UK guidelines for GNB infections

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medical education/consultancy

Joint Working Party on Multi resistant Gram-negative infection: Treatment

Peter M. Hawkey (Chair)
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Jonathan A Otter
And on behalf of the patient representative panel

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British Society for Antimicrobial Chemotherapy
British Infection Association
Healthcare Infection Society

DEFINITION-MDRGNB

- Original “resistant to multiple agents”
- ECDC “resistant to 3 or more classes”- problem of sul & amp resistance. Availability of agents and differences in breakpoints
- We have adopted “sensitive to only one or no readily available drugs”

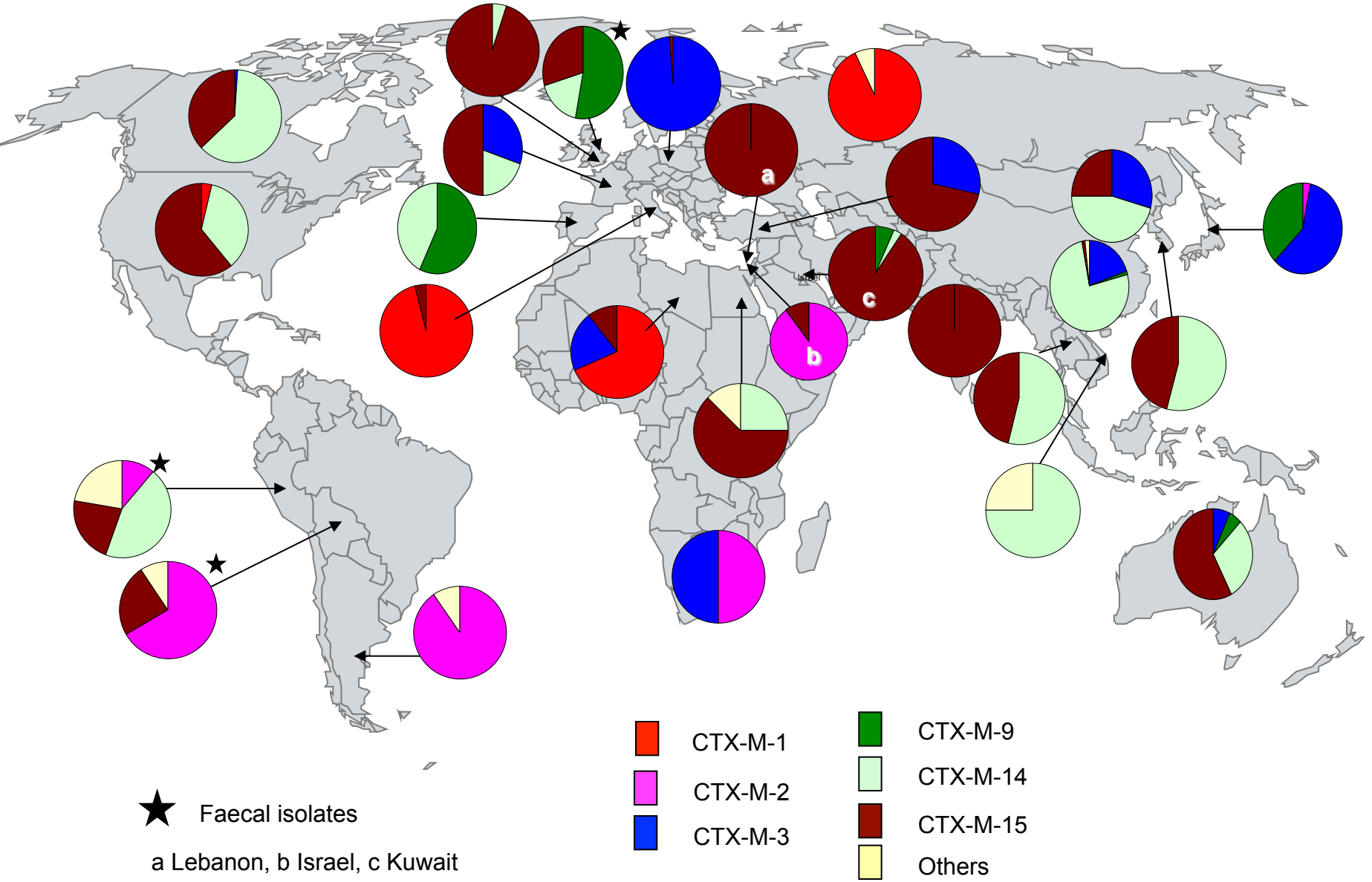
5.4 What is the scope of the guidelines?

Two sets of guidelines have been developed. We examine the background information on mechanisms and global spread, UK prevalence of resistance and prescribing, and then discuss treatment both in hospitals with intravenous antibiotics and in primary care with oral agents, ending with a consideration of antibiotic stewardship.

“The difficult is what takes a little time, the impossible is what takes a little longer”

