Current options and strategies for the treatment of drug resistant Gram negative in India

Dr Ram Gopalakrishnan

Differences between western world & India

	Western world	India
Common Isolates	Gram +ves	Gram -ves
ESBL & CR prevalence in gram –ves	Much less	Very high
Prevalence of resistance in last few years	Slow increase	Rapidly increasing
Infection control	Good	Not optimal
Generics	Very few	Many, quality unclear
Restriction of antibiotic prescription	Strict	No control

Guidelines made by western world keeping their issues in mind may not suitable for India[1]

1. Soong JH et al. Am J Infect Control 2008;36:S83-92.

The Indian scenario

- Capital of Gram negative resistance
- Poor to absent infection control but burgeoning private healthcare industry with technological advances such as transplants
- Newer drugs available abroad take time to come
- What is available is often not affordable
- Irrational combinations abound due to poor regulatory control
- Antibiotic pipeline empty

What I shall cover

- ESBL producing Enterobacteriaceae
- CR-Pseudomonas (CRPa)
- CR-Acinetobacter (CRAb)
- CR Enterobacteriaceae (CRE)
- Colistin and carbapenem resistant Enterobacteriaceae (CCRE)

Classification Schema of β-Lactamase Genes

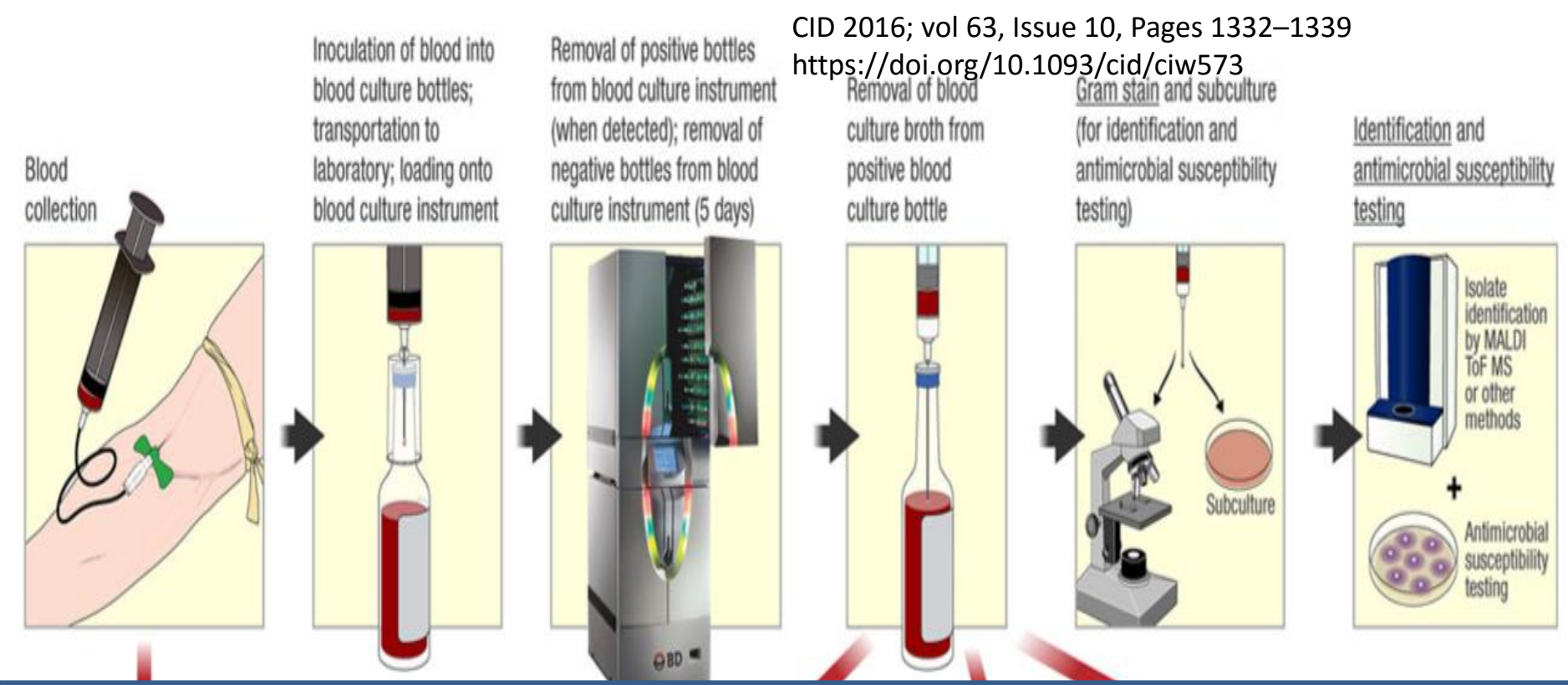
Ambler Classification	Bush/Jacoby Classification	Notable Enzyme Types
Class A	2a, 2b, 2be, 2br, 2ber, 2c, 2ce, 2e, 2f	ESBLs—TEM, SHV, CTX-M, PER Carbapenemases—KPC
Class B	3a, 3b	Carbapenemases—IMP, VIM, NDM
Class C	1, 1e	Cephalosporinases—AmpC
Class D	2d, 2de, 2df	ESBLs—OXA Carbapenemases—OXA

Principles in treatment of MDROs

Distinguish colonization from infection

- Determine sensitivity ASAP using molecular tests directly from blood cultures
- First dose supremacy is important
- Know the exact molecular mechanism of resistance and exact MICs
- Use standard antibiotics with increased doses, so PK/PD targets are still achieved
- Use nonstandard antibiotics for which resistance has not yet occurred
- Use combination therapy with antibiotics
- Use adjunctive therapies (surgery, reversal of immunosuppression)

CID 2016; vol 63, Issue 10, Pages 1332–1339
https://doi.org/10.1093/cid/ciw573



Molecular diagnosis of BSIs

- Meta-analysis: mortality risk significantly lower with mRDT than with conventional microbiology methods [OR] 0.66.
- with antimicrobial stewardship programs (ASPs) (OR, 0.64)
- number needed to treat: 20
- Time to effective therapy decreased by −5.03 hours
- aLOS decreased by −2.48 days

- mRDT should be considered as part of the standard of care in patients with BSIs

Clin Infect Dis. (2017) 64 (1): 15-23.

Rapid ID once blood culture flags identifies organism same day

- MALDI-TOF direct from blood culture bottle
  - Better for GNB than GPC
  - Can do on culture plate after 4-6 h incubation
- Rapid Multiplex PCR
  - Verigene GPC/GNB/yeast
  - FilmArray Blood Culture ID Panel
    - identifies 19 bacteria, 5 yeast, 3 resistance markers
    - reduced treatment of contaminants and broad-spectrum antimicrobial use
    - Combined with audit and feedback by an antimicrobial stewardship team, enhanced antimicrobial de-escalation.
- Carba R
- PNA-FISH
- Accelerate diagnostics: gives AST based on bacterial behaviour after antibiotic exposure on PNA-FISH

Clin Infect Dis published 20 July 2015, 10.1093/cid/civ447

Multiplex polymerase chain reaction (PCR) for rapid bacterial identification from blood cultures: ready for prime time in India?

Yamunadevi Vellore Ramanathan[1,], Rajalakshmi Arjun[2], Vidya Krishna[3], Anil Tarigopula[4], Ram Gopalakrishnan[5]*

Abstract

Introduction Early identification and determination of antimicrobial susceptibilities of microorganisms growing in blood cultures is crucial as delay can lead to increased mortality, morbidity and cost. This study was done to evaluate the usefulness of the FilmArray blood culture identification (FA-BCID) in comparison with conventional techniques in early identification and antimicrobial initiation.

Methods This was a single centre, prospective study conducted in a 24-bed critical care unit (CCU) of a tertiary care hospital at Chennai, India between October 2016 and December 2016. Patients whose blood culture bottles were flagged using the BACTEC-FX system were included. The blood culture was processed by FA-BCID and by conventional method and the results were compared.

Results A total of 36 positive blood cultures were analyzed by both FA-BCID and conventional method from patients admitted in the CCU. FA-BCID accurately identified 80% of the organisms. Of 32 isolates identified by FA-BCID, 50% (16/32) showed isolated growth of Gram negative bacteria (GNB), 37.5% (12/32) showed isolated growth of Gram positive (GP) bacteria, whereas 12.5% (4/32) showed >1 micro-organism in the same culture bottle. Overall, sensitivity, specificity, positive predictive value and negative predictive value were 100% for the identification of GP bacteria, and 69%, 100%, 100% and 76.4% for GNB, respectively. FA-BCID identified oxacillin resistance (mec A) accurately, whereas resistance mechanisms could not be predicted at all in cases of Gram negatives as the kit only has KPC gene identification system. The turnaround time of FA-BCID was a median of 2 hours compared to 2 days for the conventional method. Antibiotics were de-escalated or escalated in 47.2% of patients based on FA-BCID within a median time of 3 hours.

Conclusion FA-BCID is a significant advance in the early identification and escalation or de-escalation of treatment for bacteremia in critically ill patients, with a high sensitivity for Gram positive bacteria as compared to Gram negative bacteria. Incorporation of probes for prevalent pathogens and resistance genes would make this panel more useful in Indian settings.

J Contemp Clin Pract. 2019;5(1):24-30. doi: 10.18683/jccp.2019.1042

Table 1. FA-BCID panel constituents

Antimicrobial resistance genes
1. KPC (carbapenem resistance gene)
2. *mecA* (methicillin resistance gene)
3. *vanA/B* (vancomycin resistance gene)
Gram positive bacteria
1. *Enterococcus*
2. *Listeria monocytogenes*
3. *Staphylococcus*
4. *Staphylococcus aureus*
5. *Streptococcus*
6. *Streptococcus agalactiae* (group B)
7. *Streptococcus pneumoniae*
8. *Streptococcus pyogenes* (group A)
Gram negative bacteria
1. *Acinetobacter baumannii*
2. *Enterobacteriaceae*
3. *Enterobacter cloacae* complex
4. *Escherichia coli*
5. *Klebsiella oxytoca*
6. *Klebsiella pneumoniae*
7. *Proteus*
8. *Serratia marcescens*
9. *Haemophilus influenzae*
10. *Neisseria meningitidis*
11. *Pseudomonas aeruginosa*
Yeast
1. *Candida albicans*
2. *Candida glabrata*
3. *Candida krusei*
4. *Candida parapsilosis*
5. *Candida tropicalis*

Why combination therapy?

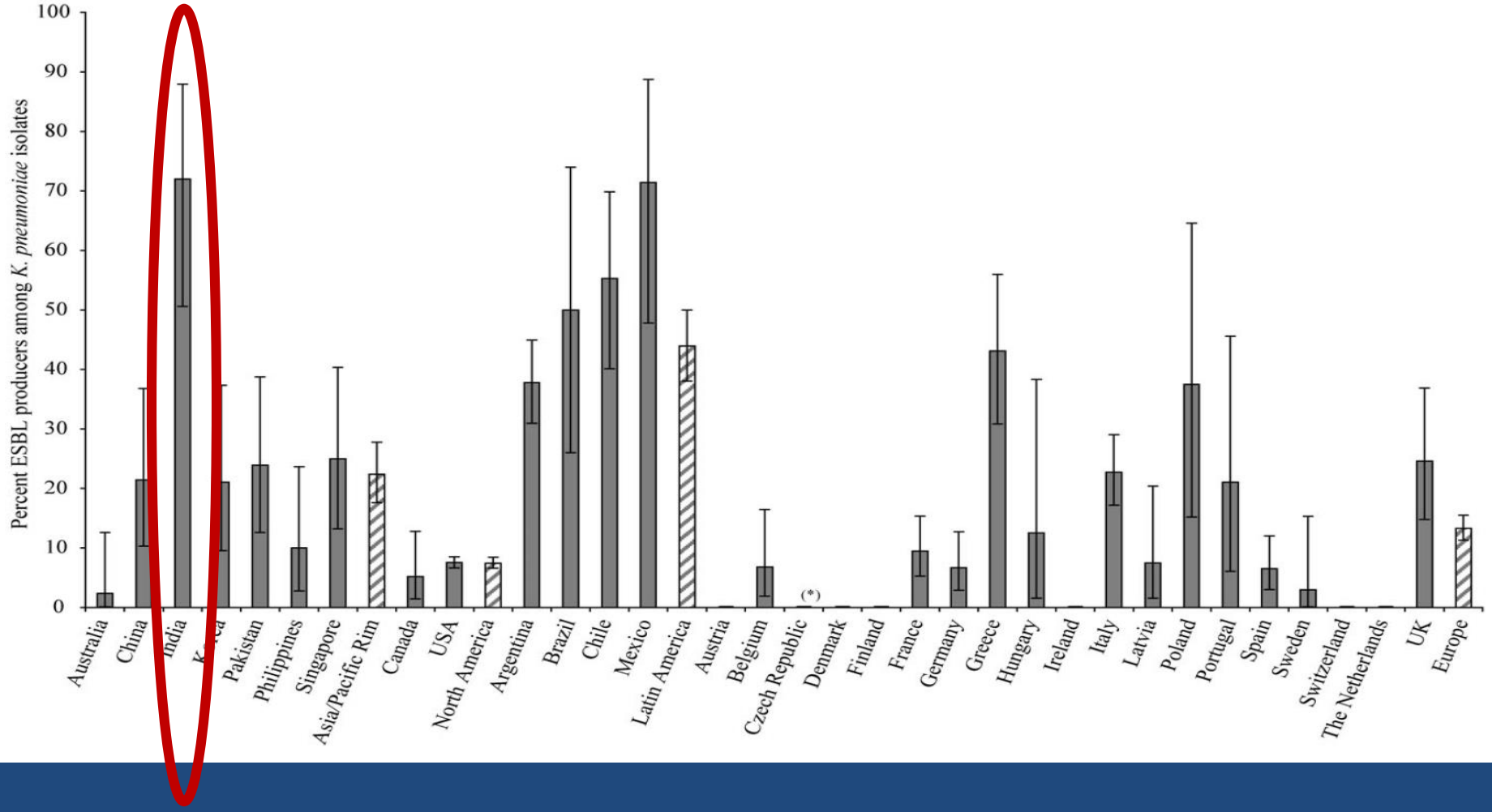
- To provide synergistic activity
  - Beta-lactam acts at cell wall and allows penetration of aminoglycoside to the ribosome
    - eg penicillin plus gentamicin for enterococcal endocarditis
  - Colistin acts as a detergent at cell membrane, allows overcoming of porin channel mediated resistance to carbapemems
- To prevent emergence of resistance while on therapy
  - eg in tuberculosis or HIV
- To broaden spectrum and ensure at least one agent effective against a resistant organism
  - When Pseudomonas is multi drug resistant (MDR)

ESBL producing Enterobacteriaceae

What are extended spectrum beta-lactamases (ESBLs)?

