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P2448 Phenotypic and genotypic comparison of the activity of beta-lactams against 3GC resistant E. coli collected from an international randomized controlled trial

Andrew Henderson*[1 2 5], Ernest Tan[5], Kyra Cottrell[5], Leah Roberts[2], Scott Beatson[2 3 4], David L. Paterson[3 5], Patrick Harris[1 5]

[1]Princess Alexandra Hospital, Infection Management Services, Woolloongabba, Australia, *[2]The University of Queensland, School of Chemistry and Molecular Biosciences, Saint Lucia, Australia*, *[3]The University of Queensland, Australian Infectious Diseases Research Centre , Saint Lucia, Australia*, *[4]The University of Queensland, Australian Cenrtre for Ecogenomics, Saint Lucia, Australia*, *[5]University of Queensland, Centre for Clinical Research, Herston, Australia*

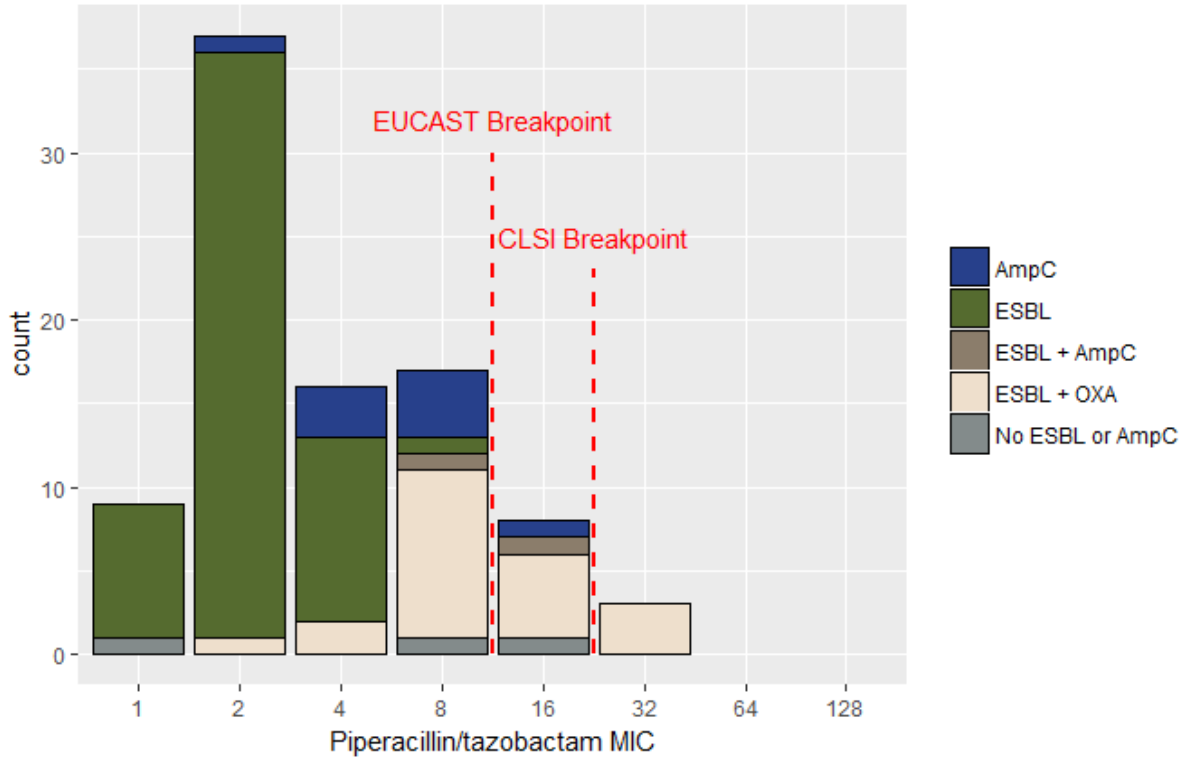
Background: Treatment choice of 3rd-generation cephalosporin (3GC)-resistant Enterobacteriaceae bloodstream infections is controversial. Widespread use of carbapenems has the potential to promote spread of carbapenemase producing Enterobacteriaceae (CPE). We aimed to assess commonly used beta-lactams against isolates cultured from patients enrolled in an international multisite randomized trial comparing treatment options for 3GC-resistant *Escherichia coli*.

Materials/methods: Minimum inhibitory concentration (MIC) testing was performed by custom broth microdilution sensititre plates (Thermo Fisher Scientific). Interpretive criteria was assessed against Clinical and Laboratory Standards Institute (CLSI) M100-S26 and 2017 European Committee on Antimicrobial Susceptibility Testing version 7.1 (EUCAST v7.1) guidelines. Whole genome sequencing was performed in 2 batches using Illumina HiSeq (100 bp paired end) and MiSeq (300 bp paired end). Antibiotic resistance genes were detected by using Abricate (v0.3) with the ResFinder database against SPAdes assemblies (v3.6.2) as implemented through the pipeline analysis tool Nullarbor (default settings).

Results: 100% of isolates were susceptible to carbapenems (ertapenem, doripenem, imipenem and meropenem), with no CPE detected. Ceftolozane/tazobactam, piperacillin/tazobactam, meropenem and cefepime $MIC_{50/90}$ were ≤0.25/0.5, 4/16, 0.03/0.06 and 8/≥32 µg/ml. Ceftolozane/tazobactam was the only non-carbapenem beta-lactam tested with > 90% of isolates susceptible according to EUCAST criteria, although piperacillin/tazobactam tested susceptible in 97% of isolates by CLSI criteria. Isolates with acquired ESBL or AmpC genes that also harboured OXA-1 beta-lactamases had elevated piperacillin/tazobactam MICs (Figure 1), however this combination did not appear to elevate carbapenem or ceftolozane/tazobactam MICs.

Conclusions: Carbapenem sparing agents for treatment of 3GC-resistant Enterobacteriaceae remains a challenge. Ceftolozane/tazobactam and piperacillin/tazobactam are potential therapeutic options. However, in isolates harboring OXA-1 beta-lactamases, phenotypic piperacillin/tazobactam MIC testing may be challenging, with the MIC distribution spanning the EUCAST and CLSI breakpoints. Studies are required to assess the clinical impact of this finding.

Figure 1. Piperacillin/tazobactam minimum inhibitory concentration (MIC) distribution grouped according to acquired beta-lactamase.


EUCAST Breakpoint
CLSI Breakpoint
count
30
20
10
0
1
2
4
8
16
32
64
128
Piperacillin/tazobactam MIC
AmpC
ESBL
ESBL + AmpC
ESBL + OXA
No ESBL or AmpC