



IMPROVED THERAPEUTIC REGIMENS FOR TREATMENT OF POST-TRAUMATIC OCULAR INFECTIONS

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Public Abstract

The U.S. Military and support personnel operate in environments that can quickly become volatile combat zones. Constant threats arise from close physical contact with enemies that use improvised explosive devices, mines, rockets and small arms fire. Armor, helmets, and safety eyewear provide some protection against penetrating trauma from explosive shrapnel. However, the limits of protective gear can often leave the face and eyes of personnel exposed. The unfortunate outcome is that more than 10% of the total number of combat injuries occur to the eyes, often resulting in blindness.

Shrapnel or other explosive projectiles can be contaminated with bacteria that can cause an intraocular infection (endophthalmitis) which results in blindness. Bacillus is a bacterium commonly found in dry soils, such as the deserts of the Middle East. Bacillus is one of the most dangerous bacterial pathogens for the eye. When Bacillus enters the eye following a traumatic event, the bacteria grow rapidly, produce toxins, and cause inflammation that damages cells inside the eye responsible for vision. Bacillus causes the majority of endophthalmitis cases following penetrating injury. In such cases, over half to two thirds of patients lose significant vision or lose the eye itself.

In the clinical setting, antibiotic drops or patches are commonly used to treat endophthalmitis. In severe cases, injection of antibiotics into the eye and surgery may be necessary. Unfortunately, Bacillus intraocular infections often do not respond to these therapies. When proper therapy is given, antibiotics can kill the bacteria and anti-inflammatory drugs may lessen inflammation. However, these drugs are useless against the toxins that Bacillus produces inside the eye. Bacillus can also migrate within the eye during the infection, out of reach of antibiotics injected into the eye. The devastating result is often rapid and irreversible loss of vision in less than two days. The speed at which blindness occurs from Bacillus endophthalmitis highlights the critical need for improvements in therapy.

The goal of this research is to test more rational and effective therapeutic regimens that will prevent vision loss and inflammation during a Bacillus endophthalmitis. Early and proper therapeutic intervention is critical in order to kill Bacillus, arrest the activity of toxins, control bacteria that may migrate to other parts of the eye, and prevent damaging inflammation. We will test a number of therapeutic agents, drug combinations, and regimens to identify the most effective in preserving vision, arresting inflammation, and limiting intraocular damage.

We will analyze the effectiveness of the following conventional therapeutic agents:

- (1) Commonly used antibiotics injected into the eye during infection;
- (2) Combinations of antibiotic and anti-inflammatory drugs injected into the eye during infection; and
- (3) Combinations of therapeutic intraocular surgery and antibiotics injected into the eye during infection.

We will also analyze the effectiveness of the following non-conventional therapeutic agents:

- (1) Combinations of anti-toxin antibody that will block the activity of Bacillus toxins plus antibiotics injected into the eye during infection;
- (2) Combinations of anti-flagellar antibody that will block the migration of Bacillus within the eye plus antibiotics injected into the eye during infection; and
- (3) Combinations of anti-proinflammatory cytokine antibody that will prevent inflammatory cells from entering the eye plus antibiotics during infection.

The effectiveness of these regimens will be analyzed in an experimental rabbit model of Bacillus endophthalmitis, a model that mimicks the human infection in both explosive inflammation and rapid vision loss. Effectiveness is determined by quantifying bacteria, inflammatory cells, and drug levels in the eye, analyzing retinal function, and observing the anatomic condition of the eye following treatment.

We anticipate that early antibiotic therapy will sterilize the eye and prevent vision loss. The addition of anti-inflammatory

drugs may also hinder inflammation, an added benefit. The non-conventional antibody therapies are designed to specifically block Bacillus toxin activity and migration within the eye, two characteristics of the bacterium that antibiotics and anti-inflammatory drugs cannot affect. We predict that anti-toxin antibody will neutralize toxin activity and anti-flagellar antibody will stop the migration of Bacillus in the eye. These effects, in conjunction with sterilization of the eye with antibiotics, may increase the likelihood of a positive therapeutic outcome.

This proposal is designed to identify therapeutic regimens that will prevent vision loss and inflammation following post-traumatic Bacillus endophthalmitis. Our research is highly relevant to the treatment of infections caused by other types of bacteria, since therapeutic agents are effective against several bacteria and non-conventional therapies can be tailored to treat all potential bacterial causes. Identifying effective treatments using drugs already in use will be of immediate clinical relevance. The effectiveness of non-conventional therapeutics is interest because of the development of resistance to conventional antibiotics. Developing effective treatments for endophthalmitis will therefore benefit not only U.S. Military and support personnel at risk on the battlefield, but also civilian populations at risk to traumatic eye injuries during war and in the workplace.

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