- First described in 1983 from Germany
- Plasmid carried enzymes made by E.coli, Klebsiella, other Enterobacteriaceae
- Break down cephalosporins, penicillins, aztreonam
- Originated from environmental Kluyvera species with subsequent cross-species transmission amongst enterobactereaciae
- CTXM-15 is commonest ESBL in India and worldwide
- Often resistance to quinolones and aminoglycosides carried on the same plasmid
- Beta-lactam/beta-lactamase inhibitors may work
- Carbapenems only reliable drug

A global study on prevalence of ESBL in K.pneumoniae of over 86,000 isolates from 266 centers



Reinert RR, Low DE, Rossi F, et al. J Antimicrob Chemother (2007) 60:1018–29.

Treatment of Infections Caused by ESBL-Producing Organisms

- "Carbapenems are the surest agents for therapy (for ESBL-producing organisms) . . . ."
- For organisms producing TEM and SHV-type ESBLs:
  - apparent in vitro sensitivity to cefepime and to piperacillin-tazobactam is common
  - but both drugs show an inoculum effect
- additional resistance mechanisms (eg, AmpC β-lactamases, OMP mutations) reduce efficacy

Jacoby GA, Munoz-Price L. *N Engl J Med* 2005;352:380-391
Clin Infect Dis 2013 56: 488-495

Clinical Infectious Diseases

INVITED ARTICLE

ANTIMICROBIAL RESISTANCE: George M. Eliopoulos, Section Editor

The Use of Noncarbapenem β-Lactams for the Treatment of Extended-Spectrum β-Lactamase Infections

Pranita D. Tamma[1] and Jesus Rodriguez-Baño[2]

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- Cephamycins eg cefoxitin
- Cefepime
- Piperacillin-tazobactam
- Cefoperazone-sulbactam

- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**
- **? Cefepime-tazobactam**

Clinical Infectious Diseases® 2017;64(7):972–80

First generation BLIs for ESBL

- ESBLs are generally inhibited by tazobactam, although production of multiple ESBLs and co-production of AmpC β-lactamase may limit the effectiveness of P/T combination.
- Additional contentious issues are
  - (i) occurrence of inhibitor resistance enzymes (e.g. TEM-IRT)
  - (ii) inoculum effect that may overwhelm the inhibitor activity, during severe infections where the bacterial population is high and
  - (iii) false-negative ESBL detection when AmpC is produced

Can we use BL/BLI for ESBL E.coli bacteremias?

- **Post Hoc Analysis of Prospective Cohorts from Spain**
  - **Predominantly E coli from urinary and biliary sources**
  - **Mortality rates same for both empirical and definitive therapy**
  - **"AMC or PTZ are suitable options for the definitive therapy of susceptible ESBL-EC strains causing BSI, mainly in the urinary and biliary tracts, which could help prevent overuse of carbapenems."**
- **Re-analysed above data based on piperacillin MIC**
  - **<2, 4-8, >8**
  - **Mortality 41% for high MIC vs 0% for low MIC**
  - **No deaths with urosepsis**

Clin Infect Dis 2012 54: 167-174
BMC Infectious Diseases 2012, **12**:245
Antimicrob Agents Chemother 2013; 57:3402–4.

Research

JAMA 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

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Table 2. Primary Analysis and Subgroup Analyses

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	.31
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	.99
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	.99
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	.26
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	.70
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	.27
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	

Now, why did pip-taz fail?

- Likely the reason is due to complex resistance mechanisms exhibited by the isolates.
- On WGS, 67.6 % showed OXA 1 narrow spectrum oxacillinases blaOXA-1 (inhibitor resistant [IRT] enzyme) in addition to ESBLs and ampCs.
- These are of course are not inactivated by tazobactam.
- ESBL can be masked by the co-production of AmpC; moreover, a high inoculum effect may cause pip-taz to fail
- Co-production of blaCTXM-15 + blaOXA-1 is too strong a combination for βL/βLI to be effective

How it has changed my practice

- I always now use carbapenems as empiric therapy for severely ill patients
- De-escalate to ertapenem rather than piptaz
- Pip-taz best reserved for less severely ill patients in whom bacteremia is unlikely or after susceptibilities are available

BL-BLIs for ESBL bacteremias: when to use

- ✖ **Avoid till bacteremia excluded!**
- ✖ **Use for non bacteremic patients with**
  - ✖ **low inoculum infections**
  - ✖ **less severely ill patients**
  - ✖ **Urosepsis or biliary sepsis**
  - ✖ **E coli rather than Klebsiella**
  - ✖ **MIC shown to be low**
  - ✖ **definitive therapy rather than empiric therapy**
- **Always use high end doses eg**
  - **Piperacillin-tazobactam 4.5g q 6h as 3h infusion**
  - **Cefoperazone-sulbactam 3g q 8h**

BL/BLIs not associated with poor outcomes in AmpC-producers

- The optimal treatment for potential AmpC-producing *Enterobacteriaceae*, including *Serratia, Providencia, Citrobacter, Enterobacter*, and *Morganella* species, remains unknown
- Conventional belief:
  - hydrolysable beta-lactam therapy, including third-generation cephalosporins and beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations, may be associated with an increased risk of treatment failure.
  - For this reason, clinicians often prescribe alternate therapies, including carbapenems
- A meta-analysis yielded a pooled OR for death within 30 days for patients receiving a BL/BLI as definitive therapy of 1.04 (95% CI 0.54–2.02).
- BL/BLI can be considered for use instead of carbapenems in less severely ill patients

Open Forum Infectious Diseases, Volume 6, Issue 7, July 2019, ofz248

Carbapenem resistant GNB

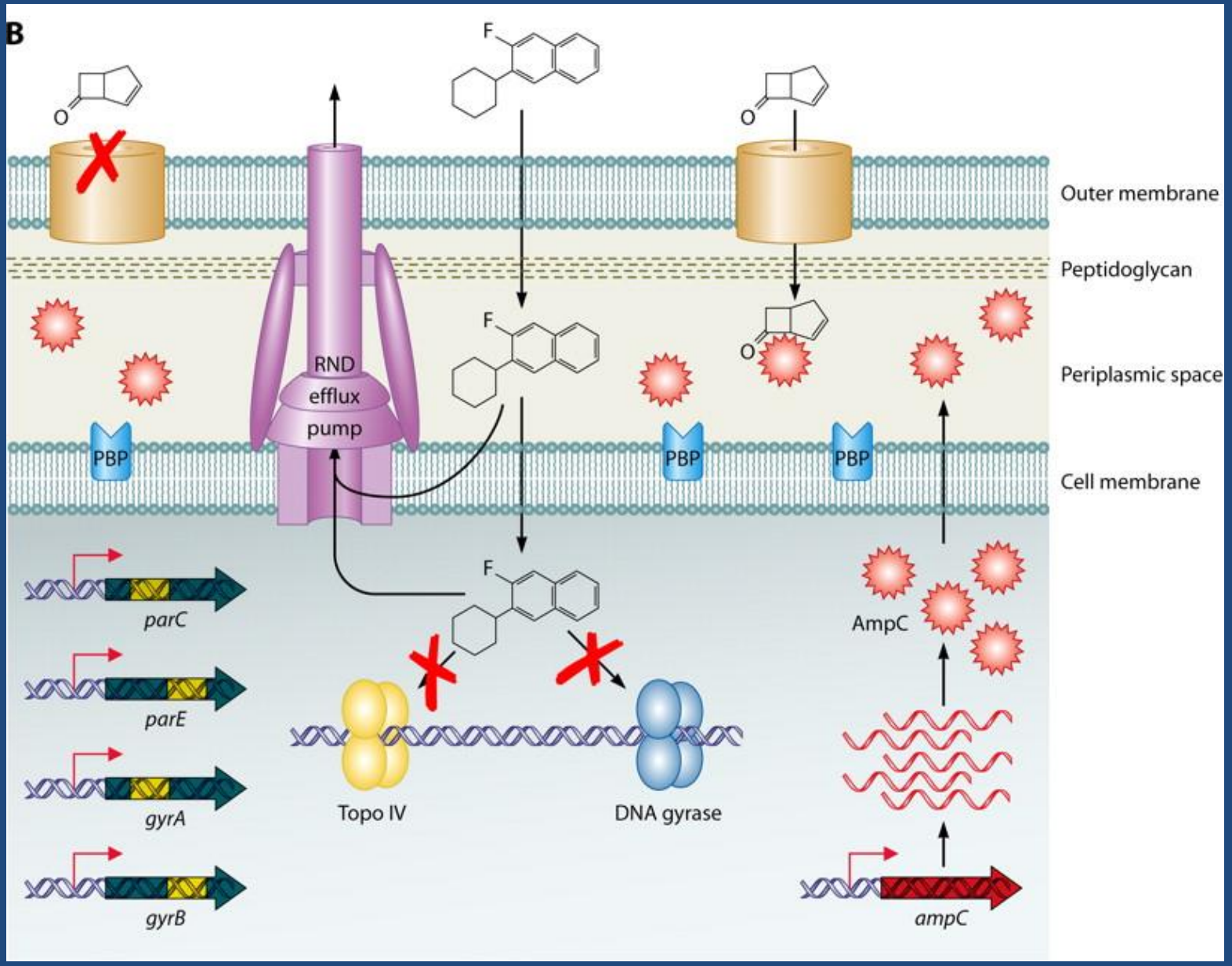
MDR *P. aeruginosa*

The resistance challenge of the ages

Pseudomonas aeruginosa bacteremia

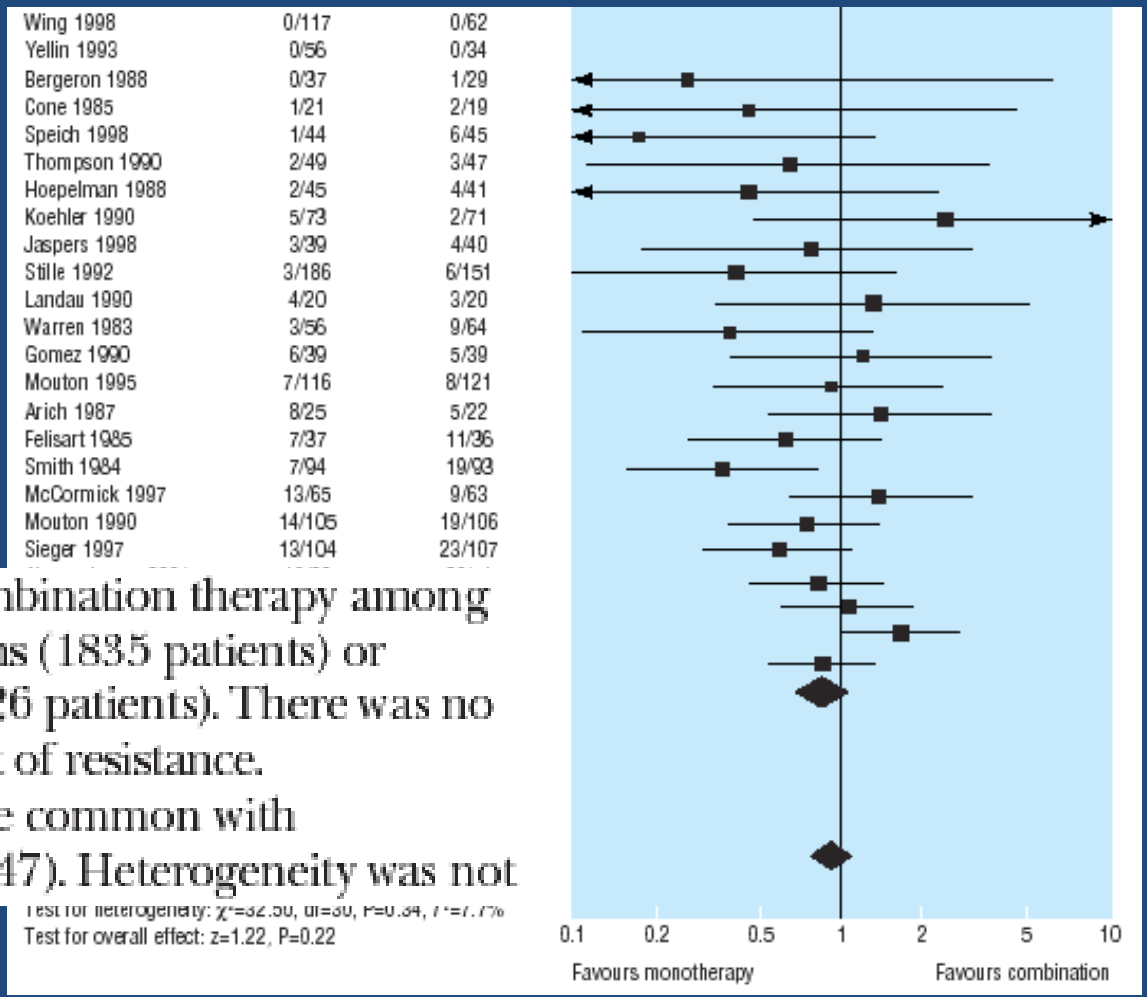
- Traditionally the most virulent Gram negative pathogen
- Main pathogen in neutropenic patients
- MICs close to breakpoint for susceptible, rather than one log lower eg pneumococcus
- 30-day mortality following *P. aeruginosa* bacteremia was 30% even in most recent trial
- Hence need for increased dose/duration/combination treatment

King of resistance: all present



β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials

Mical Paul, Ishay Benuri-Silbiger, Karla Soares-Weiser, Leonard Leibovici



0.86). There was no advantage to combination therapy among patients with Gram negative infections (1835 patients) or *Pseudomonas aeruginosa* infections (426 patients). There was no difference in the rate of development of resistance. Nephrotoxicity was significantly more common with combination therapy (0.36, 0.28 to 0.47). Heterogeneity was not

Cite this article as: BMJ, doi:10.1136/bmj.38028.520995.63 (published 2 March 2004)

What we were taught regarding P. aeruginosa bacteremia

- 1983 to ~ early 2000s
  - Should be treated with a combination of
    - An anti-Pseudomonal beta-lactam
    - An aminoglycoside
- Early 2000s to 2013
  - single effective anti-Pseudomonal beta-lactam antibiotic sufficient
  - Mortality in first 48 hrs reduced with adding an aminoglycoside only if started as empiric therapy immediately after blood cultures drawn

(Clin Infect Dis 2005;41;149)(*Antimicrob Agents Chemother 2003;47:2756-64)*

In 2013, lots of new data on Pseudomonas bacteremia!

