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Award Number: W81XWH-07-1-0280

TITLE: Improved Therapeutic Regimens for Treatment of Post-Traumatic Ocular Infections

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REPORT DATE: May 2008

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				<i>Form Approved</i> OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) 01-05-2008		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 15 APR 2007 - 14 APR 2008	
4. TITLE AND SUBTITLE Improved Therapeutic Regimens for Treatment of Post-Traumatic Ocular Infections				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-07-1-0280	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Michelle C. Callegan, Ph.D. E-Mail: michelle-callegan@ouhsc.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Oklahoma Oklahoma City, OK 73190-1046				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Greater than 10% of battlefield injuries occur to the eyes, resulting in significant morbidity. The potential for ocular infection by trauma is high, due to the types of organisms encountered in arid environments and the delay between time of injury and adequate treatment. This proposal was designed to analyze the effectiveness of antibiotics, anti-inflammatory drugs, and non-conventional agents targeting bacterial and host virulence factors, with the goal of improving the outcome of infections that would otherwise result in significant vision loss. The first-year results highlight the need for prompt and aggressive therapy (intravitreal administration) in preventing inflammation and vision loss. Delays in treatment result in vision loss, but may not result in loss of globe architecture. The use of anti-inflammatory agents with antibiotics for intraocular infections has been controversial, and our results add little to clarify whether these drugs are of any benefit during therapy. These studies have provided new information on improvements in treatment regimens that preserve vision and ocular architecture. Further analysis of conventional and non-conventional therapies will identify those that may be implemented for future treatment of blinding bacterial infections of the eye.					
15. SUBJECT TERMS Trauma, eye, infections, therapy, antibiotics, anti-inflammatory drugs					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)
			UU	11	

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Proposal PR064081 Department of Defense CDMRP
Improved Therapeutic Regimens for Treatment of Post-Traumatic Ocular Infections
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YEAR ONE ANNUAL PROGRESS REPORT

INTRODUCTION

Greater than 10% of the total number of battlefield injuries occur to the eyes, resulting in significant morbidity.¹ The potential for ocular infection by penetrating injuries is significant, due to the nature of the organisms encountered in battlefield environments, and the delay between the time of injury and adequate therapeutic intervention. This proposal was designed to analyze the effectiveness of antibiotics, anti-inflammatory drugs, and non-conventional agents that target bacterial and host virulence factors, with the goal of improving the outcome of infections that typically result in significant vision loss. The goal is to sterilize the eye, arrest inflammation, and preserve vision following post-traumatic endophthalmitis.

BODY OF RESEARCH

Statement of Work (Abbreviated). Project tasks (experiments) included 7 experiments encompassing the Aims listed below. All experiments were performed using an experimental rabbit model of *Bacillus cereus* endophthalmitis. In the model, 100 bacilli/0.1 ml are injected into the mid-vitreous of one eye, while the contralateral eye is injected with 0.1 ml PBS (surgical control) or is left undisturbed (absolute control). At designated time points during infection, treatment was administered (intravitreal drug and/or surgery, with proper controls). At designated time points, eyes were electroretinographed (measurement of retinal function) and removed after euthanasia for analysis of myeloperoxidase activity (from inflammatory cells), drug concentrations, bacterial growth, and histology. Specific experiments included: 1) analysis of the efficacy of antibiotics or antibiotic combinations against experimental *Bacillus* endophthalmitis, 2) analysis of the efficacy of antibiotics against *B. cereus* spores in the eye before and after germination, 3) analysis of the efficacy of vitrectomy in conjunction with the most effective antibiotic for treatment of *B. cereus* endophthalmitis, 4) analysis of the efficacy of an anti-inflammatory agent, prednisolone acetate, in conjunction with the most effective antibiotic for *B. cereus* endophthalmitis, 5) analysis of the efficacy of anti-TNF α in conjunction with the most effective antibiotic for *B. cereus* endophthalmitis, 6) analysis of the efficacy of polyclonal antibody generated against *B. cereus* toxins (anti-toxin) in conjunction with the most effective antibiotic for *B. cereus* endophthalmitis, and 7) analysis of the efficacy of polyclonal antibody generated against *B. cereus* flagella (anti-flagella) in conjunction with the most effective antibiotic for *B. cereus* endophthalmitis.

Aim 1: Conventional Therapeutics. We hypothesized that proper antibiotic/anti-inflammatory and surgical intervention is critical for preserving vision during *Bacillus* endophthalmitis.

