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## Major article

# Retrospective cohort study of inappropriate piperacillin-tazobactam use for lower respiratory tract and skin and soft tissue infections: Opportunities for antimicrobial stewardship



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## Key Words:

Antimicrobial stewardship  
Antimicrobial use

**Background:** Patients with skin and skin structure infections (SSTIs) and lower respiratory tract infections (LRTIs) are frequently prescribed piperacillin-tazobactam (TZP) on hospital admission. Inappropriate broad-spectrum coverage may be associated with patient harm, excess expenditure, and escalating rates of antimicrobial resistance.

**Methods:** Patients who received empirical TZP for a diagnosis of LRTI or SSTI from January 1–June 30, 2012, were identified retrospectively. Clinical and antimicrobial data were systematically collected from electronic hospital information systems. Using published guidelines, microbiologic results, and individual clinical responses, the appropriateness of TZP use was assessed. Drug utilization after potential standard audit of therapy on day 3 was also evaluated.

**Results:** We reviewed 60 patients with SSTI and 169 patients with LRTI. Inappropriate empirical TZP therapy was found in 41.7% in those with SSTI, and a further 15% had inappropriate continuation of therapy. In LRTI patients, 38.3% received inappropriate empirical TZP, and 10.3% of the treatment courses were continued inappropriately. Community-acquired pneumonia was the most frequent diagnosis where TZP was used inappropriately (96%). A day 3 audit of therapy may have saved 256 days of TZP.

**Conclusion:** In our institution, inappropriate empirical TZP is common for community-onset infections of mild to moderate severity. A prospective audit and feedback program may be a strategy to reduce inappropriate use of TZP as empirical therapy.

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Empirical initiation of broad-spectrum antimicrobial therapy on hospital admission for signs and symptoms indicative of potential infection is common in current medical practice, and prompt antimicrobial therapy reduces mortality in septic shock.<sup>1</sup> However, most antibiotic use occurs in community-onset infections of mild to moderate severity (eg, skin and soft tissue or respiratory tract infections), and it is estimated that up to 50% of prescribed courses of antimicrobials may ultimately be unnecessary.<sup>2</sup> Inappropriate broad-spectrum coverage and the use of extended durations of antimicrobial therapy are associated with adverse events, high

costs, and escalating rates of antibiotic-resistant bacteria,<sup>3</sup> hampering the efforts of infection prevention and control programs to limit the proliferation of multidrug-resistant organisms.

Broad-spectrum agents, such as piperacillin-tazobactam (TZP), are commonly used for empirical coverage in the setting of suspected early sepsis. TZP has demonstrated efficacy in the setting of many bacterial infections. However, it is not recommended as empirical therapy in community-associated lower respiratory tract infections (LRTIs) because the spectrum of activity is excessive for the most common pathogens (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*), and it does not have activity against atypical pathogens (eg, *Mycoplasma pneumoniae*).<sup>4</sup> Similarly, its use in skin and skin structure infections (SSTIs) in patients without risk factors (eg, deep tissue infection, severe illness, bite injuries, diabetic foot ulcer) is inappropriate because its broader activity against

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gram-negative and particularly anaerobic pathogens is generally not required in this setting.<sup>2,5</sup>

Inappropriate TZP prescription also includes failure to alter therapy based on clinical improvement or laboratory results. We sought to determine the proportion of patients presenting with LRTI or SSTI treated inappropriately with TZP and to evaluate the potential for an antimicrobial stewardship audit with feedback on day 3 of therapy to ameliorate inappropriate TZP use for these indications.

## METHODS

### Study setting and type

This retrospective cohort study was conducted at St. Paul's Hospital, a large university-affiliated tertiary care institution, and Mount St. Joseph Hospital, a community hospital in Vancouver, Canada, with a combined total of 534 acute care beds. Both hospitals are administered by Providence Health Care and share common laboratories and electronic information systems.

### Study design

A retrospective chart and electronic record review of all adult patients >18 years old who were admitted from St. Paul's Hospital or Mount St. Joseph Hospital Emergency Department between January 1 and June 30, 2012 was conducted. Patients who received TZP as empirical therapy within 24 hours of arrival were considered for inclusion. Of these patients, only those with a documented diagnosis of LRTI or SSTI were selected for data extraction from the medical record. Patients who had received oral or intravenous antibiotic therapy within a week prior to admission were excluded to prevent inclusion of patients who had failed first-line antimicrobial therapies and may therefore require broad-spectrum treatment. Patients with a competing indication for long-term antibiotic therapy, such as concomitant infection (eg, osteomyelitis) or suppurative lung disease (eg, cystic fibrosis), were also excluded. For patients with multiple admissions over this time period, only the first episode was included. This study was approved by the University of British Columbia–Providence Health Care Research Ethics Board.