- Single center study
- Retrospective study
- Meta-analysis
- Prospective cohort study

- Need to look at whether
  - Both antibiotics covering (true synergy)

  or
  - At least one antibiotic covering (to make sure organism covered)

- Need to look at both
  - empirical therapy: starting at time of drawing cultures
  - definitive therapy: starting at time of receipt of culture

We need an RCT

- Randomize at time of empiric treatment
- Randomize again at time of identification of Pseudomonas
- Need to recruit 1300 patients

- Such a trial unlikely to be done

Pseudomonas aeruginosa bacteremia: one drug or combination therapy?

If Pseudomonas in your practice is sensitive:

Current concept is that a single effective anti-Pseudomonal beta-lactam antibiotic sufficient

- First large prospective study: no benefit for combination in both empiric and definitive stages

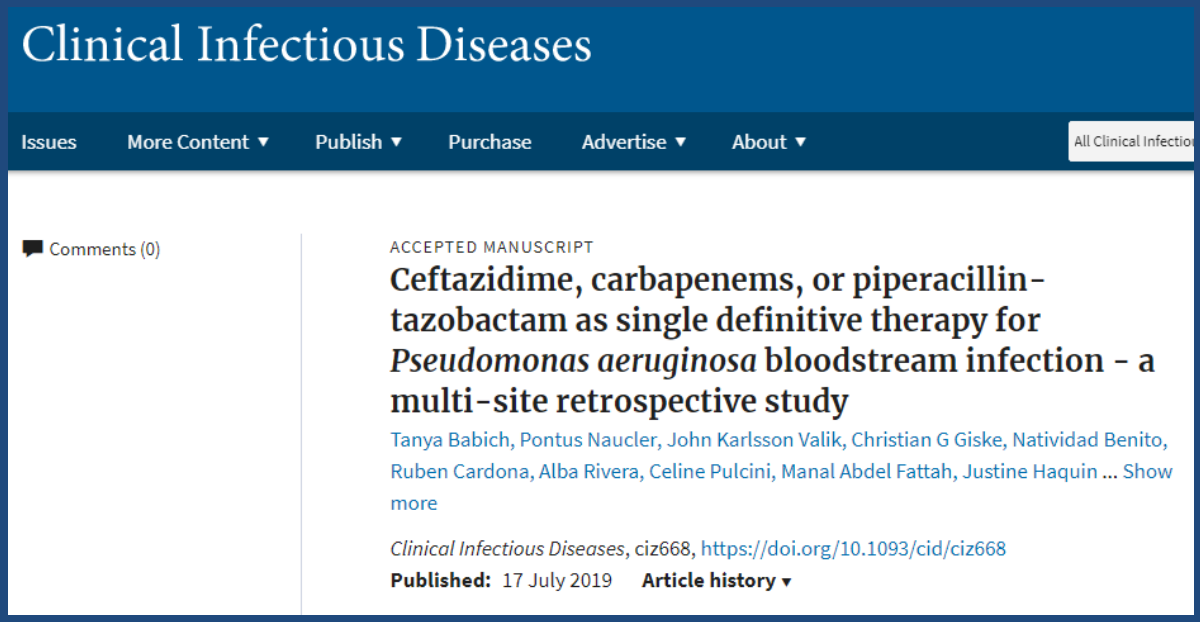
If Pseudomonas in your practice is MDR:

- Can start with empiric combination therapy
  - To ensure at least one agent effective against a resistant organism
  - to prevent emergence of resistance (no clinical data to support this)
- No role for adding aminoglycoside after blood culture returns or continuing for entire duration of therapy

(Clin Infect Dis 2005;41;149) (Antimicrob Agents Chemother 2003;47:2756)
(Clinical Infectious Diseases Advance Access published April 11, 2013)

Monotherapy or combination therapy for P aeruginosa VAP?

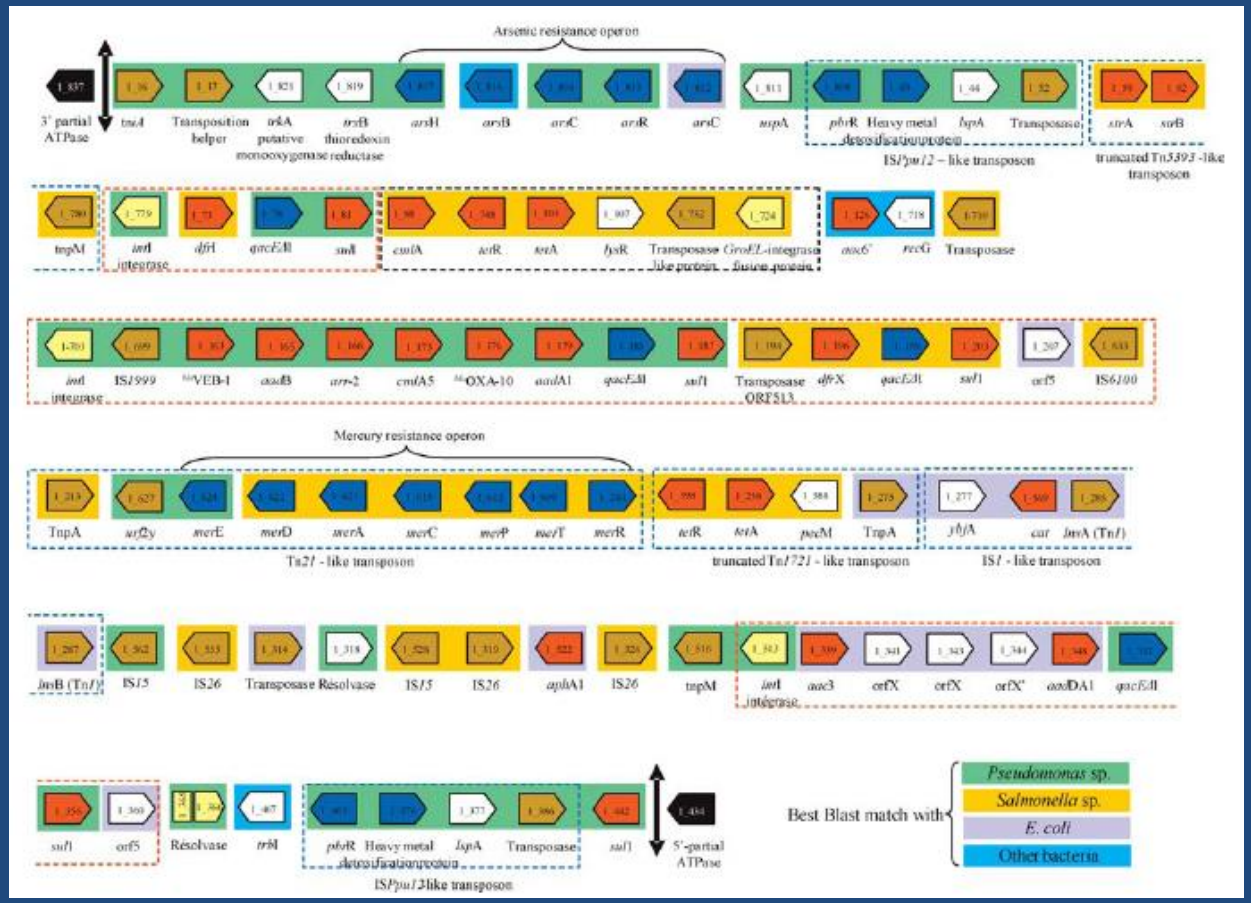
- Monotherapy
  - AST known
- Combination therapy
  - Pending AST
  - in septic shock or at a high risk for death
- IDSA recommends against aminoglycoside monotherapy
  - Aminoglycosides do not reach high lung tissue levels, use only till bacteremia excluded



- No significant difference in mortality, clinical, and microbiological outcomes or adverse events
- Higher rates of resistant *P. aeruginosa* after patients were treated with carbapenems, along with the general preference for carbapenem-sparing regimens, suggests using ceftazidime or piperacillin-tazobactam for treating susceptible infection.

CR Acinetobacter

“The Resistance Island”



86 Kb, 88 orfs, 82 orfs from another source and 45 resistance genes

AbaR1-10!

Fournier et al., PLoS Genet. 2006 Jan;2(1):e7. Epub 2006 Jan 13.

Newer β-Lactam/β-Lactamase Inhibitor for Multidrug-Resistant Gram-Negative Infections: Challenges, Implications and Surveillance Strategy for India

Balaji Veeraraghavan, Agila Kumari Pragasam, Yamuna Devi Bakthavatchalam, Shalini Anandan, V Ramasubramanian[1], Subramanian Swaminathan[2], Ram Gopalakrishnan[1], Rajeev Soman[3], O C Abraham[4], Vinod C Ohri[5], Kamini Walia[5]

Table 2: Current antimicrobial susceptibility profile, molecular resistance mechanisms, and lineages observed in India

	Cephalosporin		Carbapenems		Colistin* (among carbapenem resistance)	
	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance (chromosomal mutations)
E. coli	Up to 70%	bla_{SHV}, bla_{TEM}, bla_{OXA-1}, $bla_{CTX-M-15}$	Up to 10%	bla_{NDM}, $bla_{OXA-48\ like}$	8%	Scanty information on chromosomal mutations
K. pneumoniae	Up to 60%	bla_{SHV}, bla_{TEM}, $bla_{CTX-M-15}$	Up to 40%	$bla_{OXA-48like}$, bla_{NDM}	37%	Mutations in *mgrB*, *PhoP/Q*, *PmrA/B*
P. aeruginosa	Up to 25%	bla_{VEB}	Up to 25%	bla_{VIM}, bla_{NDM}, bla_{IMP}	<5%	Mutations in *PhoP/Q*, *PmrA/B*, *ParR/S*
A. baumannii	Up to 70%	bla_{TEM}, bla_{PER}	Up to 70%	$bla_{OXA-23/24like}$, bla_{NDM}	<5%	Mutations in *PmrA/B*, *Lpx*

Indian J Med Microbiol 2018;36:334-43.

Table 2: Current antimicrobial susceptibility profile, molecular resistance mechanisms, common mobile genetic elements and lineages observed in India

	Cephalosporin		Carbapenems		Colistin* (among carbapenem resistance)		MGEs	Lineages
	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance (chromosomal mutations)	Associated with resistance	International/ Indian high risk clones
E. coli	Up to 70%	bla_{SHV}, bla_{TEM}, bla_{OXA-1}, $bla_{CTX-M-15}$	Up to 10%	bla_{NDM} $bla_{OXA-48\ like}$	8%	Scanty information on chromosomal mutations	IncFII - 93% IncFIA - 87% IncFIB (AP001918) - 63% IncL1-40 Col (BS512) - 43 Integron - Class 1	ST131/ST167
K. pneumoniae	Up to 60%	bla_{SHV}, bla_{TEM}, $bla_{CTX-M-15}$	Up to 40%	$bla_{OXA-48like}$ bla_{NDM}	37%	Mutations in *mgrB, PhoP/Q, PmrA/B*	ColKP3-44 IncFIB - 24 IncR - 24 IncFIA - 22 IncFIB (pQil) - 22 Integron - Class 1	ST258/ST14, ST231
P. aeruginosa	Up to 25%	bla_{VEB}	Up to 25%	bla_{VIM}, bla_{NDM}, bla_{IMP}	<5%	Mutations in *PhoP/Q, PmrA/B, ParR/S*	IncP Integron - Class 1	ST111, ST233 ST235, ST244 ST357/ST664 ST1047, ST823, ST773
A. baumannii	Up to 70%	bla_{TEM}, bla_{PER}	Up to 70%	$bla_{OXA-23/24like}$, bla_{NDM}	<5%	Mutations in *PmrA/B, Lpx*	Integron - Class 1 Insertion sequences - ISAba1	ST457, ST195 ST862

Treatment options for MDR Acinetobacter

- Carbapenems
  - However MIC50 to carbapenems is 128 and MIC90 is 256
- Sulbactam
- Aminoglycosides
- Tigecycline
- Rifampin
- Polymyxins
- Minocycline

Sulbactam

- Sulbactam is a class A $^{N}_{L}$-lactamase inhibitor with intrinsic whole-cell activity against certain bacterial species, including Acinetobacter baumannii.
- antibacterial activities of sulbactam vary widely across contemporary A. baumannii clinical isolates and are mediated through inhibition of the penicillin-binding proteins (PBPs) PBP1 and PBP3, with very low frequency of resistance
- the rare pbp3 mutants with high levels of resistance to sulbactam are attenuated in fitness.