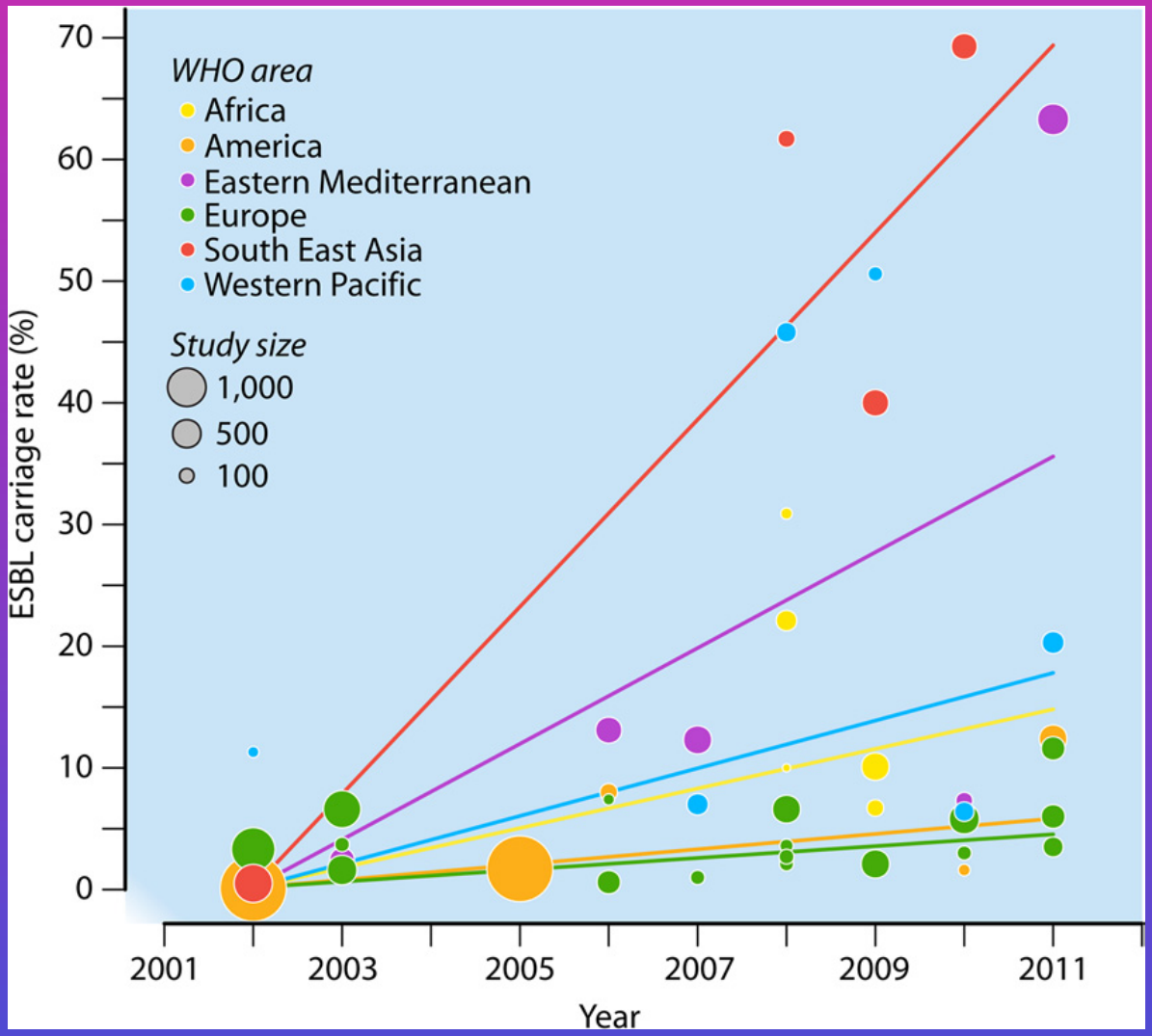
F. Nansen (1861-1930) Polar explorer

Proportions and country distributions of CTX-M ESBL genotypes



Hawkey & Jones 2009 JAC 64 Suppl 1 i3-i10

ESBL carriage rates in the community



Woerther et al. Clin Microbiol Rev. 2013:26; 744-58

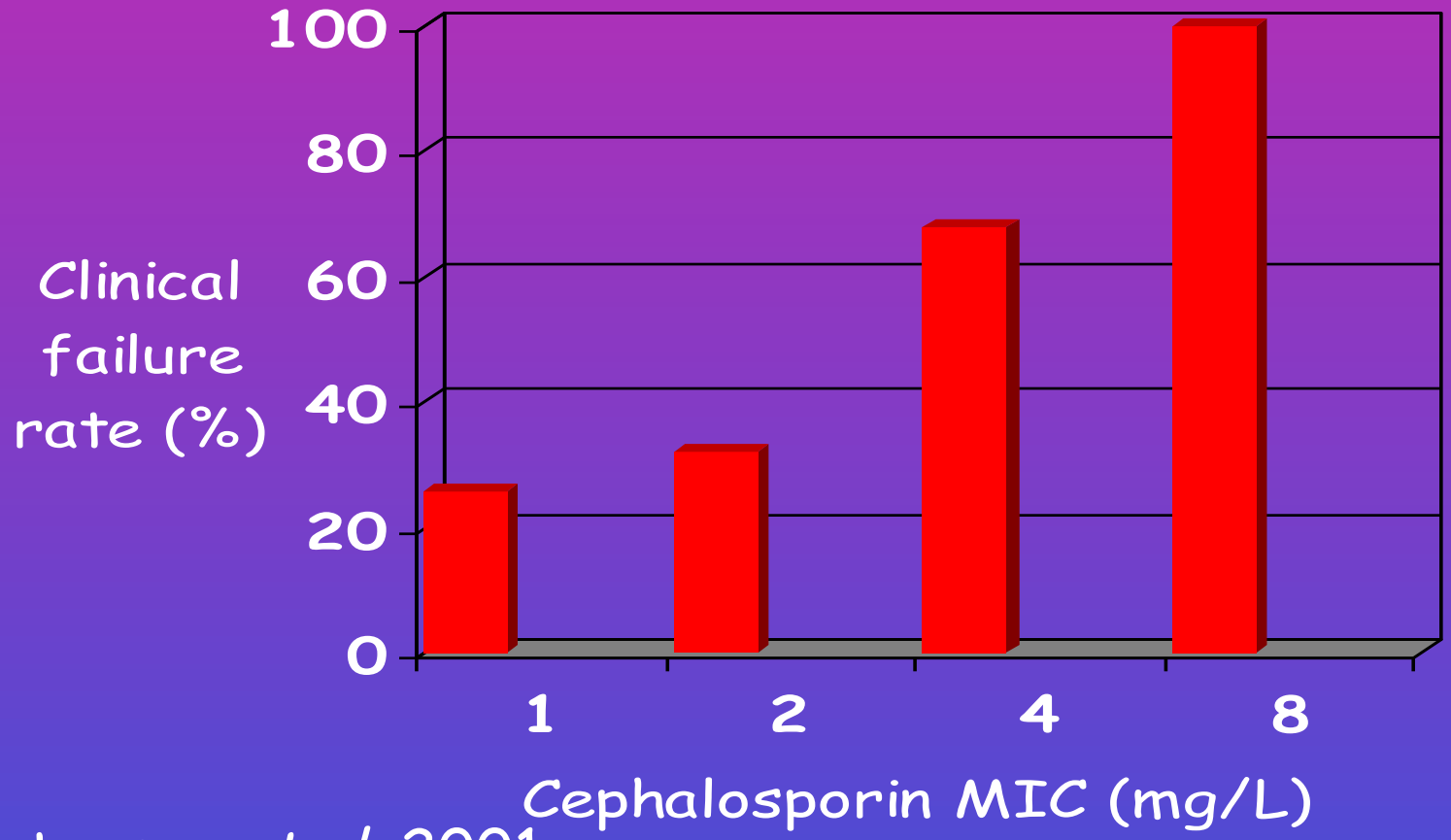
Distribution of CTX-M genotypes according to global origin

Global origin	*bla*$_{\text{CTX-M}}$	*bla*$_{\text{CTX-M 9/14}}$	*bla*$_{\text{CTX-M 15}}$	ST131/Others
Europe n=571	46 (8.1%)[a]	15 (2.5%)	31(5.4%)[a]	8/23
MESA n=152	34 (22.4%)[a]	7 (4.5%)	27 (17.8%)[a]	6/21

[a] $p < 0.0002$

Wickramasinghe et al. al.J Antimicrob Chemother (2012)**67 :** 1108-13

Patients failing cephalosporin treatment for serious infections caused by ESBL-producers



Paterson *et al*, 2001

Antibacterial resistance rates of genetically diverse cephalosporin-resistant *E.coli* from 3 geographically distinct centres in India

No and % resistant

	E. coli ($n = 98$)			
	CTX-M positive ($n = 72$)		CTX-M negative ($n = 26$)	
Antibacterial agent	*n*	%	*n*	%
Gentamicin	63	88	16	62
Trimethoprim	65	90	21	81
Ciprofloxacin	68	94	19	73
Piperacillin/tazobactam	32	44	5	19
Aztreonam	66	92	16	62
Cefoxitin	31	43	3	12
Ceftazidime	70	97	15	58
Cefotaxime	72	100	18	69
Cefpodoxime	72	100	26	100
Cefepime	61	85	12	46
Meropenem	0	0	0	0
Ertapenem	0	0	0	0

Ensor, V.M., *et al*, 2006, J Antimicrob Chemother, **58**:1260-3

Agents for treating infections caused by ESBL producers

Intravenous

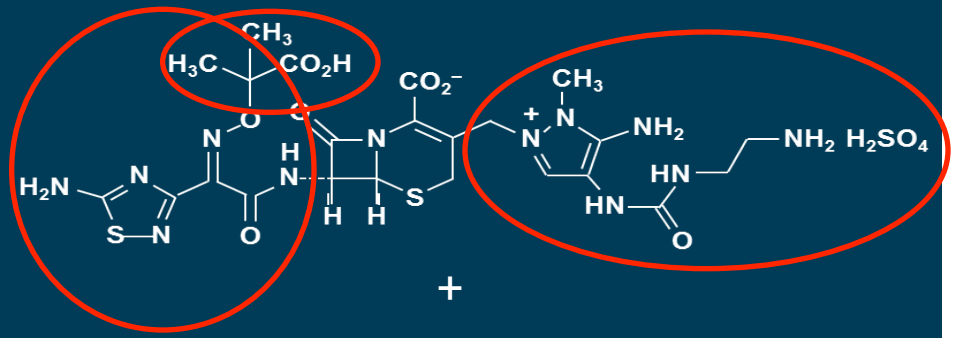
- Carbapenems
- Gentamicin or amikicin (if susceptible)
- Temocillin
- Tigecycline
- Colistin
- Fosfomycin
- Ceftolozane/tazobactam

Oral agents

- Nitrofurantoin
- Fosfomycin
- Cefixime or Pivmecillinan with Co-amoxiclav

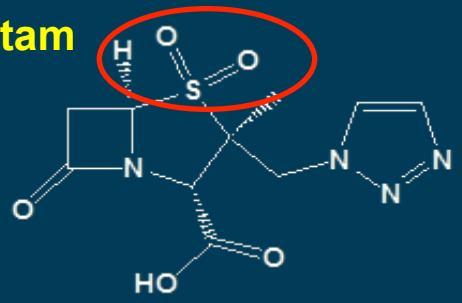
Structure Activity Relationship

Ceftolozane



+

Tazobactam



Ceftolozane

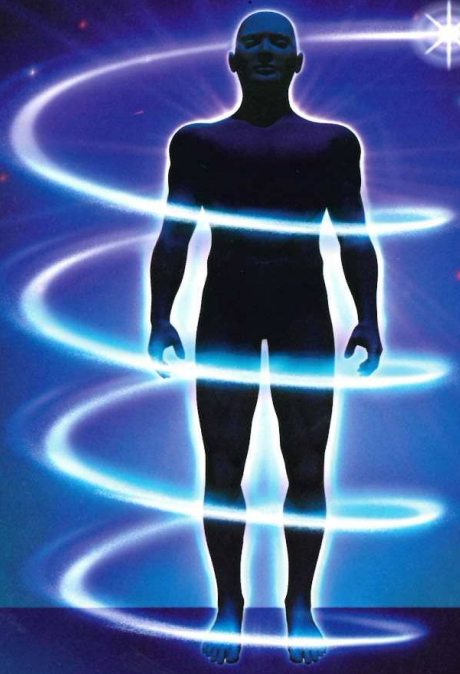
- Aminothiadiazole ring 7-position side chain provides enhanced activity against Gram-negative bacilli
- Dimethylacetic acid moiety provides improved antipseudomonal activity
- Pyrazole ring on the 3-position side-chain confers stability against AmpC β-lactamases

Tazobactam

- Sulfone group at position 1 facilitates bond formation with β-lactamases, leading to inhibition

Zhanel et al. *Drugs*. 2014;74:31-51.

Hard-Hitting Empiric Monotherapy You Can Trust



Carbapenem Power[1], Cephalosporin Tolerability[2]
The Flexible Carbapenem[1]

MERONEM® meropenem

"Meronem" is a trademark of the AstraZeneca group of companies
Detailed prescribing information is available on request.

