

# Early Treatment Is Key for Neuropathic Pain

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VANCOUVER, B.C. — The best approach to managing neuropathic pain is to treat it early, when it is most likely to respond, according to Dr. Rob Hewko, a psychiatrist at Vancouver (B.C.) General Hospital.

“Neuropathic pain is common and extremely incapacitating,” said Dr. Hewko

at the annual Canadian Hospitalist Conference. About 5%-10% of people will develop the condition in their lifetime.

And although this type of pain is classically associated with postherpetic neuralgia and diabetic neuropathy, it can arise from a diverse group of other illnesses and events, such as gallbladder and cardiac surgery, lupus, and chemotherapy.

Neuropathic pain has a complex pathogenesis that involves several mechanisms,

he said at the conference, which was sponsored by the University of British Columbia. These include sensitization of peripheral nerves, activation of the dorsal horn nuclei in the spinal cord, and changes in descending inhibition from the brain.

Diagnosis can be challenging, for a variety of reasons: the diverse symptomatology, the numerous etiologies, patients' difficulty in articulating their symptoms, and the variable response to treatment.

A number of tools are available to help with diagnosis and assessment. “I would suggest that you choose one of these and use it exclusively, unless you have unlimited time,” Dr. Hewko advised. In cases in which the diagnosis is uncertain, he recommended the DN4 pain questionnaire (Pain 2005;114:29-36), which can be completed in about 10 minutes.

The best management of chronic neuropathic pain is effective management of acute neuropathic pain, Dr. Hewko said.

Most patients with acute neuropathic pain “will get better over time, so that's your backup position—do nothing and hope they get better,” he said. “But there's a downside to that, which is the longer you wait, the less likely they are to respond to treatment.”



**‘The longer you wait, the less likely [patients with neuropathic pain] are to respond to treatment.’**

DR. HEWKO

Medication strategies can exploit the nature of neuropathic pain, by using agents with differing actions to target the different mechanisms and to potentiate each other. First-line agents include two of the tricyclic antidepressants (nortriptyline and desipramine), gabapentin, and pregabalin.

Opioids should not be used as first-line agents because patients rapidly develop tolerance to them in this setting, according to Dr. Hewko. And amitriptyline should not be used at all because of its many adverse effects.

National pain societies generally recommend a single-agent approach to the initial pharmacotherapy for neuropathic pain. However, he noted, “the likelihood of an excellent response to a single agent is really low in my experience.”

He therefore recommended combining two first-line agents—a tricyclic antidepressant plus either gabapentin or pregabalin—as initial therapy. The drugs should be started at low dosages and titrated every 24-48 hours.

This approach has the advantage of producing rapid relief. Fully 90%-95% of patients with acute neuropathic pain have a response within several days.

Third-line agents, such as opioids, cannabinoids, and topiramate, should be selected with consideration of the mechanism they target so that they complement other agents being used.

Among the opioids, which are more effective against peripheral than against central neuropathic pain, “methadone is the best option because it is the only narcotic that has an [N-methyl-D-aspartate] antagonistic effect,” he observed.

Measures such as cognitive-behavioral therapy and spinal cord stimulation can be useful when pain persists despite medical therapy.

Dr. Hewko is a member of a medical advisory board for Pfizer Canada. ■

## BRIEF SUMMARY

Please see package insert for full prescribing information.

## Azactam® aztreonam IV/IM 1g/2g

**INDICATIONS AND USAGE:** To reduce the development of drug-resistant bacteria and maintain the effectiveness of AZACTAM® (aztreonam for injection, USP) and other antibacterial drugs, AZACTAM should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms:

**Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Citrobacter species*\* and *Serratia marcescens*.\*

**Lower Respiratory Tract Infections**, including pneumonia and bronchitis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Proteus mirabilis*, *Enterobacter species* and *Serratia marcescens*.\*

**Septicemia** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*\* and *Enterobacter species*.

**Skin and Skin-Structure Infections**, including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter species*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Citrobacter species*.\*

**Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter species* including *E. cloacae*\*, *Pseudomonas aeruginosa*, *Citrobacter species*\* including *C. freundii*\* and *Serratia species*\* including *S. marcescens*.\*

**Gynecologic Infections**, including endometritis and pelvic cellulitis caused by *Escherichia coli*, *Klebsiella pneumoniae*\*, *Enterobacter species*\* including *E. cloacae*\* and *Proteus mirabilis*.\*

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

**Concurrent Therapy:** Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected as etiologic agents, therapy should be initiated using an anti-anaerobic agent concurrently with AZACTAM (see **DOSE AND ADMINISTRATION**). Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing of the causative organism(s), appropriate antibiotic therapy should be continued.