Sulbactam

- Presence of a beta-lactam agent (e.g., ampicillin) in combination with the BLI does not appear to contribute activity or synergy
- Results of antimicrobial susceptibility tests (e.g., with agar dilution or the E test) of BL/BLI combinations at fixed concentrations must be interpreted with caution
  - may indicate susceptibility when an isolate is actually resistant
- Monotherapy not recommended
- Available as a stand alone agent in India
- Recommended dose is 1 g of sulbactam every 3 h or 4 h (total daily dose of 6–8 g)

Minocycline

- The US FDA recently approved a new formulation of intravenous minocycline for the treatment of Gram positive and Gram negative infections, including MDR Acinetobacter
- Mainly bacteriostatic, but bactericidal in combination with carbapenems or colistin against *Acinetobacter baumannii*; so recommended in combination
- availability of CLSI susceptibility breakpoints with *Acinetobacter* and minocycline
  - ≤4 µg/mL for susceptibility
  - 8 µg/mL for intermediate
  - ≥16 µg/mL for resistance
- Generally well tolerated, usual tetracycline issues
- Dose is 200 mg loading, then 100 mg q12h (max of 400/day)

Minocycline for CRAB infections – watch out!

- MIC breakpoints of MIC ≤4 mg/L for susceptibility and MIC ≥16 mg/L for resistance by CLSI guidelines
- The authors attempted Monte Carlo simulation for many dosing strategies (100mg, 200mg, 400mg) and show that
  - a 200mg daily dose of minocycline only had an 85% probability of target attainment (fAUC/MIC >25) at an MIC of 0.5mg/L
  - even 400mg daily yielded 0% PTA at an MIC of 4mg/L
- Conclusions:
  - 1. The CLSI breakpoints for minocycline against A. baumannii are rather liberal. If one has to use the agent for serious infections consider a high dose – more than or equal to 400mg per day.
  - 2. Always get an MIC when you are attempting to use minocycline for CRAB infections.

JAC 2019 Feb 1 74(2):295

Combination therapy for Acinetobacter with colistin & rifampicin?

- Colistin may be synergistic with rifampin
  - Cell membrane effect allows increased penetration to the nucleus
- May increase colistin nephtotoxicity
- Potential for drug interactions

- RCT from Italy
- no benefit to combination of colistin with rifampicin
- 30 day mortality not affected
- More microbiologic eradication
- No difference in nephrotoxicity
- More hepatotoxicity

Antimicrob Agents Chemother 2006;50:2946-50
CID 2013

Colistin + carbapenem better than colistin + tigecycline for XDR Acinetobacter bacteremia

- 31 patients on colistin-tigecycline compared with 29 on colistin-carbapenem
- Crude 14 day mortality was 35% vs 15% (NS)
- Breakthrough bacteremia in 18% vs 0% (p=0.059)
- Excess 14d mortality if tige MIC>2 (p=0.009)
- Conclusion: tigecycline combination not appropriate for bacteremia, add carbapenem instead

Crit Care Med 2015;43(6):1194-204

J Antimicrob Chemother 2018; **73**: 22–32
doi:10.1093/jac/dkx368 Advance Access publication 24 October 2017

Journal of Antimicrobial Chemotherapy

Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis

Kirati Kengkla[1], Khachen Kongpakwattana[2], Surasak Saokaew[1–3,6], Anucha Apisarnthanarak[4] and Nathorn Chaiyakunapruk[2,3,5,6]*

- No treatment options significantly increased clinical cure rate.
- The triple therapy consisting of colistin, sulbactam and tigecycline had the highest rank among all treatments compared with colistin in combination with sulbactam (RR 1.17, 95% CI 0.56–2.44), colistin monotherapy (RR 1.28, 95% CI 0.63–2.61) and tigecycline monotherapy (RR 1.38, 95% CI 0.63–3.04).
- **Colistin in combination with sulbactam was associated with a significantly higher microbiological cure rate**
- No significant differences in all cause mortality were noted between treatment options.

THE LANCET
Infectious Diseases

Articles

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, MD, Prof George L Daikos, MD, Emanuele Durante-Mangoni, MD, Dafna Yahav, MD, Prof Yehuda Carmeli, MD, Yael Dishon Benattar, MA, Anna Skiada, MD, Roberto Andini, MD, Noa Eliakim-Raz, MD, Amir Nutman, MD, Oren Zusman, MD, Anastasia Antoniadou, MD, Pia Clara Pafundi, Amos Adler, MD, Yaakov Dickstein, MD, Ioannis Pavleas, MD, Rosa Zampino, MD, Vered Daitch, MA, Roni Bitterman, MD, Hiba Zayyad, MD, Fidi Koppel, BA, Inbar Levi, MA, Tanya Babich, MA, Prof Lena E Friberg, PhD, Prof Johan W Mouton, MD, Ursula Theuretzbacher, PhD, Prof Leonard Leibovici, MD

Published: 15 February 2018

DOI: https://doi.org/10.1016/S1473-3099(18)30099-9 | CrossMark

- Colistin (9-mu loading, followed by 4·5 mu q12h) vs
- Colistin with meropenem (2-g prolonged infusion q8h).
- Most infections were caused by *Acinetobacter baumannii* (312/406, 77%).
- No significant difference between colistin monotherapy (156/198, 79%) and combination therapy (152/208, 73%) was observed for clinical failure at 14 days after randomisation (risk difference −5·7%, 95% CI −13·9 to 2·4; risk ratio [RR] 0·93, 95% CI 0·83–1·03).
- Results were similar among patients with *A baumannii* infections (RR 0·97, 95% CI 0·87–1·09).

How it has changed my practice

- Addition of meropenem unnecessary if colistin sensitive
- If you have started with empiric combination therapy with meropenem, colistin alone enough after DST available
- Add sulbactam in difficult cases

Therapy of carbapenem resistant Acinetobacter: my recommendations

- First decide whether true infection or colonization
- Remove lines, do source reduction
- Colistin is the cornerstone
- Monotherapy adequate if colistin sensitive
- Use high dose minocycline if sensitive
- In septic shock or non resolving bacteremia, add high dose sulbactam (8-12g/d) or minocycline
- Try anything else found sensitive eg chloramphenicol
- Look at MICs rather than just sensitive vs resistant

- Pray!

CR E coli and Klebsiella

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

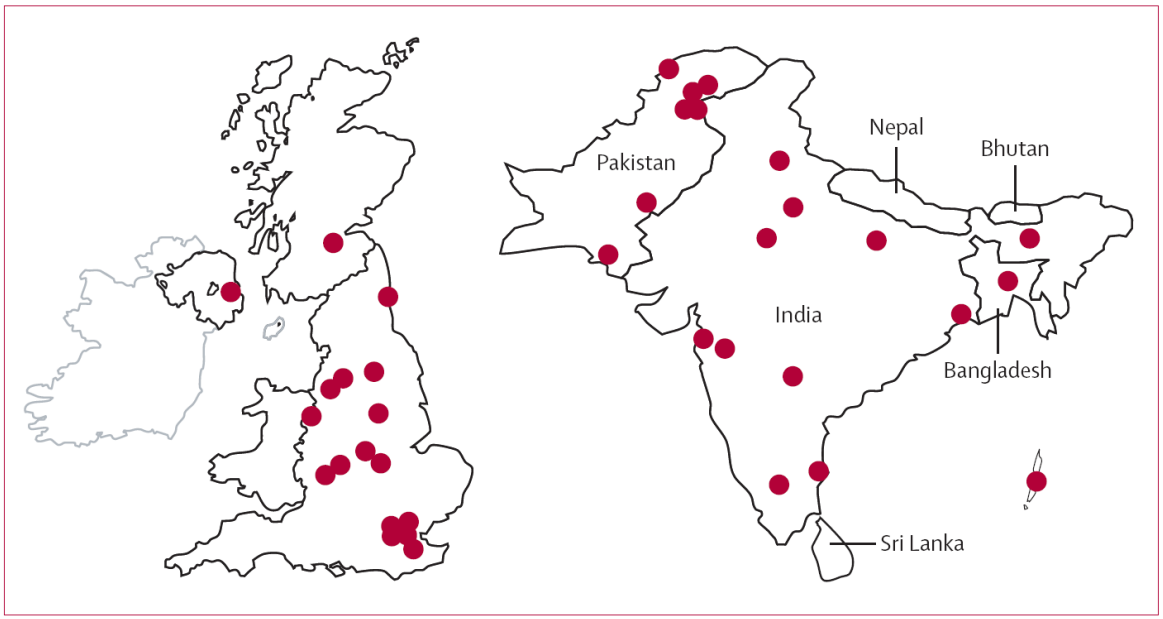


Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

www.thelancet.com/infection Published online August 11, 2010 DOI:10.1016/S1473-3099(10)70143-2

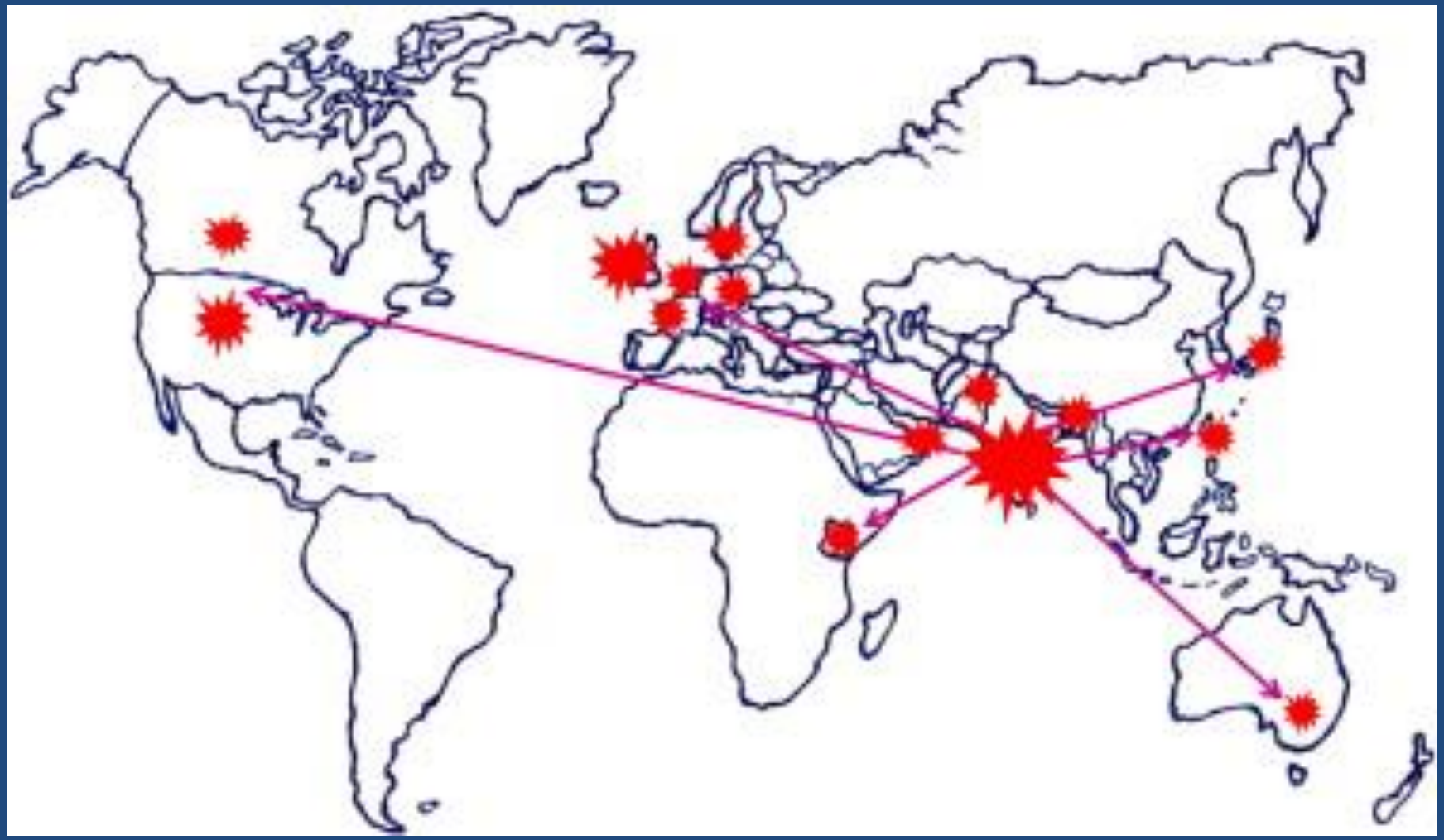
www.thelancet.com/infection Published online April 7, 2011 DOI:10.1016/S1473-3099(11)70059-7

