Harris PNA, Tambyah PA, Lye DC, et al. **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**. *JAMA*. 2018;320(10):984-994.

AKA: the MERINO Trial

<table>
<tr><td>Background</td><td>See slides
Clinical equipoise exists, so can we use a carbapenem-sparing regimen (e.g. piperacillin-tazobactam) to treat ceftriaxone-resistant BSI to put let resistant pressure on carbapenems?</td></tr>
<tr><td>Aims</td><td>“Test the hypothesis that a carbapenem-sparing regimen (piperacillin-tazobactam) is noninferior to a carbapenem (meropenem) for the definitive treatment of blood-stream infection (BSI) caused by ceftriaxone-nonsusceptible[e.g. ESBL] E. coli or Klebsiella spp that test susceptible to piperacillin-tazobactam.”</td></tr>
<tr><td>Study Design</td><td>

International, multicenter, open-label, parallel group, RCT

<table>
<tr><td>Inclusion Criteria
Age ≥ 18 years (≥ 21 in Singapore)
≥ 1 positive BCx with E. coli or Klebsiella spp.
Nonsusceptible to 3GC
Susceptible to TZP or MEM
Randomized ≤72 hours from index BCx draw</td><td>Exclusion Criteria
Allergy to trial drug
Not expected to survival >96 hours
Treatment without curative intent
Polymicrobial bacteremia
Pregnant or breastfeeding
Need for additional antibiotics active against GNR</td></tr>
</table>

Enrollment between 2/2014 and 7/2017
1:1 randomization based on study site and stratification
Stratification criteria: organism, source of infection, severity
Random permuted blocks of 2 and 4 patients
Study medications
Meropenem 1g IV q8h with 30-minute infusion
Piperacillin-tazobactam 4.5g IV q6h with 30-minute infusion
Step-down therapy allowed on day 5 after randomization
Outcomes

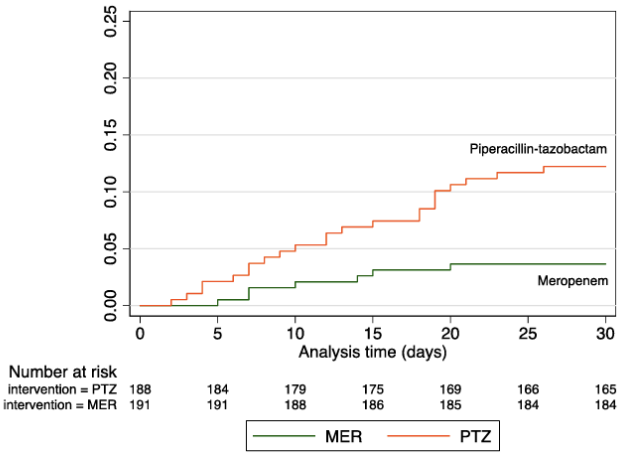
<table>
<tr><td>Primary Outcome
All-cause 30-day mortality after randomization</td><td>Secondary Outcomes
Time to clinical & microbiologic resolution from randomization
Clinical & microbiologic success at day 4 from randomization
Microbiologic resolution on or before day 4 from randomization
Relapsed bloodstream infection after end of treatment but before day 30 from randomization
Secondary infection with study-drug resistant organisms or C. difficile infection up to day 30 from randomization</td></tr>
</table>

Sample Size calculation
Expected mortality of 14% with a 5% noninferiority margin
Needed 454 patients total for 80% power with a 1-sided α level of 0.025

</td></tr>
</table>

	• Statistical analysis
	  • Primary analysis population were all patients randomized who received at least 1 dose of the correctly assigned treatment
	  • Analyzed a per protocol population
	  • Miettinen-Nurminen method used to determine CIs for risk differences
	  • Secondary outcomes were tested without adjustments for multiple comparisons with 2-sided statistical testing and $p < 0.05$ indicating significance
	  • Included pre-specified subgroup analyses of the primary outcome
	  • Several logistic regression models used to evaluate factors such as homogeneity of treatment effects, various clinical variables, etc.
	• **DSMB established to perform interim analyses**

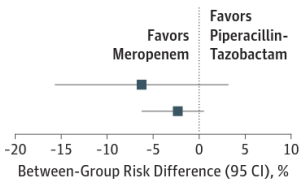
Results	Demographics & Clinical Characteristics • 1,646 patients screened→391 randomized→379 included in 1˚ analysis (Figure 1) • Generally well-balanced clinical characteristics in treatment groups (see Table 1 on slide) Primary Outcome • All-cause mortality at 30 days: 23/187 (**12.3%**) in TZP vs. 7/191 (**3.7%**) MEM (Risk difference, 8.6%, 1-sided 97.5% CI, **-∞ to 14.5%**; p = 0.9 for noninferiority) • Multivariable analysis: aOR 3.41 (1-sided 97.5% CI, 0-8.38)