Aim 1.1 Antibiotics: Intravitreal administration of antibiotics against vegetative and spore forms of *B. cereus* during the early logarithmic bacterial growth stage of endophthalmitis.

Summary: In Wiskur *et al.*², we published that intravitreal administration of antibiotics at 2 h or 4 h postinfection successfully preserved vision following experimental *B. cereus* endophthalmitis. These studies were expanded to analyze the fate of the eye after our latest analysis point of 8 h postinfection.

Experimental Design Summary: Eyes were intravitreally infected with 100 CFU *B. cereus*. 0.1 mL of gatifloxacin (0.3%), vancomycin (1.0%), or a combination of both antibiotics at these concentrations were intravitreally injected at either 2, 4, or 6 h postinfection. Eyes were analyzed at 12, 24, and 36 or 48 h postinfection by bacterial quantitation, electroretinography, inflammatory cell quantitation, and histology (N $\geq$ 5 eyes per group).

Progress To Date: All antibiotic treatments sterilized all eyes, except vancomycin administered at 6 h, as previously described.² Retinal function analysis is summarized in Figure 1. The results demonstrate the importance of early

Figure 1. Retinal function analysis of eyes with *B. cereus* endophthalmitis and treated with intravitreal gatifloxacin (Gat, 0.3%), vancomycin (Vanc, 1.0%), or gatifloxacin + vancomycin at 2, 4, or 6 h postinfection. Values are mean $\pm$ SEM of $N \geq 5$ eyes/group.

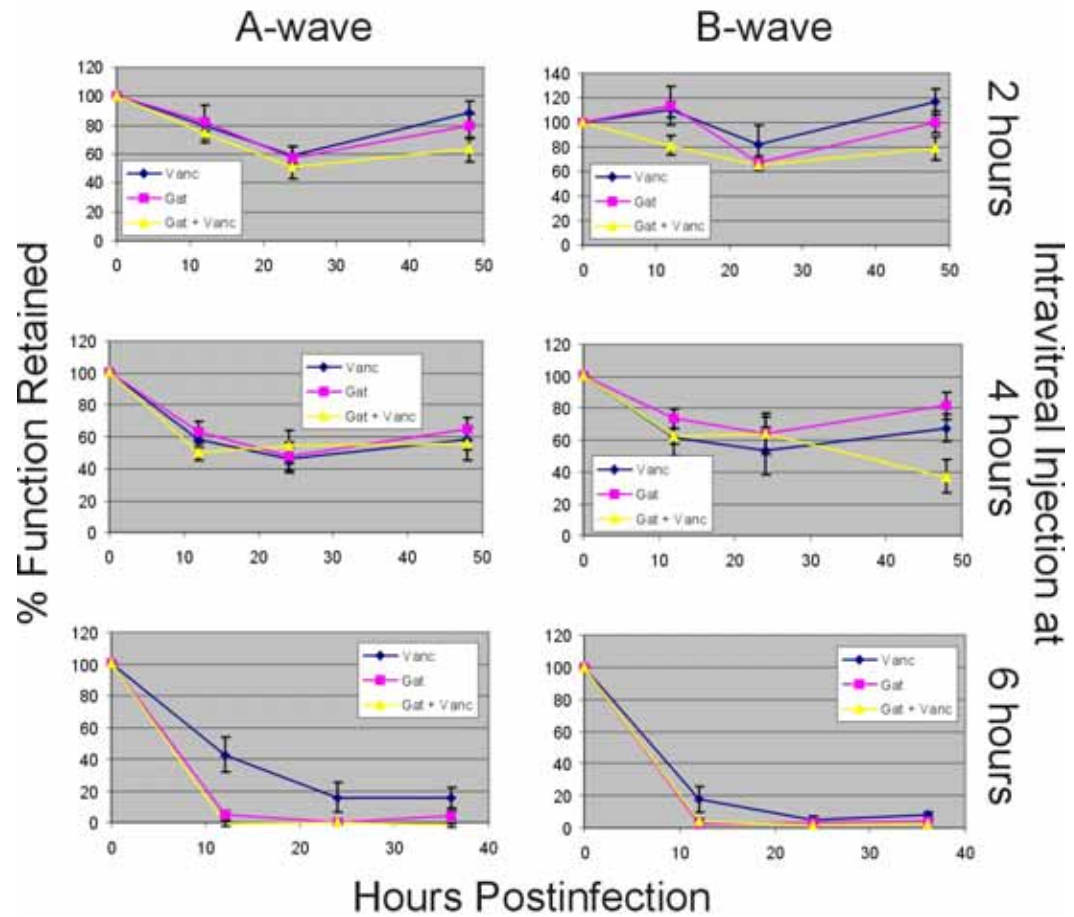
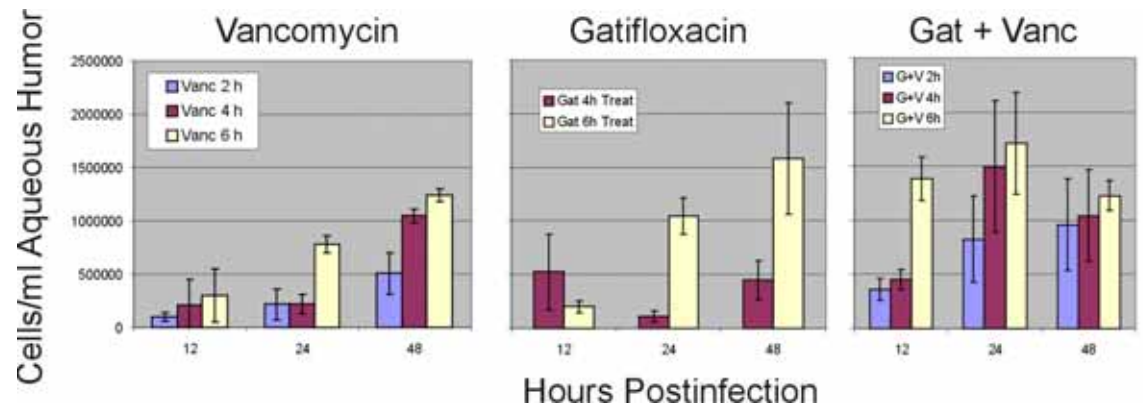