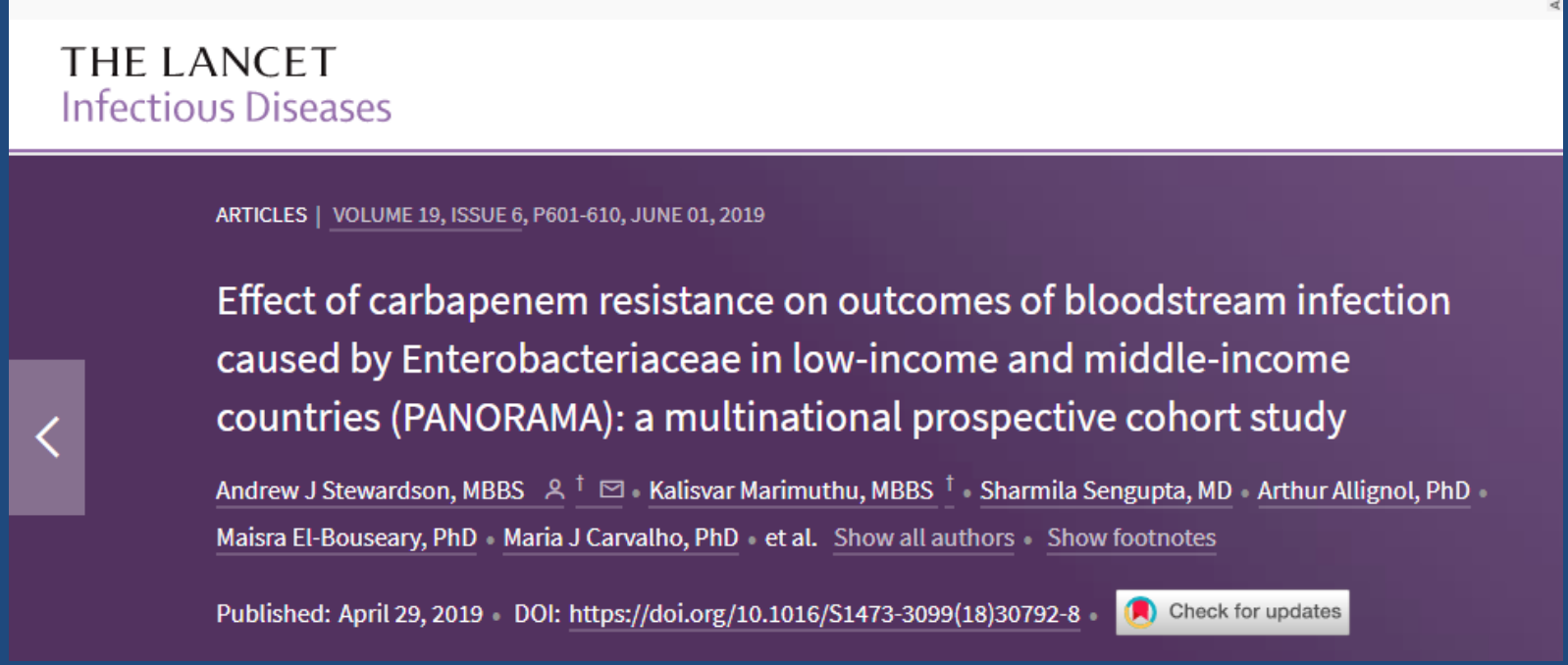
Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Figure 1: Map of NDM-1-positive samples from New Delhi centre and surrounding areas

NDM-1 has spread worldwide





THE LANCET
Infectious Diseases

ARTICLES | VOLUME 19, ISSUE 6, P601-610, JUNE 01, 2019

Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study

Andrew J Stewardson, MBBS † • Kalisvar Marimuthu, MBBS † • Sharmila Sengupta, MD • Arthur Allignol, PhD • Maisra El-Bouseary, PhD • Maria J Carvalho, PhD • et al. Show all authors • Show footnotes

Published: April 29, 2019 • DOI: https://doi.org/10.1016/S1473-3099(18)30792-8 • Check for updates

- Crude mortality was
  - 20% for patients with CSE bloodstream infection and
  - 35% for patients with CRE bloodstream infection.
- Carbapenem resistance was associated with
  - an increased length of hospital stay (3·7 days)
  - increased probability of in-hospital mortality (1·75)
  - decreased probability of discharge alive (0·61).

Summary on Carbapenemases

- Metallo-enzymes
  - Eg NDM-1, spreading in communities
- OXA series
  - Eg OXA 48, spreading in communities
- KPC
  - Limited to hospital Klebsiella, easier to control eg Israel
- Indian data (Vellore)
  - E coli: NDM >>OXA >NDM+VIM >NDM+OXA
  - Klebsiella:OXA-48 >NDM >NDM+OXA-48 >NDM+VIM+OXA-48

Newer β-Lactam/β-Lactamase Inhibitor for Multidrug-Resistant Gram-Negative Infections: Challenges, Implications and Surveillance Strategy for India

Balaji Veeraraghavan, Agila Kumari Pragasam, Yamuna Devi Bakthavatchalam, Shalini Anandan, V Ramasubramanian[1], Subramanian Swaminathan[2], Ram Gopalakrishnan[1], Rajeev Soman[3], O C Abraham[4], Vinod C Ohri[5], Kamini Walia[5]

Table 2: Current antimicrobial susceptibility profile, molecular resistance mechanisms, and lineages observed in India

	Cephalosporin		Carbapenems		Colistin* (among carbapenem resistance)	
	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance (chromosomal mutations)
E. coli	Up to 70%	bla_{SHV}, bla_{TEM}, bla_{OXA-1}, $bla_{CTX-M-15}$	Up to 10%	bla_{NDM}, $bla_{OXA-48\ like}$	8%	Scanty information on chromosomal mutations
K. pneumoniae	Up to 60%	bla_{SHV}, bla_{TEM}, $bla_{CTX-M-15}$	Up to 40%	$bla_{OXA-48like}$, bla_{NDM}	37%	Mutations in *mgrB*, *PhoP/Q*, *PmrA/B*
P. aeruginosa	Up to 25%	bla_{VEB}	Up to 25%	bla_{VIM}, bla_{NDM}, bla_{IMP}	<5%	Mutations in *PhoP/Q*, *PmrA/B*, *ParR/S*
A. baumannii	Up to 70%	bla_{TEM}, bla_{PER}	Up to 70%	$bla_{OXA-23/24like}$, bla_{NDM}	<5%	Mutations in *PmrA/B*, *Lpx*

Indian J Med Microbiol 2018;36:334-43.

Table 2: Current antimicrobial susceptibility profile, molecular resistance mechanisms, common mobile genetic elements and lineages observed in India

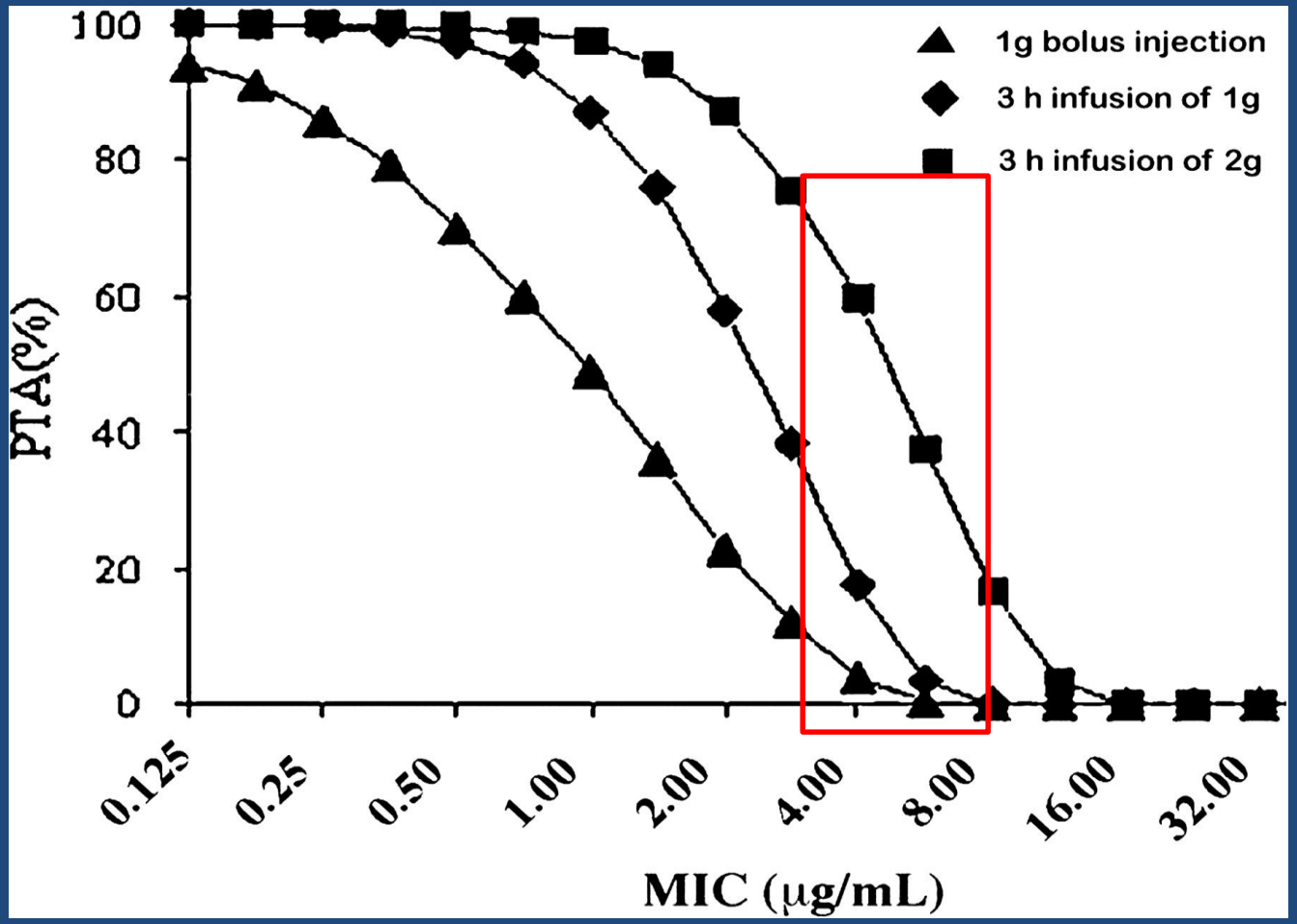
	Cephalosporin		Carbapenems		Colistin* (among carbapenem resistance)		MGEs	Lineages
	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance	Percentage resistance	Molecular mechanism of resistance (chromosomal mutations)	Associated with resistance	International/ Indian high risk clones
E. coli	Up to 70%	bla_{SHV}, bla_{TEM}, bla_{OXA-1}, $bla_{CTX-M-15}$	Up to 10%	bla_{NDM} $bla_{OXA-48\ like}$	8%	Scanty information on chromosomal mutations	IncFII - 93% IncFIA - 87% IncFIB (AP001918) - 63% IncL1-40 Col (BS512) - 43 Integron - Class 1	ST131/ST167
K. pneumoniae	Up to 60%	bla_{SHV}, bla_{TEM}, $bla_{CTX-M-15}$	Up to 40%	$bla_{OXA-48like}$ bla_{NDM}	37%	Mutations in *mgrB, PhoP/Q, PmrA/B*	ColKP3-44 IncFIB - 24 IncR - 24 IncFIA - 22 IncFIB (pQil) - 22 Integron - Class 1	ST258/ST14, ST231
P. aeruginosa	Up to 25%	bla_{VEB}	Up to 25%	bla_{VIM}, bla_{NDM}, bla_{IMP}	<5%	Mutations in *PhoP/Q, PmrA/B, ParR/S*	IncP Integron - Class 1	ST111, ST233 ST235, ST244 ST357/ST664 ST1047, ST823, ST773
A. baumannii	Up to 70%	bla_{TEM}, bla_{PER}	Up to 70%	$bla_{OXA-23/24like}$, bla_{NDM}	<5%	Mutations in *PmrA/B, Lpx*	Integron - Class 1 Insertion sequences - ISAba1	ST457, ST195 ST862

Strategies for CR Klebsiella

- Higher mortality in patients with CRKP than those having CSKP (pooled crude OR 2.80; 95% CI 2.15 – 3.65) (*Ann Clin Microbiol Antimicrob* 2017; 16:18)
- High dose carbapenem
  - Cure rates based on MIC
    - 69% if <4
    - 60% if 8
    - 29% if >8
    - Problem is that MIC50 is 64 and MIC90 is 256 (Vellore)
- Double carbapenem
  - Ertapenem acts as a suicide substrate, give high dose meropenem 1 hr later
  - Works only vs KPC
- Combination treatment
  - Tigecycline
  - Fosfomycin
  - Colistin

Exp Rev Anti Infect Ther 2013;11(2)

Example of the probability of target attainment of a chosen pharmacokinetic-pharmacodynamic target with 3 dosage regimens of meropenem in relation to MIC values.



Theuretzbacher U Clin Infect Dis. 2012;54:1785-1792

Clinical Infectious Diseases

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

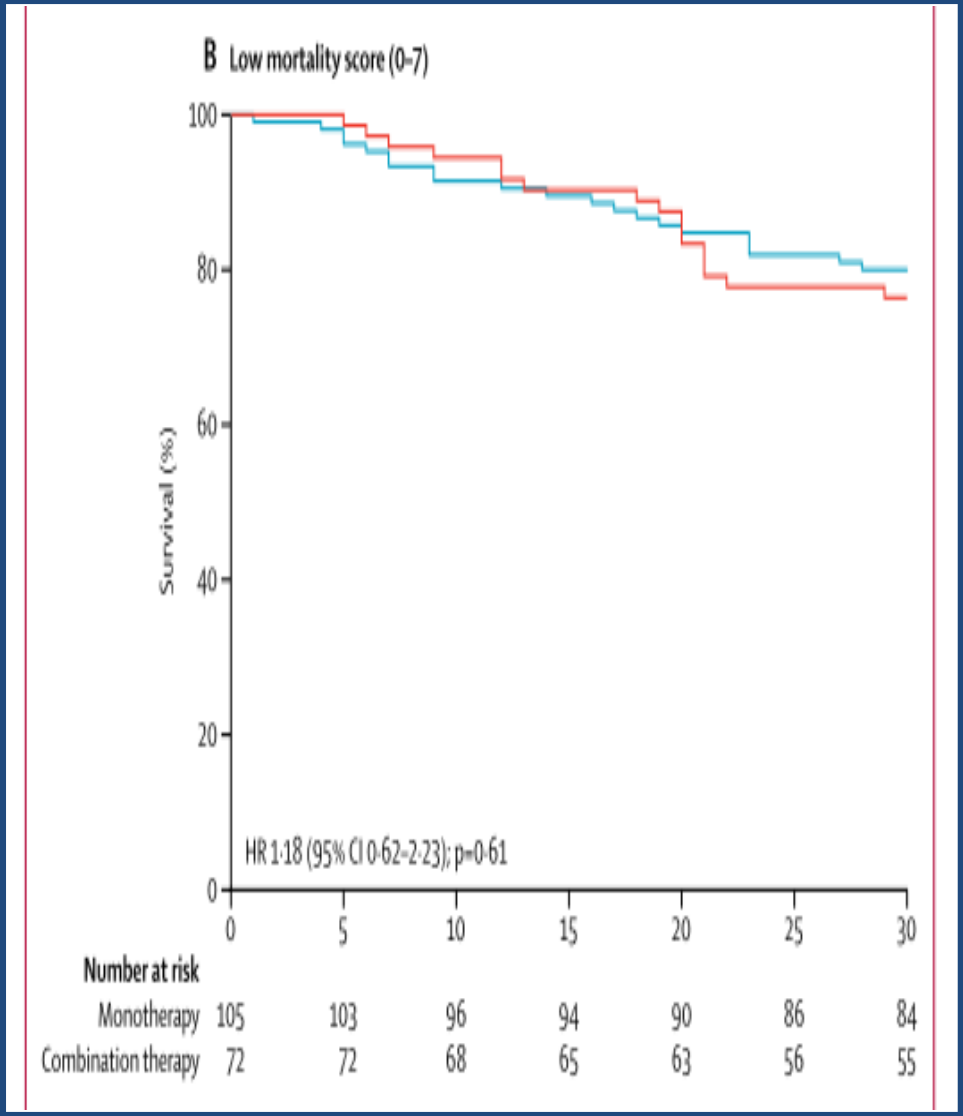
Belén Gutiérrez-Gutiérrez, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†*