### Definitions

Diagnosis of SSTI on admission required documentation of clinical findings indicating warmth, erythema, and induration of skin and subcutaneous tissue, with or without pain.<sup>6</sup> SSTIs were classified into 3 mutually exclusive groups: (1) cellulitis, (2) cutaneous abscess, or (3) SSTI with additional complicating factors (either cellulitis or abscess with deep tissue infection, bacteremia, intensive care unit admission, diabetic ulcer, peripheral arterial disease, human or animal bite, or severe infection necessitating surgical debridement).<sup>7</sup>

Presence of LRTI required documentation of clinical or radiographic findings of an LRTI. Because of the limited sensitivity of chest radiograph for LRTI diagnosis, a subset of patients without confirmatory radiography were included as suspected cases based on clinical grounds. Patients with LRTI were divided into community-acquired pneumonia (CAP) following standard definitions<sup>4</sup> and health care-associated pneumonia (HCAP) (defined as patients hospitalized in an acute care hospital for ≥2 days within 90 days of the infection; nursing home or long-term care facility residents; those with chemotherapy or wound care within 30 days of the current infection; or receipt of hemodialysis).<sup>4</sup>

Prescription of TZP as empirical therapy was deemed appropriate when it was adherent to published guidelines for CAP, HCAP, and SSTI.<sup>4,5,8</sup> Empirical TZP for patients requiring intensive care admission for severe illness was also classified as appropriate. Prescription of TZP was deemed inappropriate when it was discordant from applicable guideline recommendations for empirical therapy. De-escalation of therapy was considered appropriate if patients were documented as having clinical improvement (eg, 2 consecutive days with temperature ≤37.8°C, hemodynamic stability, tolerating oral medications, normal mental status). A switch to oral agents commonly prescribed for pneumonia (eg, amoxicillin-clavulanate, moxifloxacin) or for skin and soft tissue infection (eg, cephalexin) was considered appropriate in the absence of culture information. Discontinuing TZP and initiation of narrower-spectrum antimicrobial therapy was also considered appropriate when supported by clinically relevant microbiologic culture results. The continuation of TZP despite clear clinical improvement, or after microbiologic testing confirming a causative pathogen was finalized, was considered inappropriate.

### Data sources and data collection

Patients who received TZP within 24 hours of admission were identified using the pharmacy database. A single researcher (T.C.H.) reviewed the admission and discharge diagnoses for patients to select eligible patients for detailed review of the chart and electronic record. Patient demographics, all recorded comorbidities, clinical history of presentation, all available microbiologic results, radiographic findings, and details of antimicrobial therapy (agent, dose, and route) over the course of the admission were recorded.

The number of days of inappropriate TZP therapy that could be averted by antimicrobial stewardship program intervention was estimated by a retrospective audit of therapy beginning on day 3 of admission for each patient. At day 3, therapy was classified as appropriate or inappropriate by the previously defined criteria. If therapy was defined as appropriate, opportunities for de-escalation were assessed on each subsequent day of hospital admission based on clinical improvement or microbiologic results. This retrospective audit assumed a hypothetical 85% uptake of suggestions for narrowing of therapy during each patient's course in hospital.

The primary outcomes included the following: (1) proportion of patients who received inappropriate empirical and continued TZP for each admitting syndrome, and (2) total number of inappropriate days of TZP.

## RESULTS

Patient identification and selection of eligible patients are shown in Fig 1. Overall, there were 169 eligible patients identified to have received TZP for LRTI and 60 patients who received it for SSTI.

### SSTIs

A total of 60 eligible admitted patients with SSTI were prescribed TZP. The demographics and clinical characteristics of these groups are displayed in Table 1.

Microbiologic data were available for 42 (93.3%) patients with either abscess or a complicated infection. Eighteen patients had a single organism, and 24 had multiple organisms on culture. The most common pathogens were methicillin-susceptible *Staphylococcus aureus* (n = 12), streptococci (n = 12), methicillin-resistant *St. aureus* (n = 10), and coagulase-negative staphylococci (n = 7). Gram-negative pathogens were isolated in patients with complicated SSTI, but only 3 patients with either abscess or a complicated

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