In the Literature

Piperacillin-Tazobactam and Extended-Spectrum β-Lactamase–Producing Escherichia coli


Carbapenems are generally recommended as the antibiotics of choice for the treatment of most infections due to aerobic gram-negative bacilli that produce extended-spectrum β-lactamasas (ESBLs). Recently, however, a group from Hospital Universitario Virgen Macarena in Sevilla, Spain, analyzed data from 6 published prospective cohort studies of patients with bloodstream infections (BSIs) due to ESBL-producing Escherichia coli and concluded that combination treatment with a β-lactamase combined and a β-lactamase inhibitor (amoxicillin-clavulanate or piperacillin-tazobactam) resulted in outcomes similar to that seen with carbapenem therapy [1].

The same group has now reanalyzed the data to determine the effect of the piperacillin minimum inhibitory concentration (MIC) on the outcome of patients treated with piperacillin-tazobactam. Included in this analysis were all patients from the combined cohorts who received piperacillin-tazobactam regardless of MIC (patients with resistant isolates were excluded from the previous study), but required that the bacteremia be monomicrobial, that criteria for the presence of sepsis were met, and that the first dose of piperacillin-tazobactam (>90% received 4.5 g every 6 hours with an unspecified duration of infusion) was given within 24 hours of phlebotomy for blood culture.

Patients were stratified on the basis of the following piperacillin MICs of the organism causing their infection: ≤2 mg/L (low), 18 patients (46.1%); 4–8 mg/L (intermediate), 10 (23.6%); and ≥8 mg/L (high), 11 (28.2%). US investigators likely would have devised different MIC categories, since those of Retamar et al reflect the EUCAST susceptibility break point of ≤8 mg/L, whereas the CLSI breakpoint is ≤16 mg/L. Patients in each category were similar at baseline. The small number of patients in each group did not allow for multivariable analysis, but consideration of individual factors other than MIC revealed that only presentation with severe sepsis or septic shock was associated with increased mortality. Mortality, however, was significantly greater among patients with high MICs, compared with those with low MICs (41.1% vs 0%; \(P = .02\)). None of the 11 patients with urosepsis died, regardless of MIC. When patients with urosepsis were excluded, the mortality among patients with BSI due ESBL-producing E. coli was 44.4% (4/9) for those whose organisms had high MICs, 57.5% (3/8) for those whose organisms had intermediate MICs, and 0% (0/11) for those whose organisms had low MICs.

The finding that a urinary tract infection as the source of bacteremia was readily treated regardless of MIC is instructive but not entirely unexpected and may have accounted, at least in part, for the failure to find evidence of the superiority of carbapenem treatment in the group’s previous study, since two-thirds of the patients in that analysis had urosepsis. The very high concentrations of piperacillin-tazobactam achieved in the urine, despite the primarily biliary excretion of piperacillin, may be sufficient to overcome resistance and provide rapid and effective source control.

While the number of patients in each MIC category was relatively small, the trend appears solid: no patient infected with an organism with a piperacillin MIC of <2 mg/L died, whereas mortality in the combined intermediate and high piperacillin MIC groups was approximately 4 in 10. I believe it can be concluded, in the absence of strong evidence to the contrary, that piperacillin-tazobactam is inadequate therapy for patients with BSI due ESBL-producing E. coli, unless the urinary tract is the source of the bacteremia (but why take a chance?). It seems to me that this conclusion can likely be extended to other members of the Enterobacteriaceae, as well.

Reference


Ouch! Why That Infection Hurts

Chiu IM, Heesters BA, Ghasemlou N, et al. Bacteria activate sensory neurons

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The pain associated with soft-tissue infections is generally considered to result not from bacterial proliferation directly, but rather from the resultant inflammatory response. The real answer, however, is not that straightforward. Chiu et al explored the cause of infection-associated pain in a mouse hind-foot model by inoculation of a strain of community-acquired methicillin-resistant *Staphylococcus aureus*. Hyperalgesia, manifested as mechanical, heat, and cold hypersensitivity each appeared within 1 hour, peaked at 6 hours, and began to decrease after 24 hours. Tissue swelling, which did not correlate with pain, peaked immediately, with a second peak at 48 hours. An influx of neutrophils and monocytes began at 6 hours, peaking at 48 hours, and began to decline at 72 hours. Chemokine levels peaked early, and the concentrations of the proinflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) also increased. Although TNF-α and IL-1β can directly sensitize nocireceptors, their concentration did not correlate with hyperalgesia. The bacterial density peaked at 6 hours and then decreased over time, with the bacterial cells often found in close proximity to dermal nocireceptors.

Mechanical and thermal hyperalgesia were not reduced in knockdown mice with impaired TLRA-dependent innate immune responses. Monocyte and neutrophil depletion by use of a monoclonal antibody was associated with significantly increased mechanical and heat hypersensitivity, as well as increased bacterial density. Heat-killed bacteria induced action potentials in selected neurons, and heat-killed *S. aureus* and *Streptococcus pneumoniae* each elicited hyperalgesia in the mouse footpad. Bacterial N-formylated peptides induced mechanical but not heat hyperalgesia upon injection, while α-hemolysin, a *S. aureus* virulence factor, activated nociceptors, probably as the result of membrane pore formation, and was sufficient to induce mechanical, heat, and cold hypersensitivity. Further experiments found that activated nociceptors release neuropeptides that downregulate the local inflammatory response and allow increased bacterial proliferation.

In summary, these experiments demonstrate that pain associated with this murine model of bacterial infection is caused not by the inflammatory response, but rather is a direct effect of products secreted by *S. aureus*. N-formyl peptides directly activate nociceptors, whereas α-hemolysin activates neuronal elements by forming membrane pores and allowing ion flux. The activated sensory neurons in turn release neuropeptides that reduce the influx of neutrophils and monocytes and also suppress the migration of T and B cells to draining lymph nodes. Thus, it appears that *S. aureus* itself is the cause of the pain of local soft-tissue infections and that it has developed a mechanism by which it simultaneously reduces the inflammatory response to the infection, allowing it to flourish.

Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved 2013. DOI: 10.1093/cid/cit623