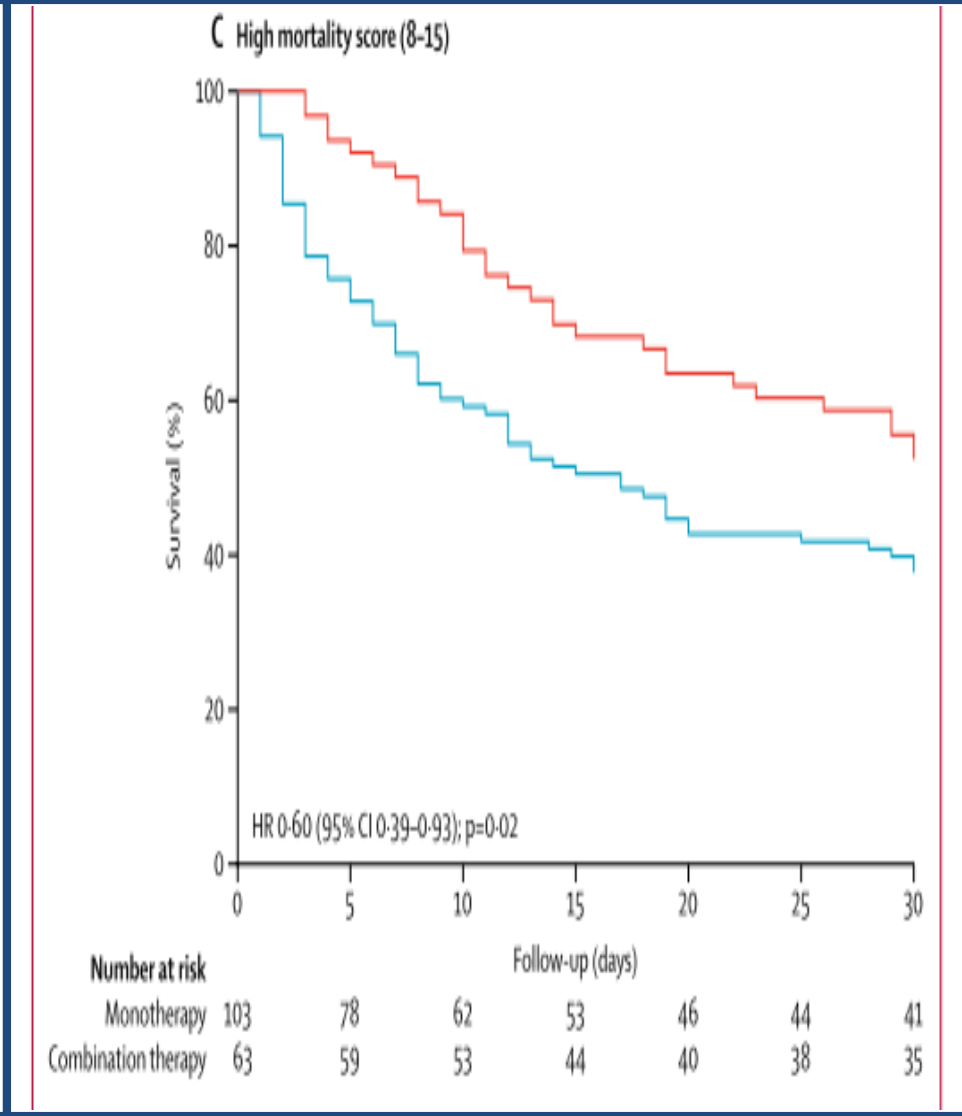
Lancet Infect Dis 2017; 17: 726–34

	Crude analysis		Adjusted analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per year)	1·00 (1·00–1·01)	0·32	..	..
Male sex	0·93 (0·70–1·24)	0·62	..	..
Klebsiella pneumoniae	1·29 (0·83–2·02)	0·25	..	..
OXA-type carbapenemase	1·43 (1·00- 2·05)	0·05	..	..
Nosocomial acquisition	1·83 (1·06- 3·16)	0·03	..	..
Source other than urinary or biliary tracts†	2·12 (1·37- 3·29)	0·0009	1·72 (1·09–2·72)	0·02
ICU admission	1·55 (1·16–2·08)	0·003	..	..
Charlson comorbidity index score (per unit)	1·10 (1·05–1·16)	<0·0001	1·13 (1·07–1·20)	<0·0001
Mechanical ventilation	1·76 (1·32–2·34)	<0·0001	..	..
Mental status: not alert	2·45 (1·82–3·29)	<0·0001	..	..
Chronic kidney disease	1·33 (0·97–1·84)	0·08	..	..
Chronic liver disease	1·58 (1·08–2·31)	0·02	..	..
Leukaemia or metastatic cancer	1·61 (1·12–2·31)	0·009	..	..
Pitt bacteraemia score (per unit)	1·17 (1·13–1·22)	<0·0001	1·09 (1·04–1·15)	0·0003
Severe sepsis or septic shock	3·87 (2·78–5·39)	<0·0001	3·11 (2·14–4·51)	<0·0001
Early appropriate therapy (started in ≤2 days after infection)	0·84 (0·59–1·21)	0·35	..	..
Appropriate therapy (started in ≤5 days after infection)	0·44 (0·33–0·61)	<0·0001	0·45 (0·33–0·62)	<0·0001
High-mortality-risk centre	2·25 (1·69–2·99)	<0·0001	2·37 (1·74–3·22)	<0·0001
Study period 2004–11 (reference 2012–13)	1·52 (1·09–2·13)	0·01	1·43 (1·02–2·01)	0·04

HR=hazard ratio. OXA=oxacillinase. ICU=intensive care unit. *All variance inflation factor values of the variables included in the final multivariate model were less than 1·4. We included variables with a univariate p value of 0·2 or less for mortality in the initial model. †Biliary tract infections included cholecystitis and cholangitis.

Table 2: **Univariate and multivariate Cox regression analyses for mortality of patients with bacteraemia due to carbapenemase-producing Enterobacteriaceae**


B Low mortality score (0–7)
Survival (%)
100
80
60
40
20
0
HR 1·18 (95% CI 0·62–2·23); p=0·61
0
5
10
15
20
25
30
Number at risk
Monotherapy 105 103 96 94 90 86 84
Combination therapy 72 72 68 65 63 56 55


C High mortality score (8–15)
Survival (%)
100
80
60
40
20
0
HR 0·60 (95% CI 0·39–0·93); p=0·02
0
5
10
15
20
25
30
Follow-up (days)
Number at risk
Monotherapy 103 78 62 53 46 44 41
Combination therapy 63 59 53 44 40 38 35

Conclusion

- Interpretation: appropriate therapy was associated with a protective effect on mortality among patients with BSIs due to CPE.
- Combination therapy when started empirically was associated with improved survival only in patients with a high mortality score.
- Patients with BSIs due to CPE should receive active therapy as soon as they are diagnosed, and monotherapy should be considered for those in the low-mortality-score stratum.

How it has changed my practice

- I start with two drugs in sick patients at risk for CRE, typically colistin with a second agent
- Single drug enough for more stable patients

- Many caveats:
  - MIC not looked at
  - Very few NDM-1

Special Article

Newer β-Lactam/β-Lactamase Inhibitor for Multidrug-Resistant Gram-Negative Infections: Challenges, Implications and Surveillance Strategy for India

Balaji Veeraraghavan, Agila Kumari Pragasam, Yamuna Devi Bakthavatchalam, Shalini Anandan, V Ramasubramanian[1], Subramanian Swaminathan[2], Ram Gopalakrishnan[1], Rajeev Soman[3], O C Abraham[4], Vinod C Ohri[5], Kamini Walia[5]

Table 6: New β-lactam/β-lactamase inhibitor to India specific Gram-negative organism, will it be beneficial?

β-lactam/ βLI	FDA approval/ Indications	Infusion length/renal dose adjustment	Spectrum of activity against MDR Gram-negative organism	Remarks to Indian specific AMR scenario
Ceftazidime-avibactam	Approved/cIAI, UTI, pneumonia/2.5 g IV q8h	2 h/Yes, (CrCl, mL/min) >50 (2.5g q8h) 31-50 (1.25g q8h) 16-30 (0.94g q12h) 6-15 (0.94g q24h) ≤5 (0.94g q48h)	AmpC, ESBL, and KPC producers, and some OXA-48, but not active against MBLs (NDM, VIM, IMP, VEB, PER), or *Acinetobacter* OXA-type carbapenemases	High burden of NDM and OXA-48 producing Gram-negative bacilli
Ceftolozane-tazobactam	Approved/cIAI and cUTI/1.5 g (1 g ceftolozane and 0.5 g tazobactam) IV q8h	2 h/Yes, (CrCl, mL/min) >50 (1.5g q8h) 30-50 (750 mg q8h) 15-29 (375 mg q8h) ESRD on HD (750 mg × 1 then 150 mg q8h)	AmpC, ESBL, and MDR *P. aeruginosa*, but not active against carbapenemases	Higher percentage of ESBL and carbapenemase co-producers
Meropenem-relebactam	FDA approved/ cUTI/4g (2 g of meropenem + 2 g of vaborbactam) IV q8h	3 h/yes, (CrCl, mL/min) >50 (4 g q8h) 30-49 (2g q8h) 15-29 (2g q12h) <15 (1g q2h)	AmpC, ESBL, and KPC producing *Enterobacteriaceae* but not for most *A. baumannii* and *P. aeruginosa*	High prevalence of NDM, OXA-48 and OXA-51producers
Aztreonam-avibactam	Not approved (in pipeline)/cIAI and pneumonia	NA	KPC and AmpC-producing *Enterobacteriaceae*, MBLs, but not against *A. baumannii*	May be suitable for treating carbapenem-resistant *Enterobacteriaceae* and MDR *P. aeruginosa*
Imipenem-relebactam	Not approved (Phase III trial)/cIAI and cUTI	NA	AmpC, ESBL, KPC-producers but not against OXA-48 *K. pneumoniae*, MBLs, and AmpC and OXA-51 *A. baumannii*	High prevalence of OXA-48 + MBL + AmpC co-producers

Indian J Med Microbiol 2018;36:334-43.

Ceftazidime-avibactam

- Combines the anti-Pseudomonal activity of ceftazidime with avibactam
- Renders it active versus ESBLs and serine beta-lactamases such as KPC-2
- 93% of OXA-48 sensitive
- Not active against NDM-1 and other MBLs, poor for Acinetobacter, no anaerobic activity
- Side effects include vomiting, nausea, constipation and anxiety
- Initially approved for cIAI, in combination with metronidazole and complicated urinary tract infections (cUTI), now for HAP and VAP
- As good as comparator including carbapenems vs UTI/IAI caused by ceftazidime resistant bacteria (Lancet ID, 20 April, 2016)
- Non-inferior to meropenem for VAP (Lancet ID Vol **18, No. 3**, p285–295, March 2018)
- Avibactam is a potent, competitive, reversible inhibitor of the L2 beta-lactamase of S maltophilila, used for treatment with aztreonam (*Antimicrob Agents Chemother* 2017 Oct 1)
- High rates of resistance to CAZ-AVI vs NDM-1 *Enterobacteriaceae* species (Clin Infect Dis. (2016)doi: 10.1093/cid/ciw398)
- Combined off label with aztreonam for NDM-1

Ceftazidime-Avibactam works well for OXA 48

- In this prospective study evaluating 57 patients with CRE infections mediated by OXA 48, Ceftazidime-avibactam was used as a monotherapy in most of the patients (81%).
- Almost half the patients had severe infection (defined as presence of sepsis or septic shock). The most frequent sources of infection were intra-abdominal (28%), followed by respiratory (26%) and urinary (25%).
- Mortality at 14 days was 14%.
- In multivariate analysis, the only mortality risk factor was INCREMENT-CPE score >7 (HR 11.7, 95% CI 4.2–20.6).
- This real time data provides further confidence to use this agent in infections due to OXA 48 CRE.

