Burn Center Monograph: 
*Acinetobacter baumannii* Infections

Developed in collaboration with:

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For US healthcare professionals.
Burn wounds are particularly at risk for bacterial infection or colonization because of breakdown of the skin barrier. Current literature and clinical data from global burn centers indicate that *A. baumannii* has become the most rapidly emerging organism isolated from burn patients.

In recent years, the global hospitalized burn population has developed *A. baumannii* isolates with expanded antimicrobial resistance to commonly used anti-infective agents, including the carbapenems.

One of the older agents for the treatment of *A. baumannii* is minocycline, a tetracycline antibiotic initially introduced in the late 1960s. It is one of only 6 antimicrobial agents with FDA approval for the treatment of *Acinetobacter* infections.

In conclusion, *Acinetobacter baumannii* is a common organism cultured from many burn wound specimens. Minocycline has demonstrated efficacy in treatment of infections due to *A. baumannii*. Strict infection control measures including appropriate antibiotic use may prevent the spread of infection throughout burn units.

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Burns are a major cause of morbidity and mortality worldwide. Each year, approximately 40,000 adult patients with severe burns require hospitalization in the United States, about 4,000 of whom die of their injuries. Burns are among the most severe traumas an individual patient can sustain, as they cause anatomical, physiological, endocrinological, and immunological stress, especially when more than 20% of the skin surface is burned.

Infectious complications

Because of the severity of the injury, burn patients are at a high risk for the development of infectious complications. Infection remains the main cause of mortality among severe burn victims. After the initial resuscitation period, 75% of deaths are attributable to infectious diseases. Burn wounds are particularly at risk for bacterial infection or colonization because of breakdown of the skin barrier. Prolonged hospital stays, multiple surgical interventions and invasive procedures, as well as complex comorbidities also contribute to increased mortality.

The environment in burn units often becomes contaminated with antibiotic-resistant microorganisms, and because of disruption of skin barriers, these bacteria can colonize the burned patient and lead to hospital-acquired infections. Therefore, the control and prevention of nosocomial infections is a significant problem in this patient group. The causative agents isolated from burn patients vary by region and hospital.

Emerging multidrug-resistant bacteria (MDRB) are particularly problematic. MDRB limit therapeutic options and delay the implementation of appropriate antibiotic therapy, leading to increased morbidity and mortality, length of hospital stay, and healthcare costs. The development and use of broad-spectrum antibiotics have contributed to the emergence of invasive burn wound infections with gram-negative microorganisms.

Emerging Acinetobacter

Prior to 2004, infectious agents reported from burn wound infections were Pseudomonas spp and Staphylococcus spp. In recent years, nosocomial infections caused by A. baumannii have increased significantly. Based on current literature and clinical data from burn centers globally, A. baumannii has become the most rapidly emerging organism isolated from burn patients. One multi-year (2008-2012) study of a burn unit found Acinetobacter infections were consistently one of the most common pathogens along with Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus (MRSA).

Burn patients with Acinetobacter infections have an all cause mortality rate greater than 50%.

Most Common Organisms Cultured from Patient Specimens at the Chris Hani Baragwanath Academic Hospital Adult Burns Unit, Gauteng Province, South Africa

- **Acinetobacter baumannii**
- **Pseudomonas aeruginosa**
- **Methicillin-resistant Staphylococcus aureus**

A 5-year (2008-2012) study in the Adult Burns intensive care unit at this hospital was reported. Patients (n=341) admitted with mean severity of TBSA 30% were evaluated. Blood cultures were sampled using the unilateral double bottle principle. Culture-positive bacteremia was found in 52% of patients.

Despite new advances in burn care, A. baumannii continues to be a serious problem worldwide. In burn patients, this bacterium usually causes hospital-acquired pneumonia and other complicated infections, such as wound infections, bacteremia, and osteomyelitis. Colonization with Acinetobacter may result in delayed wound healing, graft losses, sepsis, and death.

A. baumannii is capable of surviving on surfaces for extended periods of time, including several months on dry surfaces, and can colonize throughout entire burn intensive care units.
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The Centers for Disease Control and Prevention recently rated the threat due to MDR Acinetobacter as "serious," but not urgent. However, without ongoing public health monitoring and prevention activities, the "serious" threats will most likely worsen.29

A few case-control studies in burn and non-burn populations have identified risk factors associated with the acquisition of A. baumannii—some of which are listed below:20,30,31

A large-scale prospective study associating risk factors for nosocomial burn wound infection caused by MDRB was performed by Tekin, et al. The study demonstrated that certain risk factors were associated with multidrug resistant A. baumannii infections. These included elevated APACHE II scores, first excision time of wound, admission day to the hospital, and prior usage of broad-spectrum antibiotics in the burn intensive care patient. Furthermore, the study revealed that admission of patients to a burn center and the specialist care provided there had a significant role in the management of burn infections. It contributed to early diagnosis and identification of the causative agent, appropriate antimicrobial treatments and early wound closure, fastidious wound care, and surgical debridement.18

Multidrug resistance

In recent years, the global hospitalized burn population has developed A. baumannii isolates with expanded antimicrobial resistance to commonly used anti-infective agents, including the carbapenems.3 Several factors are responsible for the emergence of multidrug resistance in A. baumannii, including the acquisition of class D carbapenem-hydrolyzing oxacillinas and/or class B metallo-β-lactamases, decreased membrane permeability because of loss of porins, and multidrug efflux pumps.32