**CONTRAINDICATIONS:** This preparation is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

**WARNINGS:** Both animal and human data suggest that AZACTAM is rarely cross-reactive with other beta-lactam antibiotics and weakly immunogenic. Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure. (See **CONTRAINDICATIONS**.)

Careful inquiry should be made to determine whether the patient has any history of hypersensitivity reactions to any allergens.

While cross-reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams (e.g., penicillins, cephalosporins, and/or carbapenems). Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure to aztreonam. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures. (See **ADVERSE REACTIONS**.)

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AZACTAM and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Rare cases of toxic epidermal necrolysis have been reported in association with aztreonam in patients undergoing bone marrow transplant with multiple risk factors including sepsis, radiation therapy and other concomitantly administered drugs associated with toxic epidermal necrolysis.

**PRECAUTIONS: General:** In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms (*Staphylococcus aureus* and *Streptococcus faecalis*) and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies in animals have not been performed.

Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

**Pregnancy: Pregnancy Category B:** Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Aztreonam is excreted in human milk in concentrations that are less than 1 percent of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

**Pediatric Use:** The safety and effectiveness of intravenous AZACTAM (aztreonam for injection, USP) have been established in the age groups 9 months to 16 years. Use of AZACTAM in these age groups is supported by evidence from adequate and well-controlled studies of AZACTAM in adults with additional efficacy, safety, and pharmacokinetic data from non-comparative clinical studies in pediatric patients. Sufficient data are not available for pediatric patients under 9 months of age or for the following treatment indications/pathogens: septicemia and skin and skin-structure infections (where the skin infection is believed or known to be due to *H. influenzae* type b). In pediatric patients with cystic fibrosis, higher doses of AZACTAM may be warranted. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES**.)

**Geriatric Use:** Clinical studies of AZACTAM did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients.<sup>19</sup> In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments made accordingly (see **DOSE AND ADMINISTRATION: Renal Impairment in Adult Patients and Dosage in the Elderly**).

**ADVERSE REACTIONS:** Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9 percent and 2.4 percent, respectively.

Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3 percent include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1 percent are listed within each body system in order of decreasing severity:

**Hypersensitivity**—anaphylaxis, angioedema, bronchospasm  
**Hematologic**—pancytopenia, neutropenia, thrombocytopenia, anemia, eosinophilia, leukocytosis, thrombocytosis

**Gastrointestinal**—abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

**Dermatologic**—toxic epidermal necrolysis (see **WARNINGS**), purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis

**Cardiovascular**—hypotension, transient ECG changes (ventricular bigeminy and PVC), flushing

**Respiratory**—wheezing, dyspnea, chest pain

**Hepatobiliary**—hepatitis, jaundice

**Nervous System**—seizure, confusion, vertigo, paresthesia, insomnia, dizziness

**Musculoskeletal**—muscular aches

**Special Senses**—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, halitosis

**Other**—vaginal candidiasis, vaginitis, breast tenderness

**Body as a Whole**—weakness, headache, fever, malaise

**Pediatric Adverse Reactions:** Of the 612 pediatric patients who were treated with AZACTAM in clinical trials, less than 1% required discontinuation of therapy due to adverse events. The following systemic adverse events, regardless of drug relationship, occurred in at least 1% of treated patients in domestic clinical trials: rash (4.3%), diarrhea (1.4%), and fever (1.0%). These adverse events were comparable to those observed in adult clinical trials.

In 343 pediatric patients receiving intravenous therapy, the following local reactions were noted: pain (12%), erythema (2.9%), induration (0.9%), and phlebitis (2.1%). In the US patient population, pain occurred in 1.5% of patients, while each of the remaining three local reactions had an incidence of 0.5%.

The following laboratory adverse events, regardless of drug relationship, occurred in at least 1% of treated patients: increased eosinophils (6.3%), increased platelets (3.6%), neutropenia (3.2%), increased AST (3.8%), increased ALT (6.5%), and increased serum creatinine (5.8%).

In US pediatric clinical trials, neutropenia (absolute neutrophil count less than 1000/mm<sup>3</sup>) occurred in 11.3% of patients (8/71) younger than 2 years receiving 30 mg/kg q6h. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15-20% of patients aged 2 years or above receiving 50 mg/kg q6h. The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of AZACTAM administered.

**Adverse Laboratory Changes:** Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

**Hepatic**—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1 percent of recipients (see above).

**Hematologic**—increases in prothrombin and partial thromboplastin times, positive Coombs' test.

**Renal**—increases in serum creatinine.

**OVERDOSAGE:** If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

\*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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Manufactured by  
Bristol-Myers Squibb Company  
Princeton, NJ 08543 U.S.A.

Printed in USA  
E1-8001A-10-00

Revised June 2008  
AZL001B00-B/J4-671A

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