Journal of Antimicrobial Chemotherapy,
Volume 73, Issue 11, 1 November 2018, Pages 3170–3175

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

- IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (difference, 23%; 95% bootstrap confidence interval, 9%–35%; *P = .001).*
- patients treated with ceftazidime-avibactam, compared with those treated within colistin, had an IPTW-adjusted probability of a better outcome of 64% (95% confidence interval, 57%-71%)
- Partial credit analyses indicated uniform superiority of ceftazidime-avibactam to colistin.
- Very useful agent to spare colistin and to treat colistin resistant Enterobacteriaceae which produce KPC-2

Role of CAZ-AVI in Indian scenario

- Can’t use for empiric monotherapy for HAI as no Acineto and CR E coli coverage
- Can use for CR Kleb only if
  - DST shows susceptibility or
  - OXA-48 on molecular testing

Meropenem-vaborbactam approved by US FDA

- U.S. FDA approved for adults with complicated urinary tract infections (cUTI).
- Designated as a qualified infectious disease product (QIDP).
- Consists of 2g meropenem and 2g vaborbactam
- All anti-Pseudomonal activity based on meropenem alone
- Compatatively meropenem-vaborbactam, approximately 98 percent of patients treated with meropenem-vaborbactam compared with approximately 94 percent of patients treated with piperacillin/tazobactam, responded
- most common adverse reactions: headache, infusion site reactions and diarrhea.
- comparable activity against *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia* (AAC 2017; 61: e00567).
- Active against KPC-2 carbapenemases but not against NDM-1 or OXA type carbapenemases seen in India.
- Trial vs standard of care for KPC-2 stopped early because of superior outcome.
- Role in India limited

Imipenem-relebactam US FDA approved

- indicated for patients who have limited or no alternative treatment options for cUTIs, including acute pyelonephritis, and cIAIs caused by specified gram-negative bacteria, including CRE
- risk for central nervous reactions
- should avoid concomitant use with anti-seizure drugs (e.g., valproic acid or divalproex sodium)

Plazomicin

- Plazomicin is an sisomycin-derived aminoglycoside that was developed to be active vs most AG modifying enzymes
- Once-daily plazomicin 15 mg/kg was noninferior to meropenem for the treatment of complicated UTIs and acute pyelonephritis caused by Enterobacteriaceae, including multidrug-resistant strains (NEJM 2019; 380:729-740).
- has been evaluated in two Phase 3 clinical trials, EPIC and CARE.
- approved by the US FDA for treatment of complicated UTI but not bacteremia
- expanded activity primarily against carbapenem-resistant Enterobacteriaceae, including *K. pneumoniae* carbapenemase producers, some metallo-β-lactamase-producers, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
- Unfortunately most MBL producers have a methylase that inactivates it

Eravacycline approved for IAI

- tetra**cycline** derivative
- antibacterial spectrum includes many highly resistant gram negatives (including some CRE and acinetobacter), MRSA, VRE, and anaerobes.
- *Pseudomonas aeruginosa* is an important exception to its broad coverage.
- The drug's approval was based primarily on clinical trials demonstrating **non-inferiority to ertapenem in intra-abdominal infections**
- **Less GI side effects than tigecycline**

FDA Approves Omadacycline for CABP and ABSSSI

- Omadacycline is a new-generation tetracycline, dosed once daily in both oral and intravenous forms, that was designed to subvert common tetracycline resistance mechanisms, including efflux and ribosomal protection.
- Among gram-positive bacteria, it exhibits excellent in vitro activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MIC_{90}, 0.5 mg/L), vancomycin-susceptible and vancomycin-resistant enterococci (MIC_{90}, 0.5 mg/L), penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* (MIC_{90}, 0.12 mg/L), and beta-hemolytic and viridans streptococci (MIC_{90}, 0.12 mg/L).
- Among gram-negative bacteria, activity is excellent against *Haemophilus influenzae* (MIC_{90}, 2.0 mg/L), and *Escherichia coli* (MIC_{90}, 2.0 mg/L).
- However, activity in vitro is less reliable against other gram-negatives and activity is generally poor against the "MP3" group (*Morganella*, *Providencia*, *Proteus*, and *Pseudomonas* spp.), with MIC_{90} ≥32 mg/L.
- Consistent with the tetracycline class, activity against atypical pathogens (e.g., *Legionella*, *Mycoplasma*) is excellent.
- Among anaerobes, activity is less reliable against gram-negatives (e.g. *Bacteroides*) than gram-positives (*Clostridium*, *Peptostreptococcus*).

10 × '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America

Table 3.
Intravenous Antimicrobials Active Against Gram-Negative Bacilli in Advanced (Phase 2 or 3) Clinical Development[a]

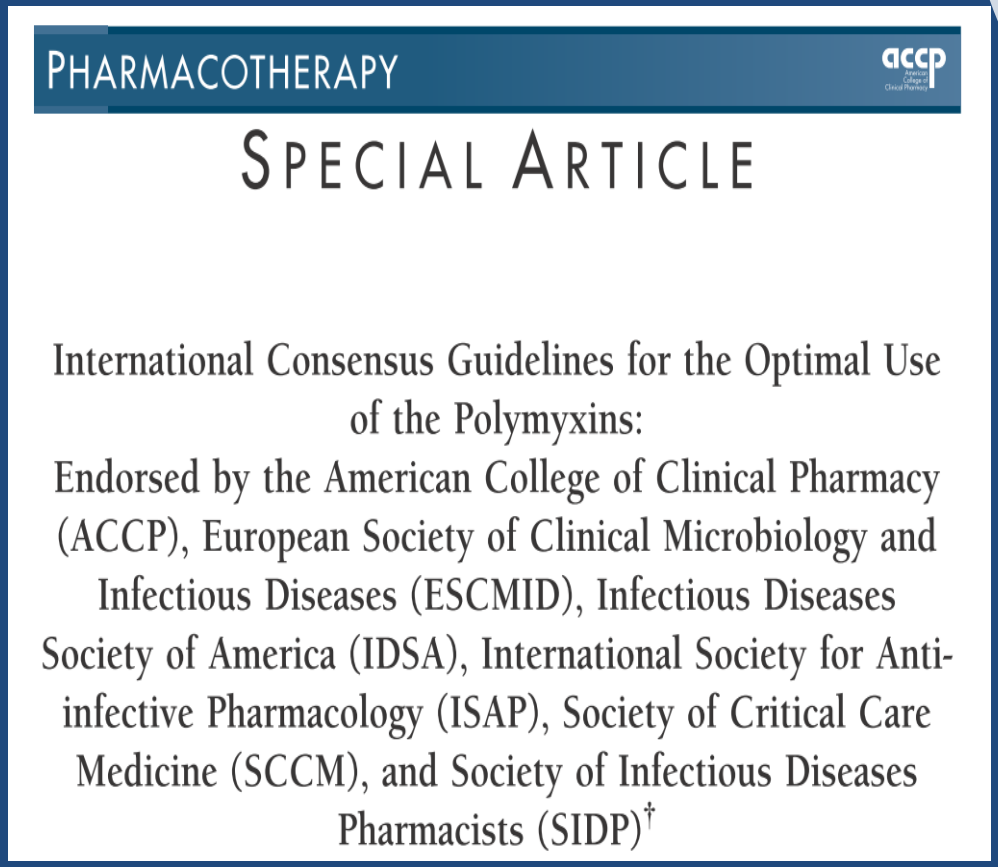
	Product	Class (Mechanism of Action)	Novel Mechanism of Action?	Status	Activity Targets							
					Enterobacteriaceae			*Psuedomonas aeruginosa*			*Acinetobacter* spp	
					ESBL	sCBP	mCBP	WT	MDR	mCBP	WT	MDR
1	Ceftolozane/taxobactam (CXA-201; CXA-101/tazobactam)	Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cUTI, cIAI)	Yes	No	No	Yes	IE	No	No	No
2	Ceftazidime-avibactam (ceftazidime/NXL104)	Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cIAI)	Yes	Yes	No	Yes	IE	No	No	No
3	Ceftaroline-avibactam (CPT-avibactam; ceftaroline/NXL104)	Anti-MRSA cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No	No	No	No	No	No
4	Imipenem/MK-7655	Carbapenem/BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No	Yes	IE	No	IE	No
5	Plazomicin (ACHN-490)	Aminoglycoside (protein synthesis inhibitor)	No	Phase 2 (cUTI)	Yes[b]	Yes[b]	IE	No	No	No	No	No
6	Eravacycline (TP-434)	Fluorocycline (protein synthesis inhibitor targeting the ribosome)	No	Phase 2 (cIAI)	Yes[b]	Yes	IE	No	No	No	IE	IE
7	Brilacidin (PMX-30063)	Peptide defense protein mimetic (cell membrane disruption)	Yes?	Phase 2 (ABSSSI)	Yes	IE	IE	IE	IE	IE	No	No

Cefiderocol: the next blockbuster?

- Goes through iron transport channels, escapes beta lactamases in peri-plasmic space (Trojan horse)
- siderophore cephalosporin cefiderocol, which has high stability against most β-lactamases, including serine- and metallo-carbapenemases.
- High activity with low MIC_{50} and MIC_{90} values against Enterobacteriaceae strains producing either one or the other, or both, of extended spectrum ß-lactamases and KPC-, OXA-48-, NDM-, VIM-, and IMP-carbapenemases
- Only 24 of the 753 multiresistant isolates (3%) showed a cefiderocol MIC ≥8 µg/mL.
- Carbapenemase-producing *Pseudomonas aeruginosa* were susceptible to cefiderocol and colistin only.
- Similarly, for carbapenemase-producing *Acinetobacter baumannii,* only cefiderocol, colistin, and tigecycline retained activity.

Therapy of CR Klebsiella: my recommendations

- First decide whether true infection or colonization
- Remove lines, do source reduction
- Ask for a molecular test such as Carba R
- Use ceftazidime-avibactam if KPC-2 or OXA-48
- For others, colistin is the cornerstone
- Fosfomycin is an option if sensitive
- Start with colistin based combination therapy empirically in sick patients:
  - 200 mg tigecycline
  - high dose carbapenem if MIC 4-16
  - Fosfomycin
  - Ceftazidime-avibactam
- Continue combination therapay if IET was correct in patients with high INCREMENT score
- Add anything else found sensitive eg chloramphenicol, amikacin
- Look at MICs rather than just sensitive vs resistant
- Pray!



Pharmacotherapy 2019;39(1):10–39

Colistin vs Polymyxin B

Colistin preferred for UTI, nebulisation, intrathecal therapy

Polymyxin B preferred for others

- Polymyxin B - Reaches therapeutic concentration faster
- CMS to colistin conversion variable
- Polymyxin B ? Less nephrotoxic
- Polymyxin B does not require renal adjustments

Pharmacotherapy 2019;39(1):10–39

Carbapenem resistant Acinetobacter treatment

Polymyxin and at least one other antibiotic sensitive

- Polymyxins should be used in combination therapy

Only Polymyxin sensitive

- Panel voted 8 – 7 in favour of monotherapy

Pharmacotherapy 2019;39(1):10–39

CRE – Polymyxin alone or in combination ?

Polymyxin and at least one other antibiotic sensitive

- Polymyxins should be used in combination therapy

Only Polymyxin sensitive

- panel voted 11-4 in favor of combination therapy
- Which non-susceptible agent ? – use the one with lowest MIC relative to their susceptibility breakpoint

Pharmacotherapy 2019;39(1):1

CCR GNB

Brief Communication

A Study of 24 Patients with Colistin-Resistant Gram-negative Isolates in a Tertiary Care Hospital in South India

Rajalakshmi Arjun, Ram Gopalakrishnan, P. Senthur Nambi, D. Suresh Kumar, R. Madhumitha, V. Ramasubramanian
Department of Infectious Diseases, Apollo Hospitals, Chennai, Tamil Nadu, India

Abstract

Background: As the use of colistin to treat carbapenem-resistant Gram-negative infections increases, colistin resistance is being increasingly reported in Indian hospitals. **Materials and Methods:** Retrospective chart review of clinical data from patients with colistin-resistant isolates (minimum inhibitory concentration >2 mcg/ml). Clinical profile, outcome, and antibiotics that were used for treatment were analyzed. **Results:** Twenty-four colistin-resistant isolates were reported over 18 months (January 2014–June 2015). A history of previous hospitalization within 3 months was present in all the patients. An invasive device was used in 22 (91.67%) patients. Urine was the most common source of the isolate, followed by blood and respiratory samples. *Klebsiella pneumoniae* constituted 87.5% of all isolates. Sixteen (66.6%) were considered to have true infection, whereas eight (33.3%) were considered to represent colonization. Susceptibility of these isolates to other drugs tested was tigecycline in 75%, chloramphenicol 62.5%, amikacin 29.17%, co-trimoxazole 12.5%, and fosfomycin (sensitive in all 4 isolates tested). Antibiotics that were used for treatment were combinations among the following antimicrobials-tigecycline, chloramphenicol, fosfomycin, amikacin, ciprofloxacin, co-trimoxazole, and sulbactam. Among eight patients who were considered to have colonization, there were no deaths. Bacteremic patients had a significantly higher risk of death compared to all nonbacteremic patients ($P = 0.014$). **Conclusions:** Colistin resistance among Gram-negative bacteria, especially *K. pneumoniae*, is emerging in Indian hospitals. At least one-third of isolates represented colonization only rather than true infection and did not require treatment. Among patients with true infection, only 25% had a satisfactory outcome and survived to discharge. Fosfomycin, tigecycline, and chloramphenicol may be options for combination therapy.

Arjun R, Gopalakrishnan R, Nambi PS, Kumar DS, Madhumitha R, Ramasubramanian V. Indian J Crit Care Med 2017;21:317-21.

