus bp)	2/4	>32/4	*Pseudomonas* sp.,	50- 70 %
Cefta/Aviba (≤ 2/4 Sus bp)	2/4	4/4	*Enterobacteriaceae, Pseudomonas sp.*	100%

Papadimitriou-Olivgeris et al., J Antimicrob Chemother 2019; 74:2051–2054.

Evaluation of Newer Agents: Enzyme and organism specific

	Active against	Not Active against	Pathogens covered	Pathogens not covered
amox/clav, pip/taz, tic/clav, cfp/sul	ESBLs	AmpCs, Carbapenemases	*Enterobacteriaceae*	*P. aeruginosa and A. baumannii*
Ceftazidime/ avibactam	ESBLs, AmpC, KPC-2, Oxa48 like	KPC-3, MBL (NDM)	CRE or colistin-resistant *Enterobacteriaceae* and *P.aeruginosa*	*A. baumannii*
Meropenem/ vaborbactam	ESBLs, AmpC, KPC-2,3	MBL(NDM), Oxa-48 like, 23/24/58 like	Carbapenem resistant *Enterobacteriaceae* (CRE)	Activity not enhanced against *P. aeruginosa, A. baumannii*
Imipenem/ relebactam	ESBLs, AmpC, KPC	MBL(NDM), Oxa-48 like,23/24/58 like	MDR Enterobacteriaceae and *P.aeruginosa*	Activity not enhanced against *A. baumannii*
Meropenem/ nacubactam	ESBLs, AmpC, KPC	MBL(NDM), Oxa-48 like, 23/24/58 like	Carbapenem resistant *Enterobacteriaceae* (CRE)	Activity not enhanced against *P. aeruginosa, A. baumannii*

Selective & cascade reporting of antibiotics

Pathogens	Susceptibility	Don't report
Gram negative pathogens	3rd Gen Cephalosporins, βL/βLI	Carbapenem, Colistin, fosfomycin and tigecycline
S. aureus	Oxacillin (MSSA)	Vancomycin, teicoplanin, linezolid and tigecycline
Enterococcus sp.,	Ampicillin and gentamicin	Vancomycin, teicoplanin, linezolid and tigecycline
Streptococcus pneumoniae	Susceptible to Oxacillin	Vancomycin, and linezolid
S. pneumoniae, R to oxacillin	Penicillin, cefotaxime MIC + S to vancomycin	Linezolid

✓ *Empirical therapy is to be changed to targeted therapy when AST report is available (within 72 hours)*

✓ *For ICU patients, ID expert recommendations to be followed for change in therapy*