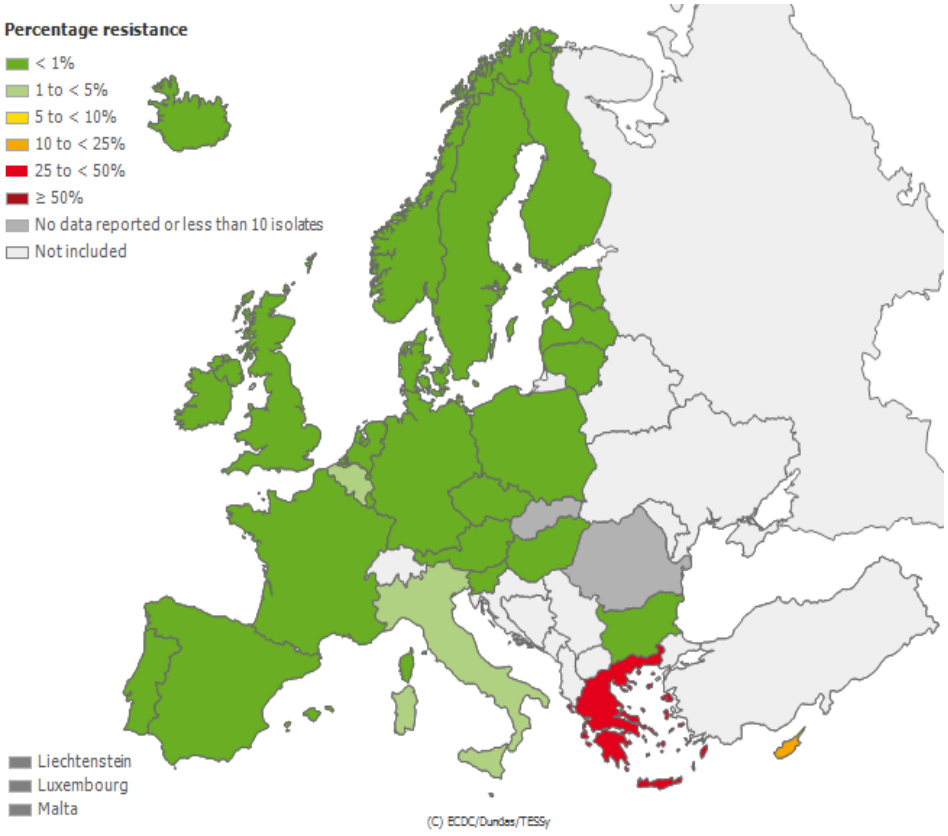
1. Verwaest C. *Clin Microbiol Infect* 2000;6:294-302.
2. Norrby SR, Gildon KM. *Scand J Infect Dis* 1999;31:3-10.

AstraZeneca

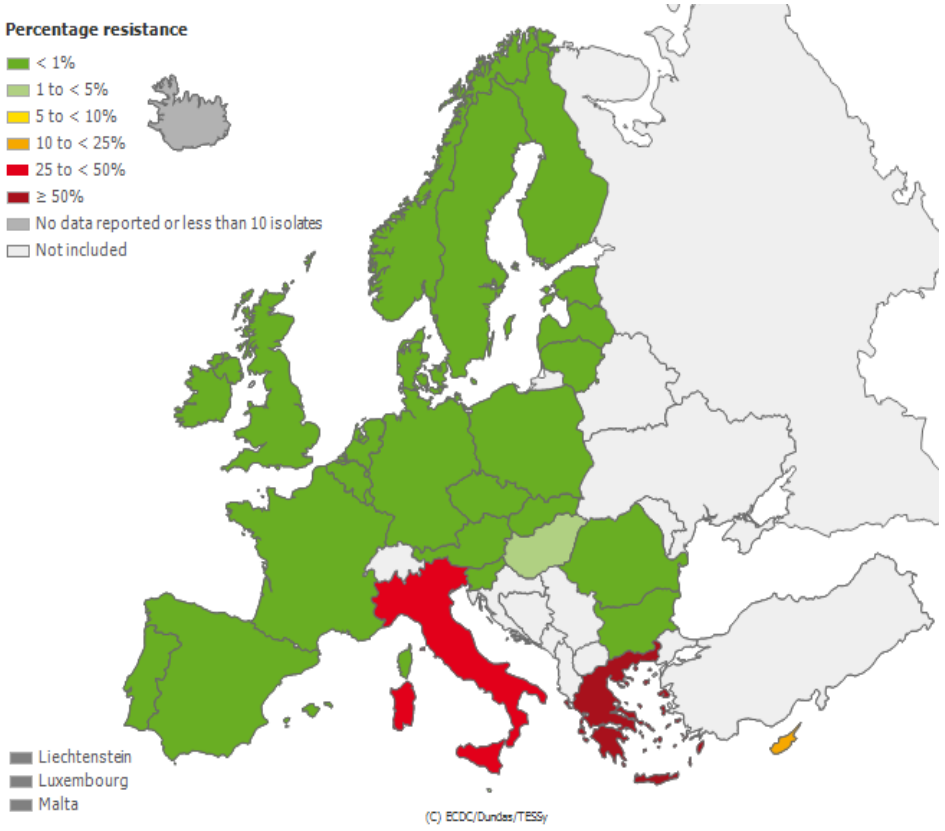
AstraZeneca Hong Kong Limited
2301 Cosco Tower, Grand Millennium Plaza
183 Queen's Road Central, Hong Kong
Tel: 2420 7388 Fax: 2422 6788

Proportion of Carbapenems Resistant (R) *Klebsiella pneumoniae* Isolates in Participating Countries

