Antimicrobial Stewardship News

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The MERINO trial: Piperacillin-tazobactam loses out to meropenem in drug-resistant blood stream infections.

Piperacillin-tazobactam (pip-tazo), one of the most common antibiotics used in inpatient settings, often shows *in vitro* susceptibility to extended spectrum beta-lactamases (ESBLs). However, recent clinical experience has suggested diminished efficacy compared to treatment with carbapanems.[1] Thus far, this data had been largely retrospective without a head-to-head comparison. To finally confirm or refute this clinical suspicion, Harris et al. compared piperacillin-tazobactam with meropenem in a prospective, randomized design for patients with Gram-negative blood stream infections in a large, multicenter, international trial (MERINO).[2] The results, published in last month's Journal of the American Medical Association (JAMA), were surprising.

The MERINO trial investigated patients with *E. coli* or *Klebsiella pneumoniae* blood stream infections with ceftriaxone or cefotaxime resistance. Patients were excluded if death was thought to be impending within the next 96 hours, but otherwise were randomized to either pip-tazo or meropenem for at least 5 days following blood culture results. After an interim analysis (at a predefined checkpoint of 340 patients enrolled) found a mortality difference of 8.6% higher in the pip-tazo group, the study was discontinued early due to concern for harm and futility. The authors concluded that "among patients with *E. coli* and *K. pneumoniae* blood stream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a non-inferior 30-day mortality." The results of this practice changing (or confirming) study were certainly striking. But in order to truly understand the results, we have to ask: what does *not* non-inferior really mean?

Non-inferiority trials in a nutshell

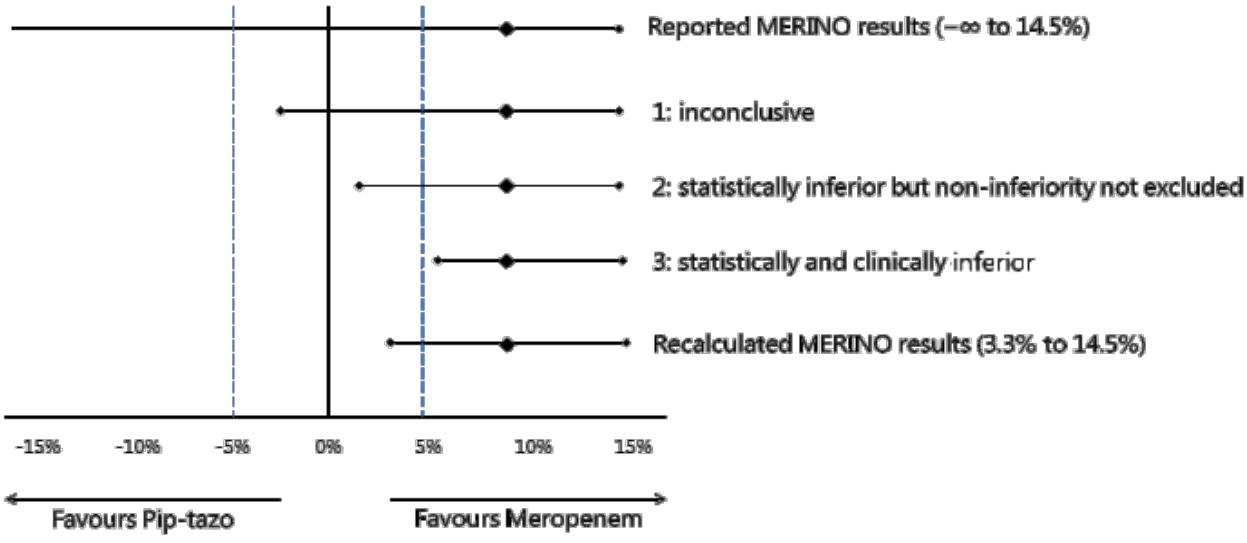
> *"A non-inferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable amount."*
> *- CONSORT Statement published in JAMA, 2012*

To interpret this trial's results, it is important to understand *how* a non-inferiority trial is structured. In the design of a non-inferiority trial, investigators decide a threshold point (or "acceptable amount"[3]) for the primary outcome at which the results indicate the two studied drugs have a *clinically* significant difference. This threshold is often based on clinical intuition as well as precedent from prior studies. In the MERINO trial, the authors decided *a priori* that a difference in 30-day mortality of less than 5% would indicate that pip-tazo was non-inferior to meropenem. Once the study concludes, the MERINO trial authors then determined the risk difference in 30-day mortality (with calculated 95% confidence intervals) between the pip-tazo group and the meropenem group. If the estimated difference in 30-day mortality between these two groups remained within the pre-determined 5% margin, pip-tazo would be considered non-inferior to meropenem.