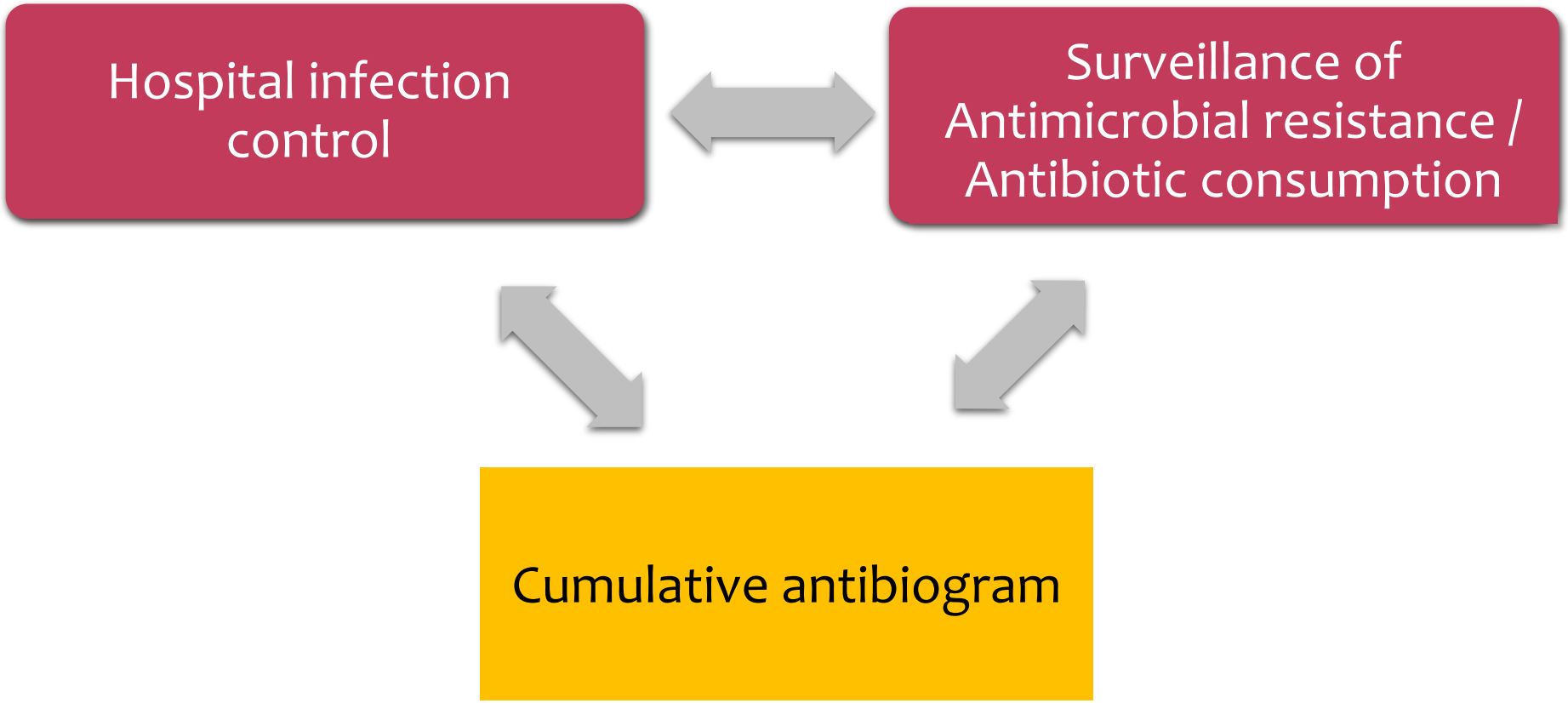
Are the recommendations prudent?

✓ Do low MICs reliably predict good outcomes?

Would treat based on low MIC & absence of ESBL/Carbapenamase

✓ Are routine tests adequately precise?

To stratify S/I/R across the now critical range of 1–4 mg/L


Hospital infection control
Surveillance of Antimicrobial resistance / Antibiotic consumption
Cumulative antibiogram

ABC Calc

Antibiotic Consumption Calculator Version 1.9

Changed to Antimicrobial consumption calculator (AMC tool)

Monnet DL. ABC Calc - Antibiotic consumption calculator
[Microsoft® Excel application]. Version 1.9, Copenhagen (Denmark): Statens Serum Institut 2006

Antibiotic policy fails

Infection control policies failing ?

- ✓ If hand hygiene adherence rate is 10-40%

  remaining % - negated by antibiotic

Antibiotic use as a cause of Hospital infection

- ✓ 3GCephalosporins and quinolones - Promotes

  Increased MRSA/GNB colonization and infection

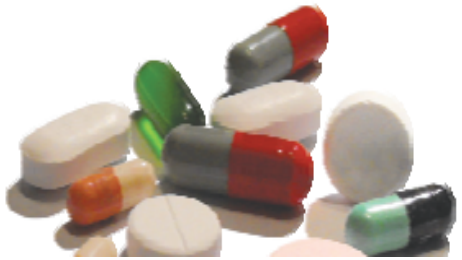
Uniform rather than Heterogenous prescribtion

Inappropriate – 'just- in- case'

- ✓Misdiagnosis or a poor quality severity assessment

World Health Organization
Regional Office for South-East Asia

Step-by-step approach for development and implementation of hospital antibiotic policy and standard treatment guidelines



http://www.searo.who.int/LinkFiles/WHD-11_ha-policy.pdf

2

Antibiotic policy[1,2]

The primary aim of the hospital antimicrobial policy is to minimize the morbidity and mortality due to antimicrobial-resistant infection; and to preserve the effectiveness of antimicrobial agents in the treatment and prevention of communicable diseases.

Scope of hospital antibiotic policy

The antibiotic policy is essentially for prophylaxis, empirical and definitive therapy. The policy shall incorporate specific recommendations for the treatment of different high-risk/special groups such as immunocompromised hosts; hospital-associated infections and community-associated infections.

The hospital antibiotic policy shall be based upon:

- spectrum of antibiotic activity;
- pharmacokinetics/pharmacodynamics of these medicines;
- adverse effects;

Thanks for your attention