2009

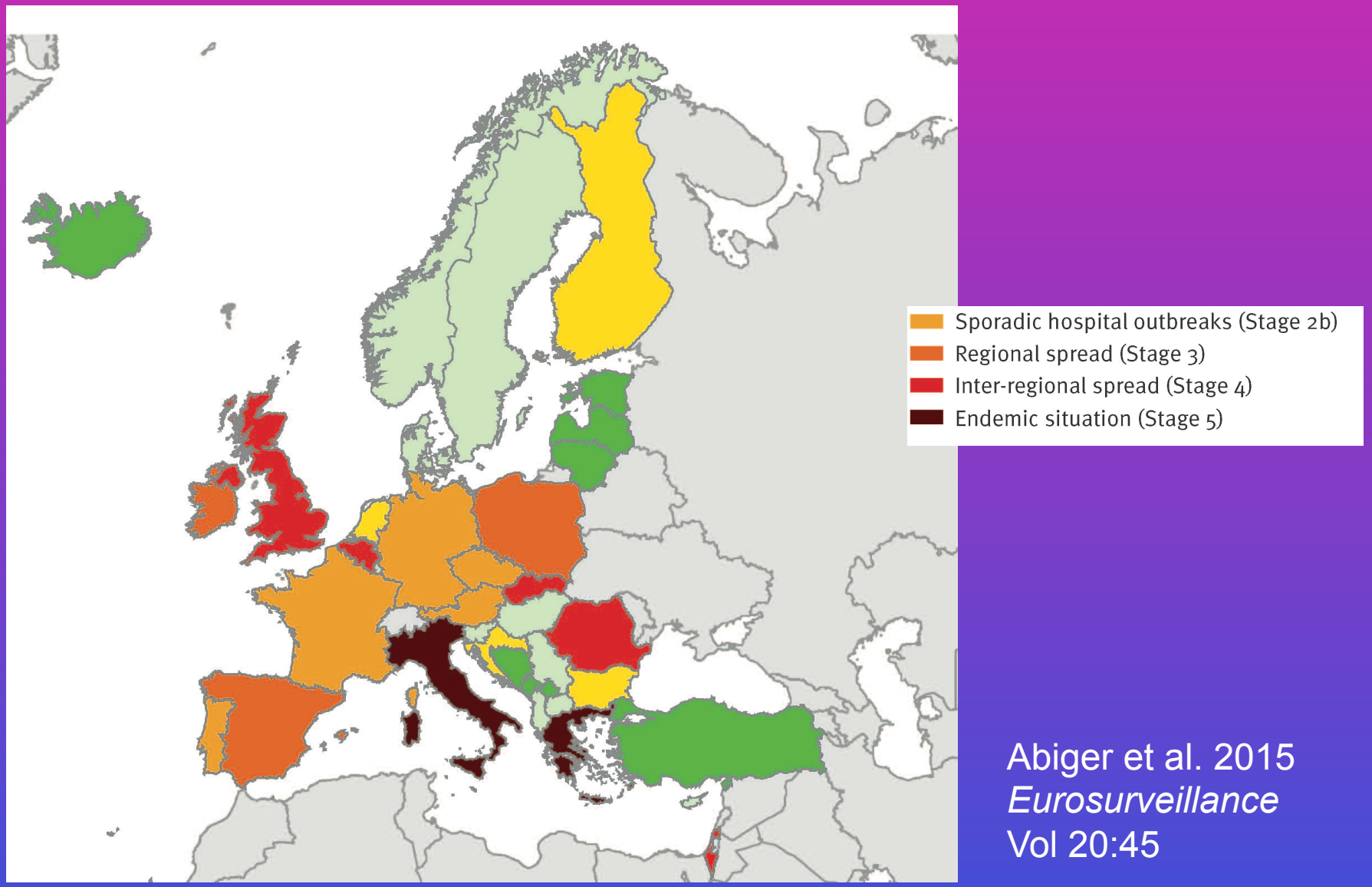


2011



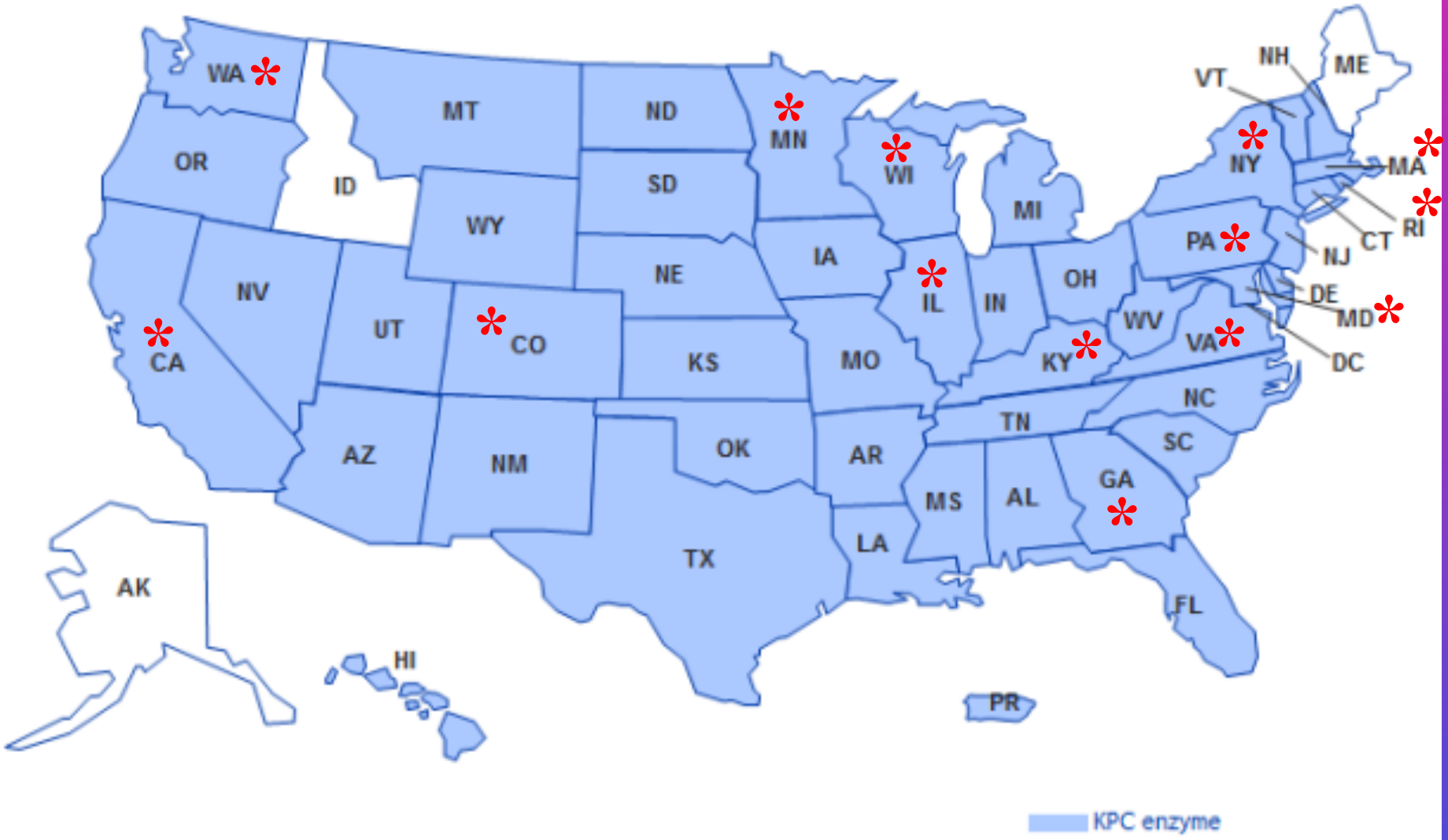
TESSy, The European Surveillance System, European Centre for Disease Prevention and Control 2012