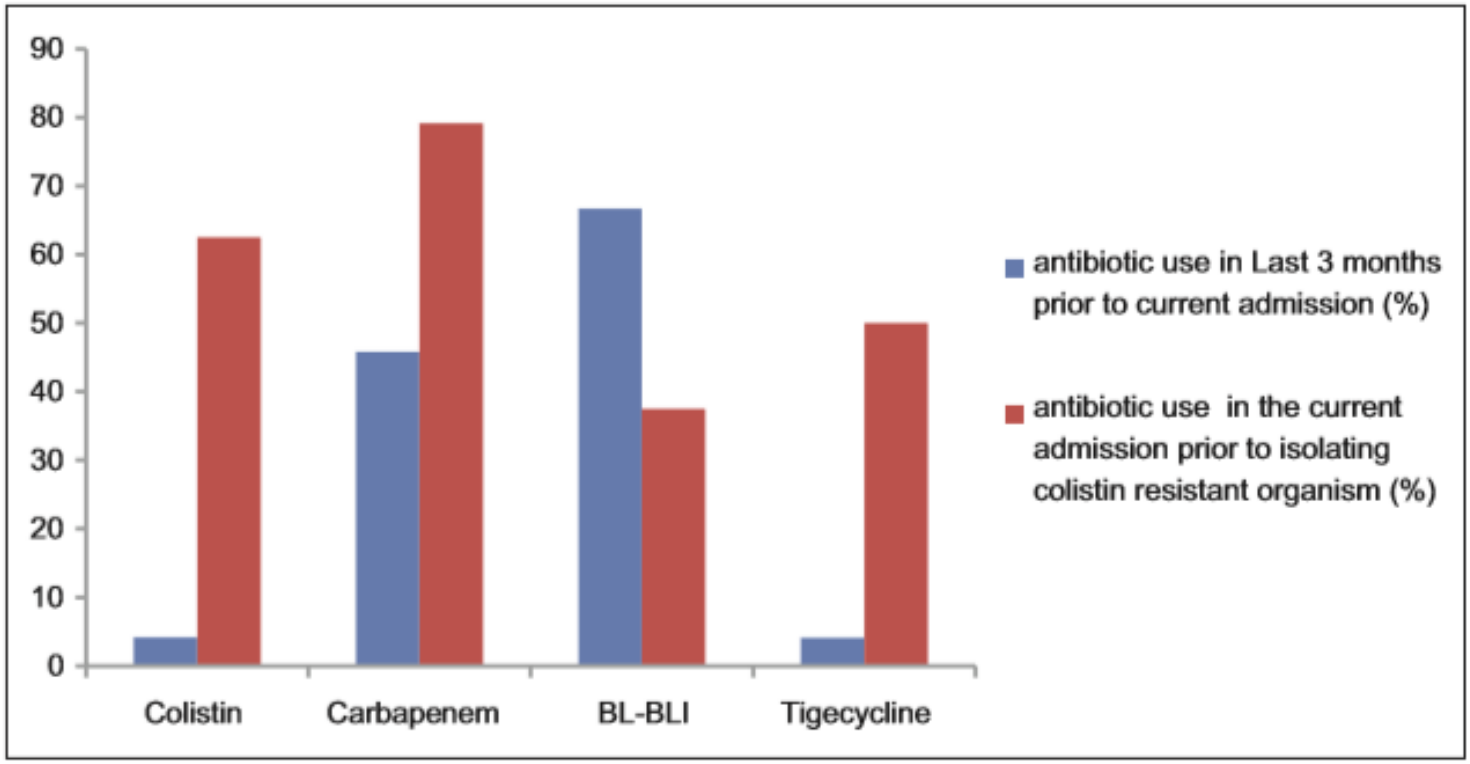


Figure 1: Antibiotic exposure in the past 3 months

Serial number	APACHE score	Charlson index	Sample	Antibiotics used for treatment	Clearance on surveillance cultures	Outcome
1	22	6	Blood	Tigecycline + co-trimoxazole	Not checked	Expired
2	24	9	Blood	Tigecycline + ciprofloxacin	Not checked	Discharged
3	12	5	Blood	Chloramphenicol + fosfomycin + doripenem	Not checked	Expired
4	25	7	Blood	Tigecycline + chloramphenicol	Not checked	Expired
5	12	5	Blood	Tigecycline + ciprofloxacin	Cleared	Expired
6	16	3	Blood	Chloramphenicol + fosfomycin	Not checked	Expired
7	10	8	Urine	Chloramphenicol + fosfomycin	Cleared	Expired
8	25	1	Urine	Chloramphenicol + fosfomycin+ imipenem	Not checked	Discharged
9	4	7	Urine	Tigecycline + chloramphenicol + colistin	Not checked	Expired
10	15	1	Respiratory	Tigecycline + colistin	Not checked	Lost to follow-up
11	18	4	Respiratory	Tigecycline + colistin	Not checked	Lost to follow-up
12	25	7	Respiratory	Tigecycline + colistin	Not checked	Expired
13	12	7	Pus	Tigecycline	Not checked	Discharged
14	2	5	Pus	Tigecycline + co-trimoxazole	Not checked	Lost to follow-up
15	12	3	Pus	Tigecycline + amikacin + colistin	Not checked	Expired
16	9	7	CSF	Tigecycline + chloramphenicol + sulbactum	Not checked	Expired

CSF: Cerebrospinal fluid; APACHE: Acute Physiology and Chronic Health Evaluation

Arjun R, Gopalakrishnan R, Nambi P S, Kumar D S, Madhumitha R, Ramasubramanian V. A study of 24 patients with colistin-resistant Gram-negative isolates in a tertiary care hospital in South India. Indian J Crit Care Med 2017;21:317-21

Conclusions

Colistin resistance among GNB, especially *K. pneumoniae*, is emerging in Indian hospitals. Recent hospitalization, prolonged current hospitalization (median of 24.5 days), presence of diabetes and CKD, use of invasive devices, and prior colistin exposure were all commonly seen. At least one-third of isolates represented colonization rather than true infection, highlighting the role of the clinician in making this distinction. Among patients with true infection, only 25% had a satisfactory outcome and survived to discharge, with bacteremia carrying an even poorer prognosis. Fosfomycin, tigecycline, and chloramphenicol may be options for combination therapy.

American Journal of Infection Control ■■ (2017) ■■-■■

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief Report

Clinical outcome of dual colistin- and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: A single-center retrospective study of 75 cases in India

Amarjeet Kaur MD [a], Sumanth Gandra MD [b], Priyanka Gupta MBBS [a], Yatin Mehta MD [c], Ramanan Laxminarayan PhD [b,d], Sharmila Sengupta MD [a,*]

AJIC
Sept 2017

93 cases of CCRKP BSI were identified.
The overall in-hospital mortality rate for patients with CCRKP BSI was 69.3% (52/75)– 18 went AMA.

Combination Therapy for High-Level Meropenem- and Colistin-Resistant Klebsiella pneumoniae Bacteremia

- 72 patients with resistant bacteremia
- Overall 30-day crude mortality was 25% with combination therapy and 44% with monotherapy.
- Use fosfomycin

Antimicrob Agents Chemother 2017 Jul 25; 61:e00406

Take home message on monotherapy vs combination therapy for CR organisms

- No RCT data for the most part
- No studies focussed on NDM-1
- No clinical data that shows that emergency of resistance reduced
- Colistin remains the cornerstone
- Subgroup of patients with shock or neutropenia may benefit in subgroup analysis, use when probability of death high
- Benefit disappears when IAT eliminated
- Consider for septic shock, CRE with high mortality score
- Knowing the MIC of carbapenems crucial to their use in combination
- Pseudomonas: combination therapy only till sensitivites known, then monotherapy
- Acinetobacter: monotherapy if colistin sensitive
- CRE: empiric combination therapy with colistin in patients at high risk of death (high dose carbapenem, tigecycline, fosfomycin, ceftazidime-avibactam)

MAJOR ARTICLE

Infectious Diseases Specialty Intervention Is Associated With Decreased Mortality and Lower Healthcare Costs

Steven Schmitt,[1] Daniel P. McQuillen,[2] Ronald Nahass,[3] Lawrence Martinelli,[4] Michael Rubin,[5] Kay Schwebke,[6] Russell Petrak,[7] J. Trees Ritter,[8] David Chansolme,[9] Thomas Slama,[10] Edward M. Drozd,[11] Shamonda F. Braithwaite,[11] Michael Johnsrud,[12] and Eric Hammelman[11]

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• CID 2014:58 (1 January) •

Open Forum Infectious Diseases

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Volume 5, Issue 3
March 2018

Article Contents

EDITOR'S CHOICE

Infectious Diseases Consultation Reduces 30-Day and 1-Year All-Cause Mortality for Multidrug-Resistant Organism Infections

Jason P Burnham ✉, Margaret A Olsen, Dustin Stwalley, Jennie H Kwon, Hilary M Babcock, Marin H Kollef

Open Forum Infectious Diseases, Volume 5, Issue 3, 1 March 2018, ofy026, https://doi.org/10.1093/ofid/ofy026

Published: 15 March 2018 **Article history** ▾

- ID consultation was significantly associated with reductions in 30-day and 1-year mortality for
- resistant *S. aureus* (hazard ratio [HR], 0.48 & HR, 0.73)
- *Enterobacteriaceae* (HR, 0.41 and HR, 0.74)

CIDS

CLINICAL INFECTIOUS DISEASES SOCIETY

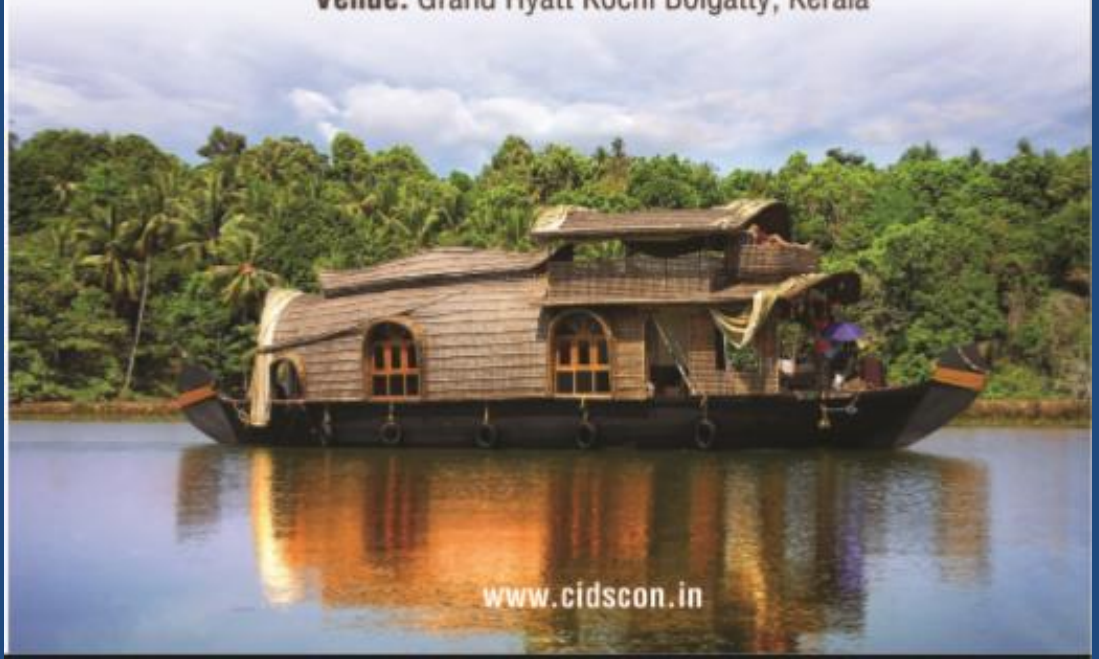
CIDSCON 2019

9th Annual Conference of Clinical Infectious Diseases Society

23rd | 24th | 25th August 2019, Kochi

Theme: Simplifying the evidence- the next step for progress in Infectious Diseases

Venue: Grand Hyatt Kochi Bolgatty, Kerala

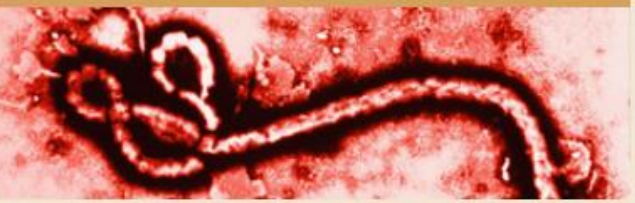


CLINICAL INFECTIOUS DISEASES SOCIETY

MISSION

Our mission is to fight against Infectious Diseases in India by educating health care professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients.

ID News - September 2018



Eravacycline FDA approved

The US FDA has approved eravacycline to treat "complicated intra-abdominal infections, providing a new option to combat the growing threat from ... more...

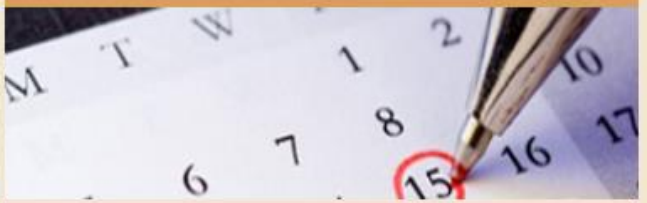
US-FDA warning: increased risk of Fournier's gangrene with SGLT2 inhibitors

The US-FDA has issued a warning regarding increased risk of Fournier's gangrene with use of ... more...

Photo Quiz - September 2018

A 40/M presented with fever of over 5 months with loss of appetite and weight. TTE revealed an echogenic mass of 1.4 X 0.4 cm on the aortic valve with aortic regurgitation & mitral regurgitation. Blood cultures grew ampicillin and gentamicin sensitive Enterococcus faecalis. He was initiated on intravenous vancomycin elsewhere. The patient subsequently developed acute kidney injury (AKI) with creatinine increasing to 6.6 mg%. On admission one month later, the patient had vomiting and fever <99˚F. TTE showed persistent vegetations ... more...

CIDS Events



CIDSCON 2019

23 - 25 Aug 2019 | Kochi

CIDS Endorsed meetings

Infectious Diseases CME for Postgraduates

Dates: Dec 2018 | **Place:** Wheeler Hall, CMC Vellore

Guideline watch - August 2018

Chandra's corner - August 2018

Challenging cases at CIDSCON

Are you an MD/DNB (Internal Med) interested in an ID career?

- DM (Infectious Diseases)
  - Three year program
  - CMC, Vellore and AIIMS, New Delhi
- FNB (National Board of Examinations):
  - Two year fellowship
  - Apollo Hospitals Chennai, Hinduja Hospital Mumbai, Apollo Hyderabad, Sterling Hospital Ahmedabad
  - For details go to NBE website
- Tamil Nadu Dr. MGR Medical University:
  - Two year fellowship
  - Global Hospitals Chennai and CMC, Vellore
  - Contact institutions for details