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INCREASED RISK OF DEATH FOR SEPSIS PATIENTS TREATED WITH BROAD-SPECTRUM ANTIBIOTICS

A new study indicates that one of the most commonly prescribed **broad-spectrum empirical antibiotics** for patients suspected of **sepsis** is associated with increased mortality.

The study, led by researchers from the University of Michigan Medical School and Veteran Affairs (VA) Anne Arbor Healthcare System, found that in patients suspected of sepsis without clear indications for **anaerobic** antibiotic therapy, the combination of piperacillin-tazobactam and vancomycin was associated with a 5% absolute increase in 90-day mortality compared to the use of cefepime and vancomycin. This regimen may contribute to one additional death per 20 patients suspected of sepsis.

Piperacillin-tazobactam, a combination of a penicillin with a beta-lactamase inhibitor administered intravenously, has a broad spectrum and strong activity against intestinal anaerobic bacteria. Clinicians choose the piperacillin-tazobactam and vancomycin combination for empirical treatment of sepsis patients to cover as many potential pathogens as possible.

Several studies have suggested that empirical use of piperacillin-tazobactam is associated with adverse outcomes in critically ill patients, including increased death rates. One hypothesis suggests that activity against intestinal anaerobic bacteria targets microorganisms with protective effects.

During a 15-month national shortage of piperacillin-tazobactam, clinicians used the other common empirical regimen for sepsis: vancomycin and cefepime, which does not have activity against anaerobic bacteria. Thus, it was found that early treatment with antibiotics with anaerobic activity could harm patients.

Using electronic health records, researchers analyzed adults with suspected sepsis treated with either regimen in the emergency department of the University of Michigan from July 2014 to December 2018. Patients with indications for broad-spectrum antibiotic therapy against anaerobes within 24 hours of presentation were excluded. The primary outcome was 90-day mortality, and secondary outcomes included days without organ failure, without the need for ventilation, or vasopressors.

Of the 7,569 patients (55% male; mean age, 63 years) with sepsis eligible for the study, 4,523 were treated with vancomycin and piperacillin-tazobactam, while 3,046 received vancomycin and cefepime. Among patients treated with piperacillin-tazobactam, 97% were admitted outside the shortage period and 3% during the shortage. There were no significant differences between treatment groups in terms of age, comorbidities, organ failure assessment scores, or time to antibiotic administration.

The piperacillin-tazobactam shortage presented a unique opportunity to hypothesize that this antibiotic (known to act on intestinal anaerobic bacteria) impacts patient conditions.

In an analysis controlling for unobserved differences in patient characteristics, 90-day mortality for patients treated with piperacillin-tazobactam was 22.5%, compared to 17.5% for those treated with cefepime, for an absolute 5% increase in 90-day mortality (95% confidence interval [CI], 1.9% to 8.1%). **Piperacillin-tazobactam** was also associated with 2.1 fewer days without organ failure (95% CI, 1.4 to 2.7), 1.1 fewer days without a ventilator (95% CI, 0.57 to 1.62), and 1.5 fewer days without vasopressors (95% CI, 1.01 to 2.01).

An additional analysis found that **metronidazole**, a strong anti-anaerobic chemotherapeutic used in sepsis patients during the piperacillin-tazobactam shortage, was also associated with increased 90-day mortality.

These findings suggest that broad-spectrum antibiotics with anti-anaerobic activity can cause harm in patients without clear indications.

Despite aligning with previous observational studies, these results contradict a recent clinical trial (ACORN - Antibiotic Choice on Renal Outcomes) that highlighted the risk of acute kidney injury and death among hospitalized adults with acute infections. The risk was not significantly different between those treated with piperacillin-tazobactam or cefepime, but ACORN compared mortality at only 14 days.

The two studies had similar results over a two-week period, but the differences at three months were dramatic. The results are vulnerable to unobserved confounding factors and may not be generalizable to other hospital units or patient populations.

Thus, more research is needed to determine why antibiotics that eliminate intestinal anaerobic bacteria are associated with poorer clinical outcomes, providing **clinicians** with reasons to reconsider the widespread use of broad-spectrum antibiotics.

In the appropriate context, treatment can save lives, and in an inappropriate context, the result can be harmful. The risk-benefit balance plays a significant role in the administration of antibiotics.

Adapted after Chris Dall, 14 May 2024