Klebsiella pneumoniae carbapenemase (KPC) 2014/15

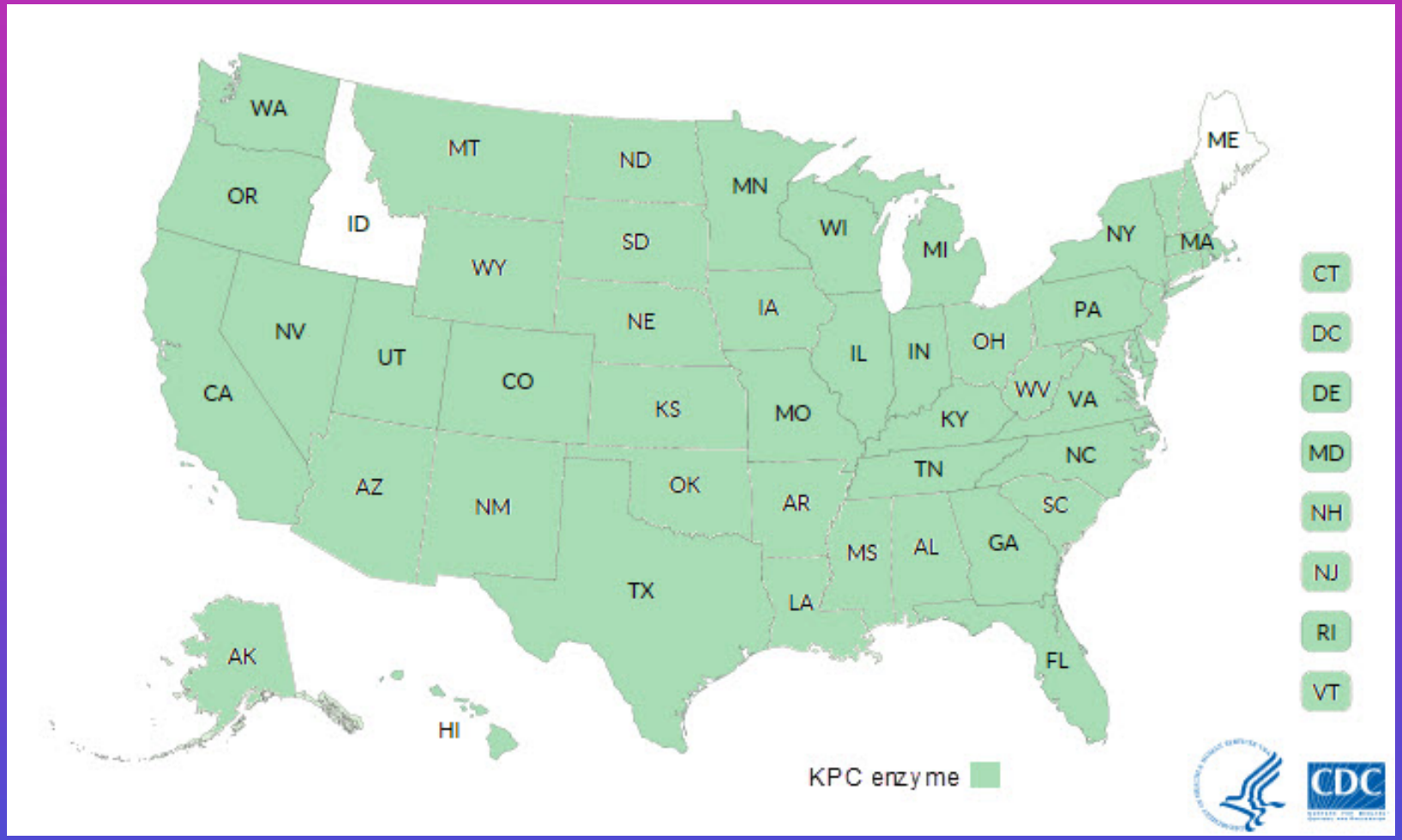


Abiger et al. 2015
Eurosurveillance
Vol 20:45

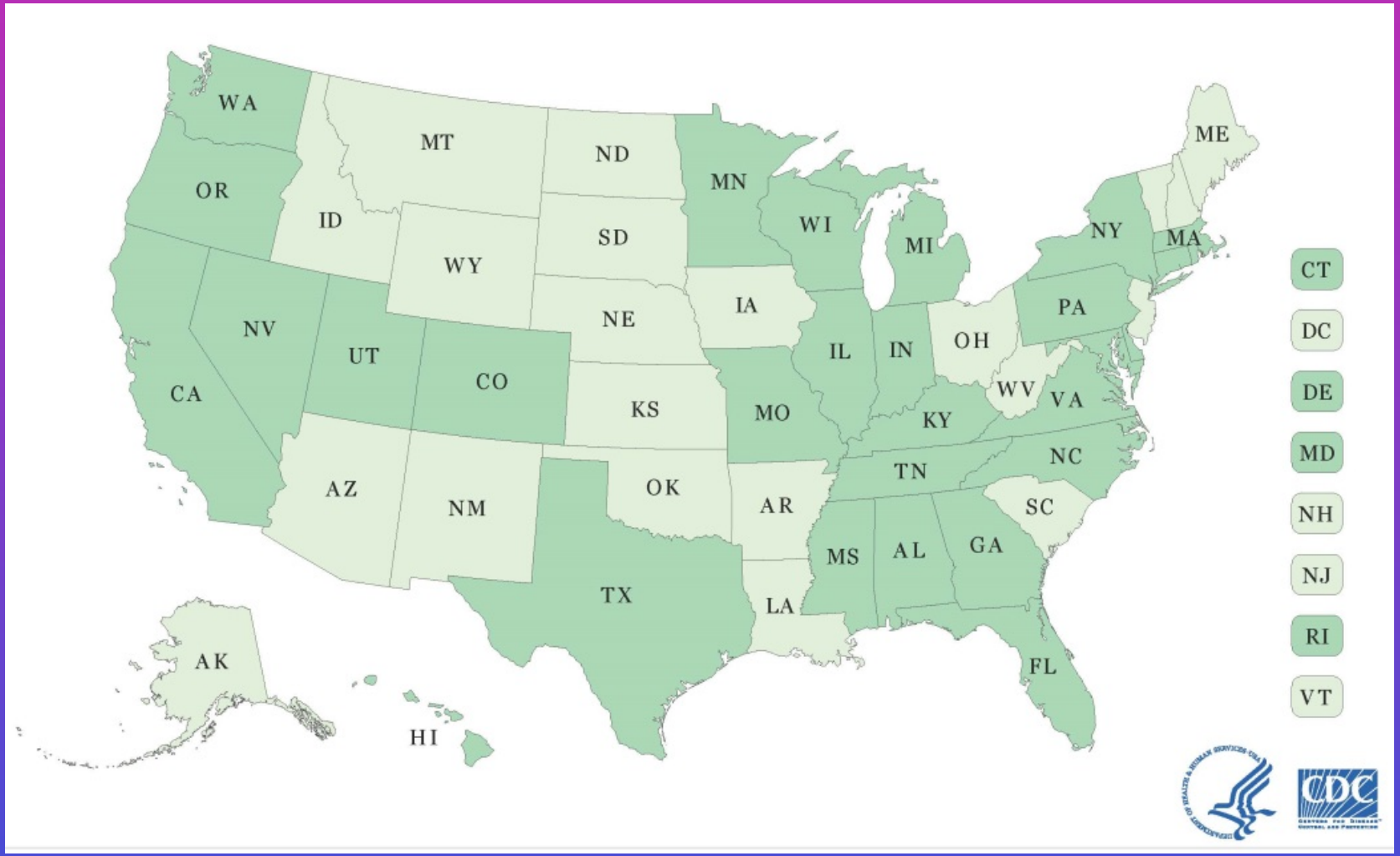
Carbapenemase-producing CRE in the US confirmed by CDC



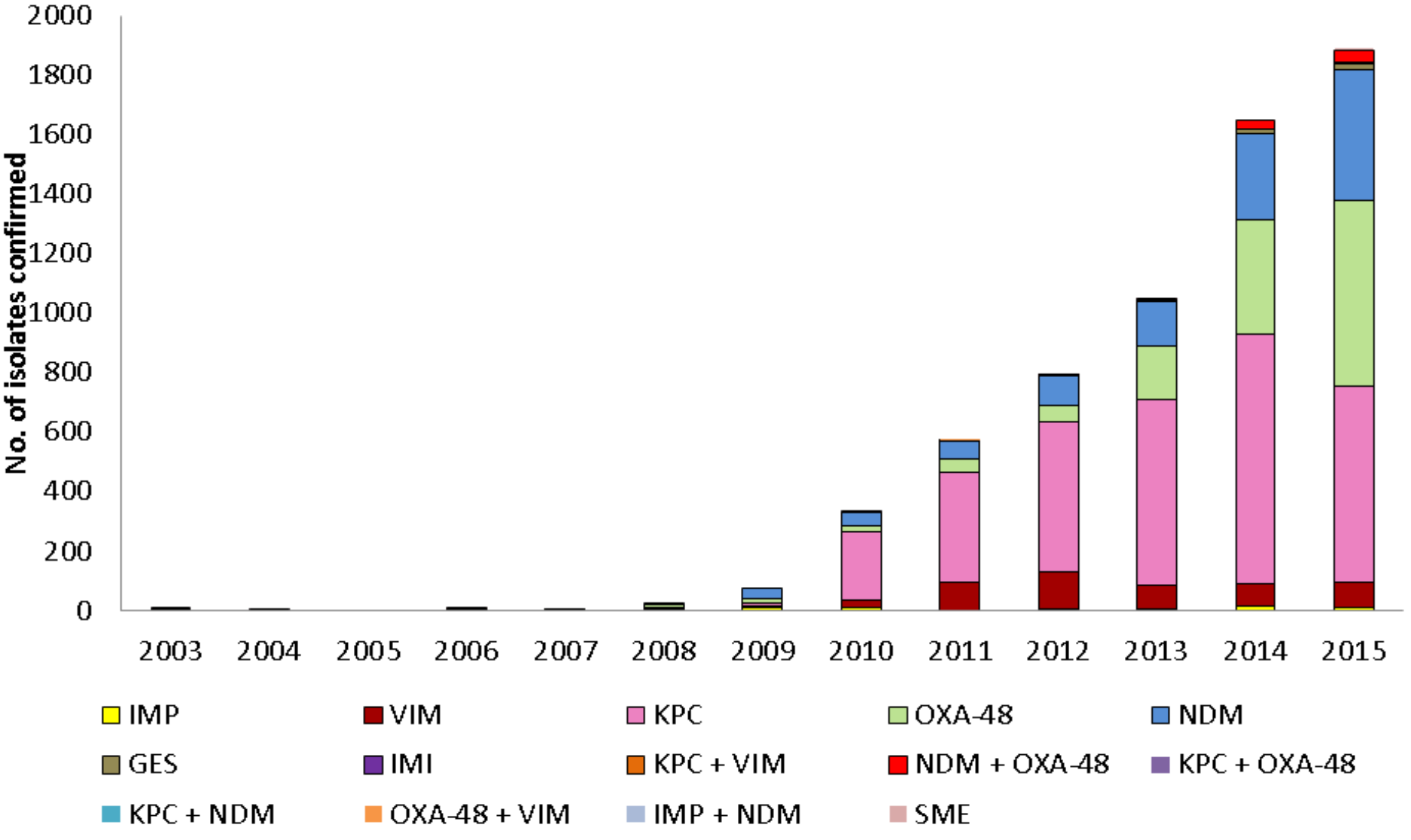
Patients with KPC-producing Carbapenem-resistant Enterobacteriaceae (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of January 2017, by state



Patients with NDM-producing Carbapenem-resistant Enterobacteriaceae (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of January 6, 2017, by state



CPE confirmed by PHE-from Laboratories in England



CCarbapenamase producing Enterobacteriaciae in West Midlands 2007-14

- 60% submitted in 2013/14 – 119 unique isolates
- 69/119 NDM; 26/119 KPC; 16/119 OXA-48 like 7/119 VIM; 1/119 NDM + OXA
- Isolates mainly *Klebsiella (*89/139 submitted),many different ST's only four ST 258
- 25/139 *E.coli,* mainly NDM,only two ST131

Findlay et al 2017 JAC

Agents for treating infections caused by carbapenemase producers

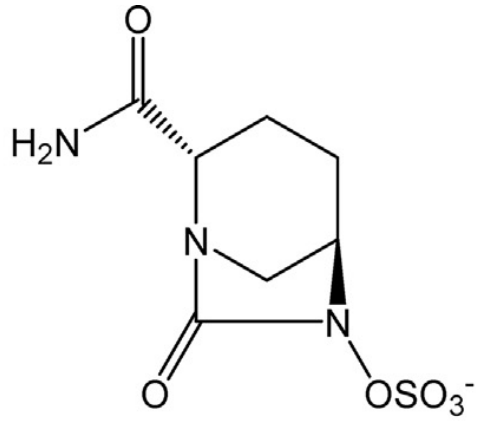
Intravenous

- Gentamicin /amikacin,ciprofloxacin (if susceptible)
- Tigecycline
- Colistin
- Temocillin if KPC in urine
- Fosfomycin
- Ceftazidime/avibactam