Therapeutic options

Due to the current lack of therapeutic options, burn care specialists and other healthcare practitioners are utilizing older antibiotics for the treatment of MDRB. One such agent is minocycline for injection, a tetracycline antibiotic initially introduced in the late 1960s and marketed under the brand name MINOCIN®.5,6,32 Mechanistically, minocycline binds to bacterial ribosomes, preventing aminoacyl-tRNA association leading to inhibition of bacterial protein synthesis and ultimately bacterial cell death.33 Minocycline is one of only 6 antimicrobial agents* with FDA approval for the treatment of Acinetobacter infections.5,6

Minocycline structure

In a 2007-2011 surveillance study of gram-negative isolates, 79% of the Acinetobacter isolates were susceptible to minocycline.34 In another study, the activity of several antibacterial agents was tested against 3 species of gram-negative bacteria obtained from a global surveillance program in 2013. Among 1,312 A. baumannii isolates, 72% were susceptible to minocycline.35

*Amikacin, ampicillin/sulbactam, doripenem, imipenem, doxycycline, and minocycline

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MINOCIN® (minocycline) for Injection

Indication
MINOCIN® (minocycline) for Injection is indicated for the treatment of infections due to susceptible isolates of designated microorganisms, including Acinetobacter species bacteria. For the full list of indications and designated susceptible pathogens, please see the full prescribing information available at www.minociniv.com.

IMPORTANT SAFETY INFORMATION

Contraindications
MINOCIN® (minocycline) for Injection is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or to any of the components of the product formulation.

Warnings

Tooth Development
MINOCIN®, like other tetracycline-class antibacterials, can cause fetal harm when administered to a pregnant woman. If any tetracycline is used during pregnancy, or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

Skeletal Development
All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

Dermatologic Reaction
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

Susceptibility of Acinetobacter isolates to various antibacterial agents:

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†Imipenem and meropenem
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MDR: resistant to 3 or more classes of antimicrobial agent (ß-lactams, aminoglycosides, carbapenems or fluoroquinolones)

In conclusion, infection is the most common and serious complication of a burn injury, and sepsis and septic shock account for more than 50% of deaths in burn patients despite improvements in antimicrobial therapies. The burn wound is an ideal environment for bacterial growth and infection. Acinetobacter baumannii is a common organism cultured in burn wound specimens. Strict infection control measures should be undertaken to prevent the spread of infection in burn units. Ongoing collaboration with the burn unit staff, infection preventionists, antimicrobial stewardship team members, and microbiologists is imperative to combat this ongoing serious threat to the worldwide burn population.

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Reported clinical success rates from recent case studies for minocycline for injection used in combination with other antibiotics in the treatment of Acinetobacter infections were 62.3% (n=48/77), 71% (n=5/7), and 73% (n=40/55). In conclusion, infection is the most common and serious complication of a burn injury, and sepsis and septic shock account for more than 50% of deaths in burn patients despite improvements in antimicrobial therapies. In the burn wound is an ideal environment for bacterial growth and infection. Acinetobacter baumannii is a common organism cultured in burn wound specimens. Strict infection control measures should be undertaken to prevent the spread of infection in burn units. Ongoing collaboration with the burn unit staff, infection preventionists, antimicrobial stewardship team members, and microbiologists is imperative to combat this ongoing serious threat to the worldwide burn population.

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In spite of in vitro data favoring the use of minocycline against MDR Acinetobacter infections, no randomized, controlled clinical trials of minocycline for injection are available to guide burn healthcare professionals in the selection of the best available therapy. To date, clinical information regarding the effectiveness of minocycline for injection is limited to a number of small, retrospective, uncontrolled case series. Reported clinical success rates from recent case studies for minocycline for injection used in combination with other antibiotics in the treatment of Acinetobacter infections were 62.3% (n=48/77), 71% (n=5/7), and 73% (n=40/55). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

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IMPORTANT SAFETY INFORMATION (continued)

Anti-anabolic Action
The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. Under such conditions, monitoring of creatinine and BUN is recommended, and the total daily dosage should not exceed 200 mg in 24 hours. If renal impairment exists, even usual oral or parenteral doses may lead to systemic accumulation of the drug and possible liver toxicity.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported with minocycline.

Central Nervous System Effects
Central nervous system side effects including light-headedness, dizziness or vertigo have been reported. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

Clostridium difficile Associated Diarrhea
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MINOCIN®, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued.

Intracranial Hypertension
Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including MINOCIN®. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and MINOCIN® should be avoided because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

PRECAUTIONS
As with other antibacterial preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

Hepatotoxicity has been reported with minocycline; therefore, minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic antibacterial therapy when indicated.

MINOCIN® (minocycline) for Injection contains magnesium sulphate heptahydrate. Because magnesium is excreted primarily by the kidney, serum levels of magnesium should be monitored in patients with renal impairment.

Because MINOCIN® (minocycline) for Injection contains magnesium, close monitoring is recommended in patients with heart block or myocardial damage.

Prescribing MINOCIN® (minocycline) for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adverse Reactions
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