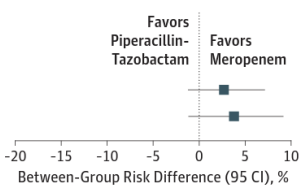
	• PP all-cause mortality: 18/170 (**10.6%**) in TZP vs. 7/186 (**3.8%**) MEM (Risk difference, 6.8%, 1-sided 97.5% CI, **-∞ to 12.8%**; p = 0.76 for noninferiority) • Pre-specified subgroup analyses (see slides) Secondary Outcomes

Figure 2. Secondary Outcomes

Measure of Success	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Clinical and microbiological success at day 4[a]	121/177 (68.4)	138/185 (74.6)	-6.2 (-15.5 to 3.1)
Microbiological success at day 4	169/174 (97.1)	184/185 (99.5)	-2.3 (-6.1 to 0.4)



Measure of Failure	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Microbiological relapse	9/187 (4.8)	4/191 (2.1)	2.7 (-1.1 to 7.1)
Secondary infection with multiresistant organism or *Clostridium difficile*	15/187 (8.0)[b]	8/191 (4.2)[c]	3.8 (-1.1 to 9.1)



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<tr><td></td><td>Microbiology (see slides)
ESBL genes in 83.5% isolates, ampC genes in 10.2%, ESBL + ampC in 2%
Narrow-spectrum oxacillinases (e.g. OXA-1) in 67.6% of isolates and “may compromise ß-lactamase inhibition by tazobactam.”</td></tr>
<tr><td>DSMB</td><td>Review of first 340 patients enrolled
Mortality difference approached pre-specified study termination point (p = 0.004)
Trial temporarily suspended to review remaining randomized patients
Study terminated early due to futility and risk of harm to enrollees</td></tr>
<tr><td>Assessment</td><td><table><tr><th>Strengths</th><th>Weaknesses</th></tr><tr><td>First RCT to test TZP vs. MEM for ESBL BSI
Pragmatic design meant to mimic real-world treatment decisions
Use of 5% NI margin
Inclusion of immunocompromised patients
Adjustment for factors associated with mortality</td><td>Drug dosing; lack of extended infusion
Very few “high-risk” or critically ill patients and lower mortality than anticipated
Majority of patients with E. coli
Empiric therapy did not match study group in majority of patients
Significantly more urinary source patients in meropenem group
More immunocompromised patients in TZP group
Step-down to carbapenem occurred in 20% of TZP group
Treated BSI for median 14 days
No patients from US (2 from Canada)
Relatively short follow-up period</td></tr></table></td></tr>
<tr><td>Authors Conclusions</td><td>“Among patients with E. coli or K. pneumoniae bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.”</td></tr>
<tr><td>My Conclusions</td><td>Higher mortality and not meeting the non-inferiority criteria with piperacillin-tazobactam supports use of a carbapenem as soon as ceftriaxone resistance or detection of an ESBL gene is reported.
Reliance on TZP MIC in the “susceptible” range does not correlate with mortality and justification of TZP use based on a susceptible MIC is not justified in these situations.</td></tr>
<tr><td>Questions</td><td>Why were these the results if all of the isolates were equally susceptible to TZP and MEM?</td></tr>
<tr><td>References</td><td>Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E, et al. A multinational, preregistered cohort study of ß-lactam/ ß-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum- ß-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother. 2016;60(7):4159-4169.
Harris PN, Yin M, Jureen R, et al. Comparable outcomes for ß-lactam/ ß-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant Escherichia coli or Klebsiella pneumoniae. Antimicrob Resist Infect Control. 2015;4:14.
Kang CI, Park SY, Chung DR, et al. Piperacillin-tazobactam as an initial empirical therapy of bacteremia caused by extended-spectrum ß-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Infect. 2012;64:533-534.
Ng TM, Khong WX, Harris PN,e t al. Empiric piperacillin-tazobactam versus carbapenems in the treatment of bacteraemia due to extended-spectrum beta-lactamase-producing Enterobacteriaceae. PLoS One. 2016;11:e0153696.</td></tr>
</table>

5. Ofer-Friedman H, Shefler C, Sharma S, et al. Carbapenems versus piperacillin-tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum- ß-lactamase-producing *Enterobacteriacaeae*. *Infect Control Hosp Epidemiol*. 2015;36:981-985.
6. Rodriguez-Bano J, Navarro MD, Retamar P, et al. ß-lactam/ ß-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum ß-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis*. 2012;54:167-174.
7. Tamma PD, Han JH, Rock C, et al. Antibacterial resistance Leadership Group. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum ß-lactamase bacteremia. *Clin Infect Dis*. 2015;60(9):1319-1325.