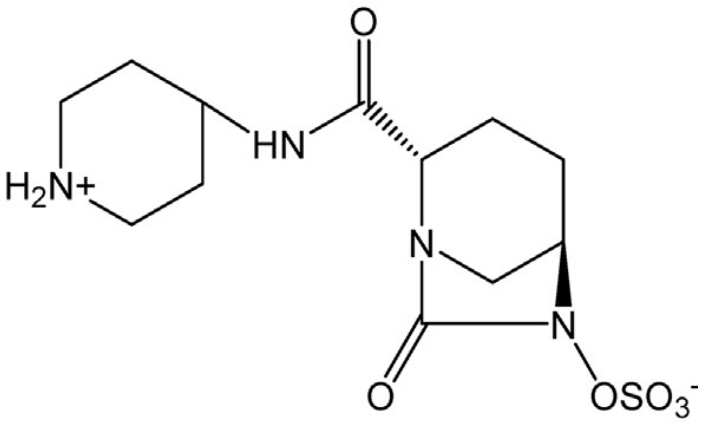
Oral agents

- Fosfomycin

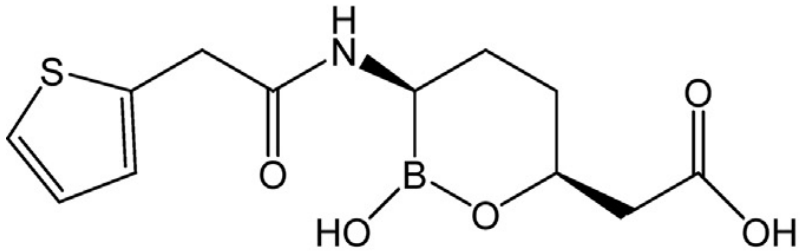
Inhibitors of serine β-lactamases



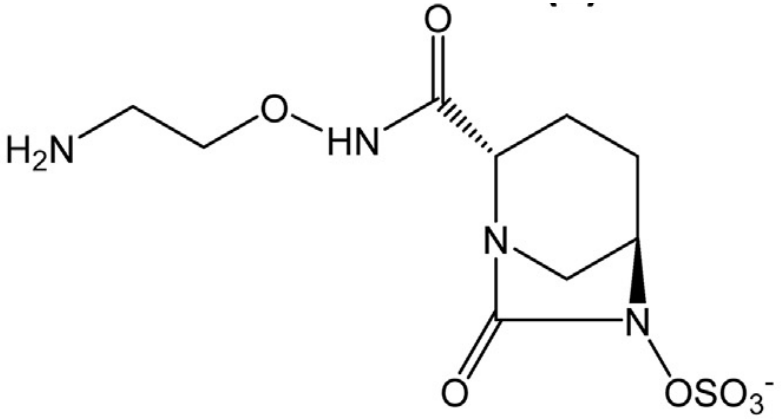
avibactam



relebactam



RPX7009



RG6080

Bush K 2016 *IJAA* 2015;46: 483-493

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: "We're Gonna Need a Bigger Boat"

Brad Spellberg[1,2] and Robert A. Bonomo[3]

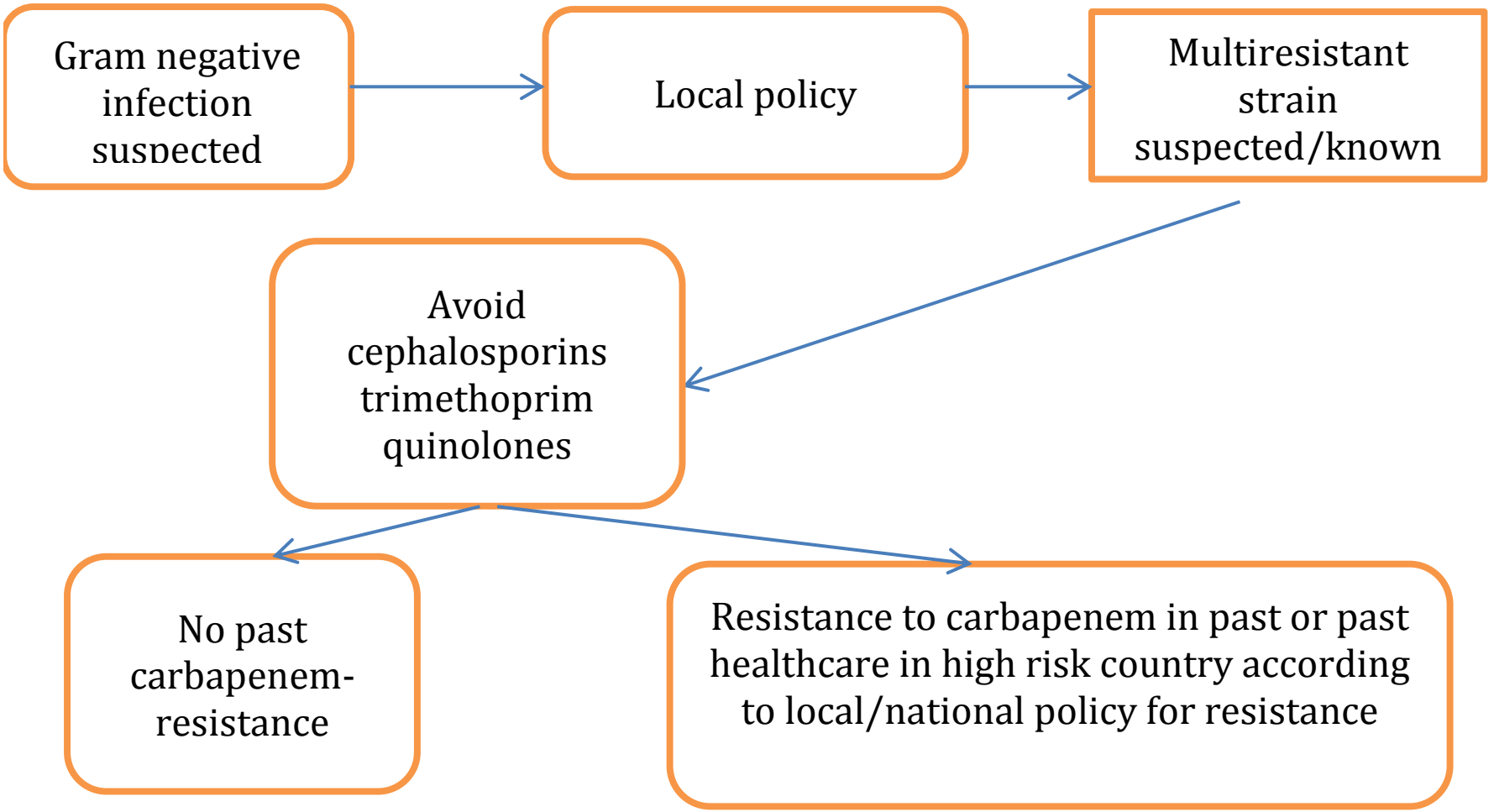
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Mutations in KPC-3 giving resistance to ceftazidime-avibactam (cazavi)

- 10/37 patients with CPE had microbiologic failure
- 3/10 failing had KPC-3 mutant strains cazavi MIC 32->256
- Impact of mutations on cazavi MICS: 179 tyr/thr 243 met > asp 179 tyr>val 240 gly
- ? Affected Ω loop binding of caz to site enhancing hydrolysis and/or reducing avibactam binding

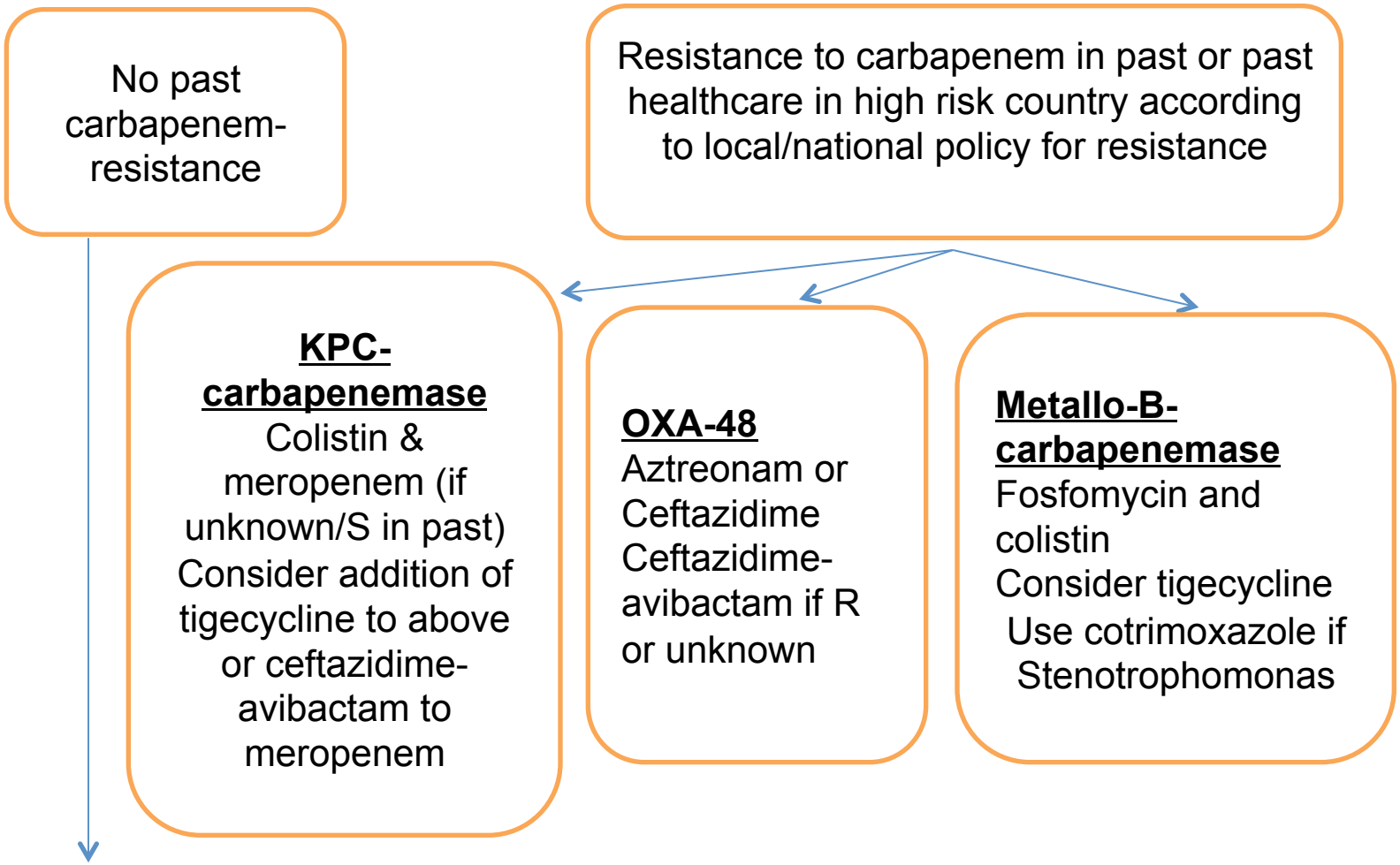
Shields AAC, 2017 E02097 Shields CID, 2016 63, 1615

Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals



Joint Working Party on MDRGNB infection: Treatment

Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals



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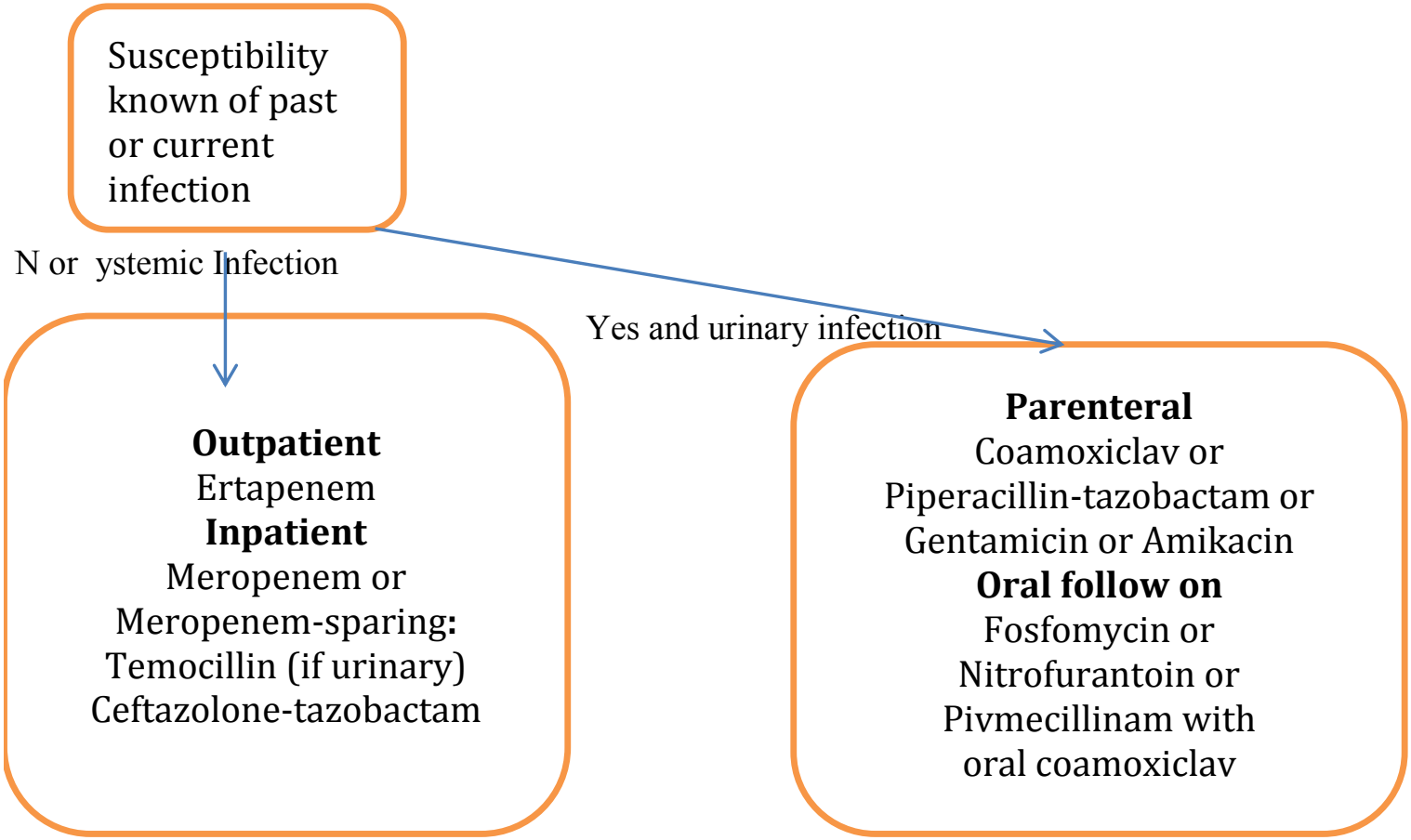


Joint Working Party on MDRGNB infection: Treatment

Fosfomycin trometamol

- Licenced in UK 1994-6, now available for uncomplicated cystitis
- Only 4 observational studies for lower UTI caused by MDRGNB[1]
- Has been used for prophylaxis of pyelonephritis in ASB of pregnancy
- PK recently reviewed[2], need for studies in upper UTI
- Little published experience with parenteral,but sucessful in 9/15 pandrug res Klebs[3]
- Will resistance rise with greater use, China 60% of KPC producers resistant with *fosA3*[4]

Nice 2013[1], Zhanel Can JID 2016, 2082693[2] , Pontikis IJAA 2014 [3],Jiang 2015, IJAA **45, 66**[4]

Pivmecillinam

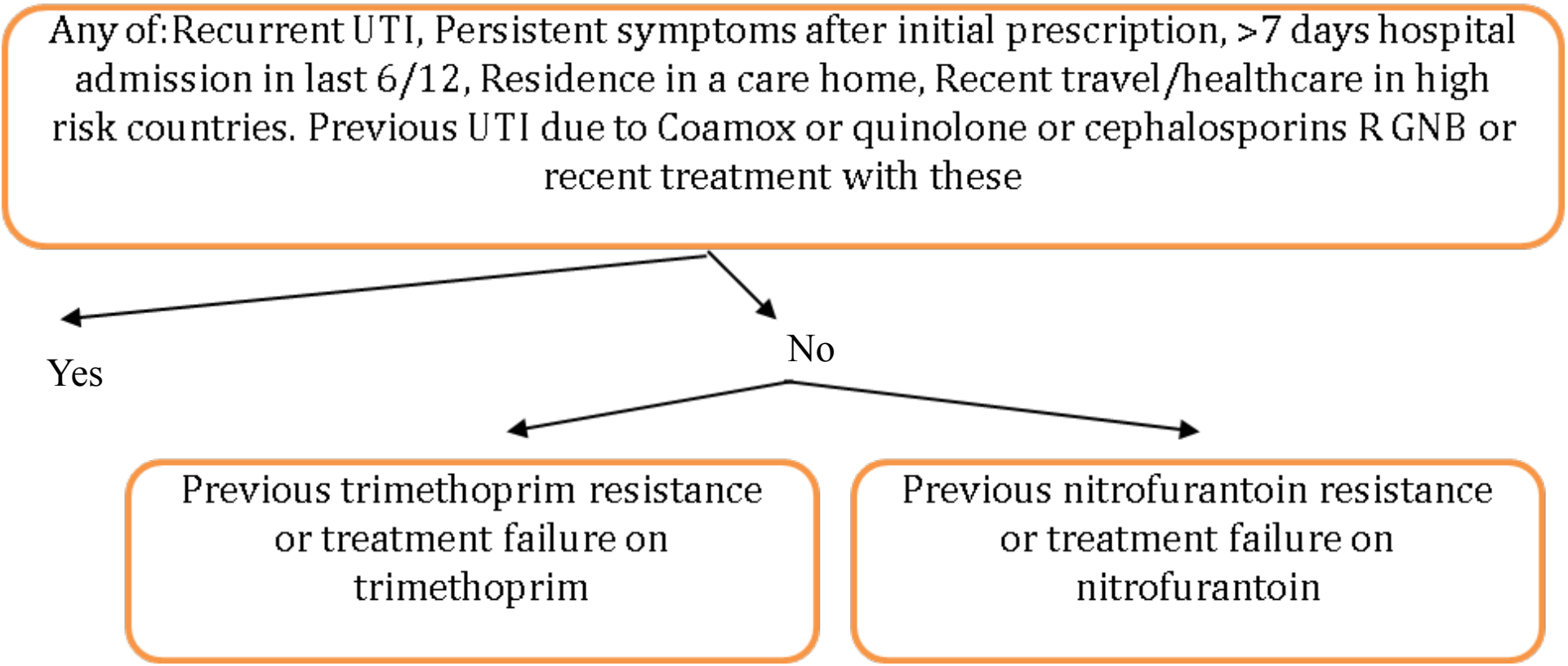
- Inactive ester converted to active mecillinam
- Against ESBL only case series available, variable results when used alone poorer against CTX-M 15,but stable to AmpC
- Combination with co-amoxiclav reduces MICs and trials needed in ESBL
- Stability to most carbapenemases, particularly KPC is poor.
- Resistance in clinical isolates is due to mutations in *cysB* resulting in reduced fitness
- A single old good RCT suggested that i.v. mecillinam with ampicillin performed well in pyelonephritis[1]

[1]Cromberg S 1995 Scan J.I.D. **27**,463

NNitrofurantoin

- Now recommend above trimethoprim for lower UTI
- Low rates of resistance (1-4%), but higher in ESBLs although resistant strains have reduced fitness
- V. Low tissue concentrations, common ESBL *E.coli* clones have pathogenicity factors for upper tract disease (e.g. ST131, ST9 etc)
- Do not use in renal impairment , rare pulmonary AE's
- Urgent need for good comparative studies in ESBLs with other agents

Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB



Joint Working Party on MDRGNB infection: Treatment

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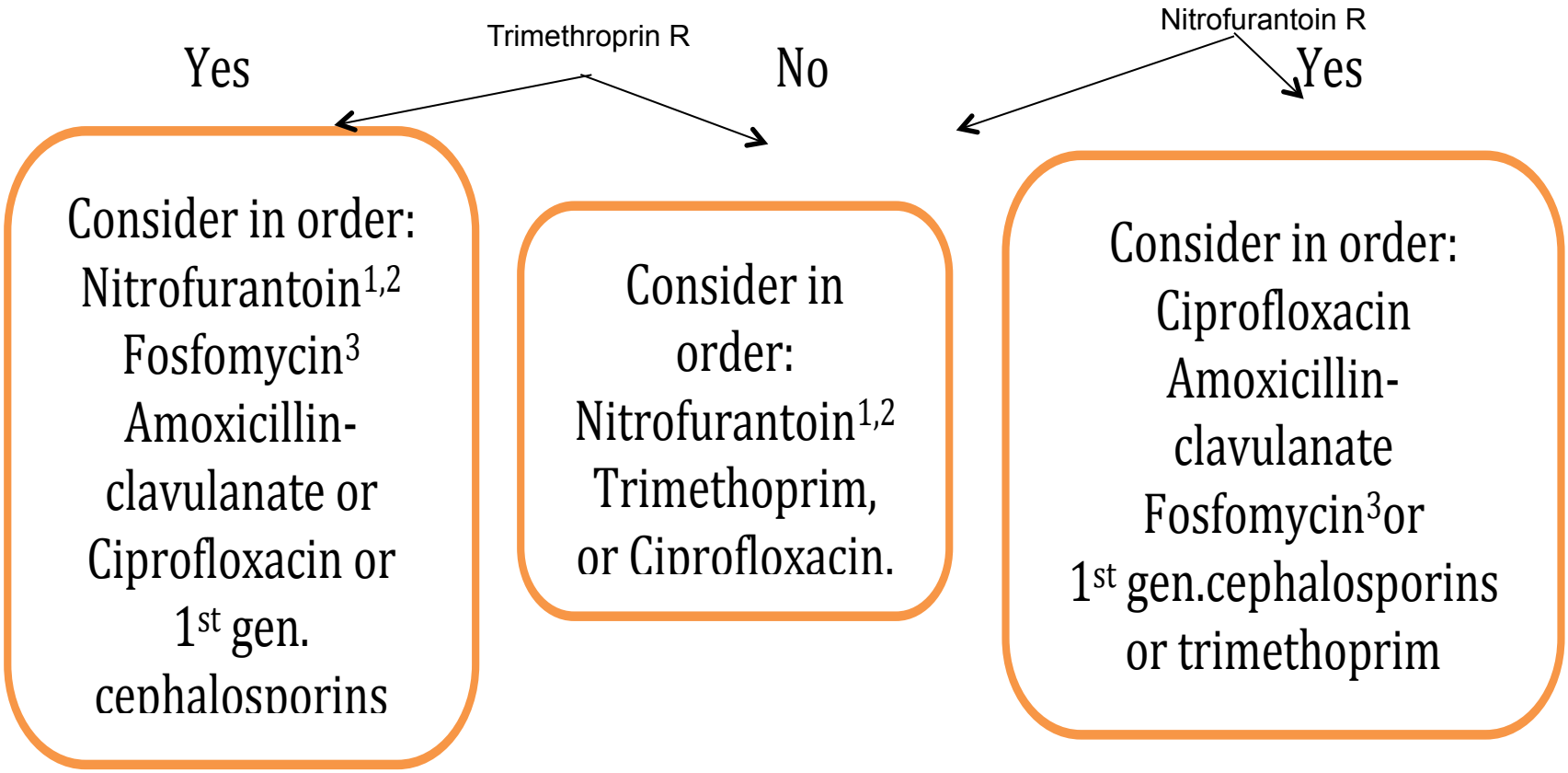

Joint Working Party on MDRGNB infection: Treatment

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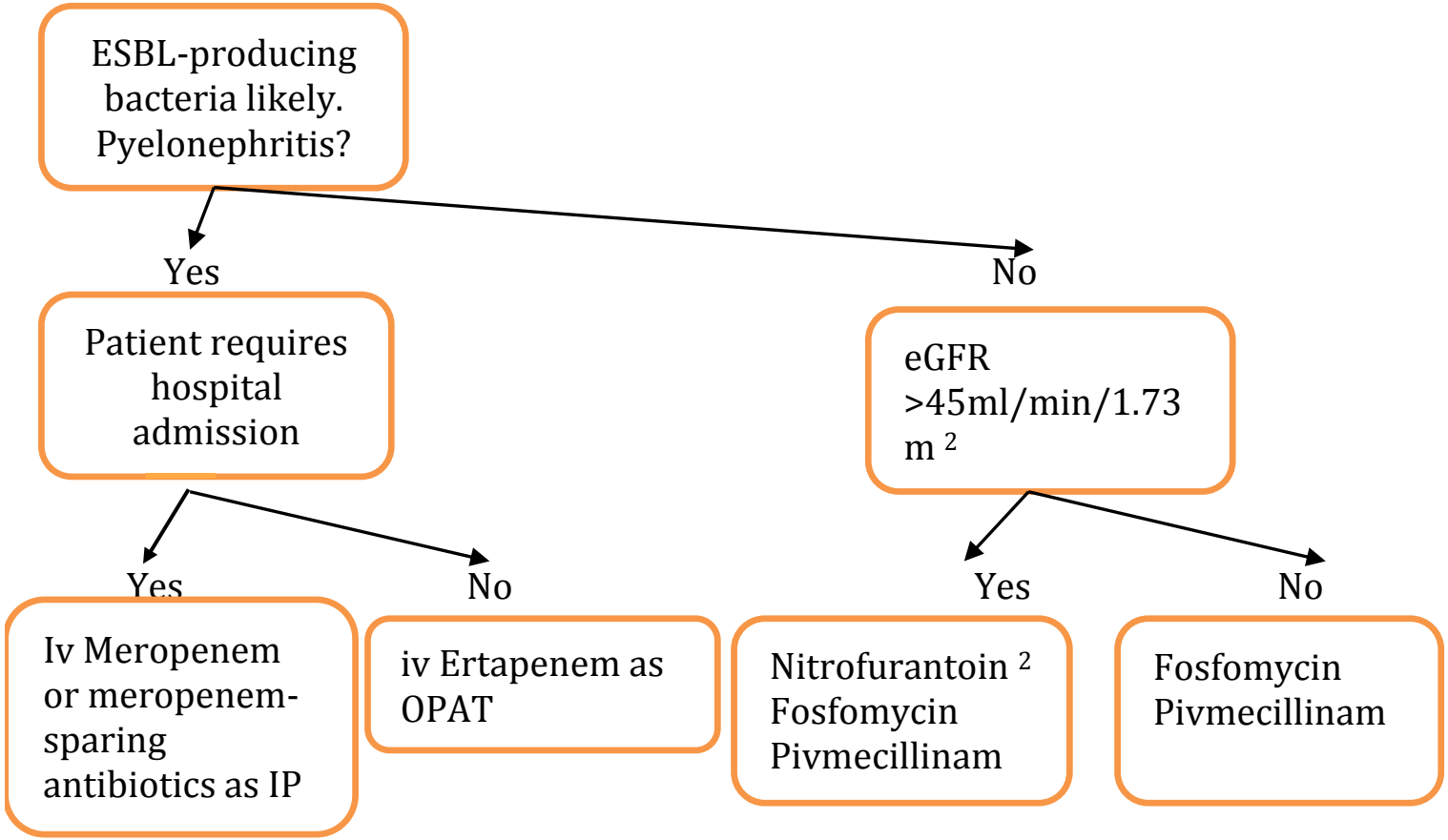

[1]Not nitrofurantoin if pyelonephritis or eGFR <45ml/min.
[2]Caution re prolonged/frequently repeated courses
[3] Not fosfomycin if pyelonephritis

Joint Working Party on MDRGNB infection: Treatment

CConclusions - 1

- We found licencing trials contribute little to the understanding of the use of agents against MDRGNB often have very low numbers of resistant bacteria.
- Very few quality in use studies with outcomes – particularly for older agents-need for new studies/registers.
- VAP and cIAI with CPE difficult and relies on combinations with colistin, tigecycline, meropenem (if MIC low) and new agents e.g. BLI’s

Conclusion 2

- The increase in nitrofurantoin use may increase pyelonephritis as trimethoprim provided cover. Lack of oral agents with activity against very resistant GNB-probably only fosfomycin.
- Empirical treatment is dictated by local and imported epidemiology.
- Risk factors other than hospital treatment abroad lacking.
- Rapid changes in epidemiology in some countries e.g. Italy,USA,China,South Asia will impact success of new & old agents.As resistance genes become integrated into community faecal flora empirical treatment of community presenting patients will be difficult. Asia current biggest risk reservoir.
- Rapid diagnostics to target susceptibilities of MDRGNB critical to better management.