The results and their interpretation

The MERINO authors ultimately found an 8.6% higher 30-day mortality in the pip-tazo arm compared to the meropenem arm during their interim analysis. As this exceeded the pre-specified 5% threshold, the authors concluded that pip-tazo did not meet criteria to qualify for non-inferiority. Reponses to the MERINO trial and interpretations of this conclusion have been varied, however. Many who are trying to understand the double-negative conclusion are asking one fundamental question: Does this data mean that pip-tazo is, in fact, *inferior* to meropenem for drug-resistant blood stream infections?

Figure 1. Risk difference for 30-day mortality



In short, the answer is likely "yes." Marc Bonten and colleagues from UMC Utrecht posted an illustrative response on this topic.[4] They argue that the confusing double-negative in the MERINO paper's conclusion boils down to confidence interval reporting, illustrated in Figure 1. As reported in the article, a single-sided confidence interval (top-line), does not allow for an inference of inferiority (or superiority, for that matter) as the confidence interval ranges from -∞ to 14.5%. A two-sided confidence interval instead allows for more specific interpretations. Determination of inferiority can be inconclusive (line #1) when a wide confidence interval is present and crosses both zero and the non-inferiority margin. In contrast, statistical and clinical inferiority can be determined if the confidence interval lies completely beyond the margin of non-inferiority, crossing neither (line #3).

The MERINO results calculated with a two-sided confidence interval, would fall where pip-tazo can be considered *statistically* inferior, without certainty with regards to *clinical* inferiority (similar to line #2). The confidence interval still encompasses *some part* of the 0 to 5% non-inferiority margin. **In summary, the results of this study indicate statistical inferiority and *likely, though not certain,* clinical inferiority of pip-tazo for ESBL blood stream infections.**

Does this particular trial apply to my patients?

This trial was designed to be "pragmatic and reflect usual care." Patients were not limited to any specific empirical therapy (prior to culture results) or step-down therapy (after 5 days of study-determined drug). Cross-over between groups was also allowed. This pragmatic design trial design, as noted by the accompanying JAMA editorial, allows the advantage of wide-range generalizability to acute care settings.[5] Interestingly, the trial design itself also biases towards a finding of non-inferiority despite what the results conclude.

No patients from the United States were enrolled. Only 2 were from North America at all. There is an important geographical difference in ESBL mechanism distribution. This fact then begs the question: would the dominant ESBL organisms in the United States act phenotypically different than those in the trial? The authors recognized this limitation and attempted to address it in their microbiologic analysis. Whole-genome sequencing data was available for 77.3% of isolates obtained in the study and the authors note that of the *E. coli* strains analyzed, the sequence types and corresponding ESBL genes in the MERINO data are consistent with strains most prevalent in the United States.

Implications for Stewardship

With this new data solidifying carbapenem therapy for ESBL or ESBL-like infections, a natural concern for an increased risk of carbapenem-resistant Enterobacteriaceae (CRE) follows. The goal of all antibiotic stewardship programs (ASPs), however, is to ensure that patients receive the right drug, in the right dose, through the right route, and for the right amount of time. In drug resistant gram-negative blood stream infections, ASPs can guide clinicians towards appropriate carbapenem therapy without delay. Optimal duration of therapy, still as yet unknown, will be the next step forward in this frontier.

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Clinical Applications

Case report: 42 year old man presents from with 4 days of flank pain, fevers, and chills. Physical exam and radiographic imaging confirm a diagnosis of pyelonephritis and he is admitted to the hospital. Patient is started empiritically on ceftriaxone. On hospital day 3, blood and urine cultures result with the organism seen below. What is the optimal initial antibiotic therapy?

Susceptibility

	Escherichia coli MIC
Amikacin	S
Ampicillin	R
Ampicillin + Sulbactam	R
Cefazolin	R
Cefepime	R
Ceftazidime	I
Ceftriaxone	R
Ciprofloxacin	S
Ertapenem	S
Gentamicin	S
Imipenem	S
Meropenem	S
Piperacillin/Tazobactam	S
Tobramycin	S
Trimethoprim + Sulfamethoxazole	R

Answer: A carbapenem.