

## LEADERS: DR. MARK V. WILLIAMS

## Helping Hospitalist Medicine Find Its Voice

As the first editor-in-chief of the Journal of Hospital Medicine, Dr. Mark V. Williams has played a key role in documenting the history of this new field.

In that role, he has watched hospital medicine grow and mature. The peer-reviewed journal, launched in January 2006, was once home to articles aimed at proving the value of adding hospitalists to an institution's roster. But now most articles focus on how to optimize care within the hospitalist model and how to more efficiently manage the hospital itself.



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DR. WILLIAMS

"We have actually rejected articles in the recent past that were descriptions of the implementation of a hospitalist program," he said. "That's already been done."

Dr. Williams, chief of the division of hospital medicine at the Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital in Chicago, is a former president of the Society of Hospital Medicine. In 1998, he established the first hospitalist program at a public hospital at Grady Memorial Hospital in Atlanta.

Despite his credentials, Dr. Williams said he was a little anxious about accepting the editor-in-chief job in 2005, not knowing what to expect. But his training in evidence-based medicine and the team of editors assembled by the Society of Hospital Medicine have made the job a lot of fun, he said.

The job has not been without challenges, he said, but not always the ones he anticipated. Dr. Williams said he was expecting to have trouble finding high-quality research articles to fill all the pages of a newly launched journal in a new field. It turned out that his biggest challenge has been sorting through the large volume of submissions and having to reject interesting articles. He and the rest of the staff have tried to address this by publishing more articles online, and in the future they hope to expand the number of issues and the number of pages.

The number of submissions shows that hospital medicine is maturing as a field, he said. "There has never been a journal focused on care delivery in the hospital, and yet this is where one-third of federal health care funding is expended."

The volume of high-quality research being conducted by hospitalists is likely to grow, Dr. Williams said, as academic institutions begin establishing divisions of hospital medicine and devoting research dollars to this area. For example, the Feinberg School of Medicine has just hired four hospitalists who will devote

most of their time to research on hospital medicine. And many other physicians at the institution are involved in smaller research projects.

"It's this investment in hospital medicine research that's going to grow the entire field long term, demonstrating the importance of hospitalists in improving care delivery and quality improvement at hospitals," Dr. Williams said.

As for the journal, he sees his next big task as helping to prepare to hand over the reins to the next editor. He also hopes to see the journal become a monthly publication sometime in the next 2 years. But he's pleased with the progress so far. For instance, the journal was listed in Medline, the National Library of Medicine's bibliographic medical database, in its first year. And a recent

measurement of the journal's most recent "impact factor" (how often it's cited by other journals) showed that it is gaining credibility within the research community.

"I've been surprised that we've achieved everything that we set out to do so fast," Dr. Williams said. ■

By Mary Ellen Schneider

**BRIEF SUMMARY**  
Please see Galaxy® plastic container (PL 2040) package insert for full prescribing information.

**Azactam®**  
aztreonam injection

**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* species including *K. 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 **DOSAGE 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 reported clinical experience has not identified differences in responses between the elderly and younger patients.<sup>1,10</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 **DOSAGE 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.

**Thawing of Plastic Containers: DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION**

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

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