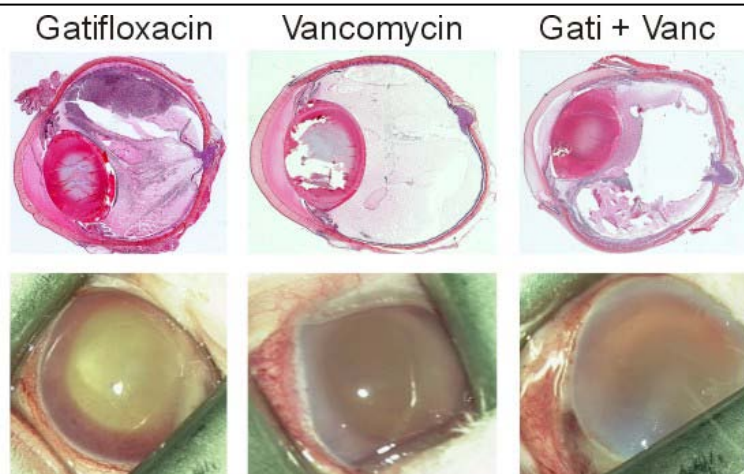
Figure 2. Inflammatory cell influx in eyes with *B. cereus* endophthalmitis and treated with intravitreal antibiotics at 2, 4, or 6 h postinfection. Values are mean $\pm$ SEM of $N \geq 5$ eyes/group.



intravitreal injection of either gatifloxacin or vancomycin (not both, as the retinal function retained was less and inflammation was greater with the combination than either antibiotic alone). In terms of better retinal function outcome, 2 h treatment > 4 h treatment > 6 h treatment, and vancomycin = gatifloxacin > vancomycin + gatifloxacin. Inflammatory cell influx into infected eyes is presented in Figure 2. In terms of least inflammation after treatment, 2 h treatment > 4 h treatment > 6 h treatment, and vancomycin > gatifloxacin > vancomycin + gatifloxacin. In approximately 45% of cases of severe *B. cereus* endophthalmitis, the eye must be removed.^{3,4} Ocular architecture remained intact following 6 h treatment with either antibiotic (Figure 3), indicating that treatment delays of 6 h may not salvage useful vision, but globe architecture may be retained.

Data Not Shown: Bacterial counts (results discussed in *Progress to Date*) and histology sections and photographs of eyes from each treatment group at all endpoints.

Figure 3. Histology and photographs of eyes with *B. cereus* endophthalmitis and treated with intravitreal antibiotics at 6 h postinfection. Eyes were photographed and harvested at 36 h postinfection. Eyes treated with gatifloxacin or combination were full inflamed and retinas were significantly damaged, but globes remained intact. Eyes treated with vancomycin alone had less inflammation, less retinal damage, and globes remained intact. Data are representative of N=3 eyes per group.



Treatment at 6 h, Harvest at 36 h

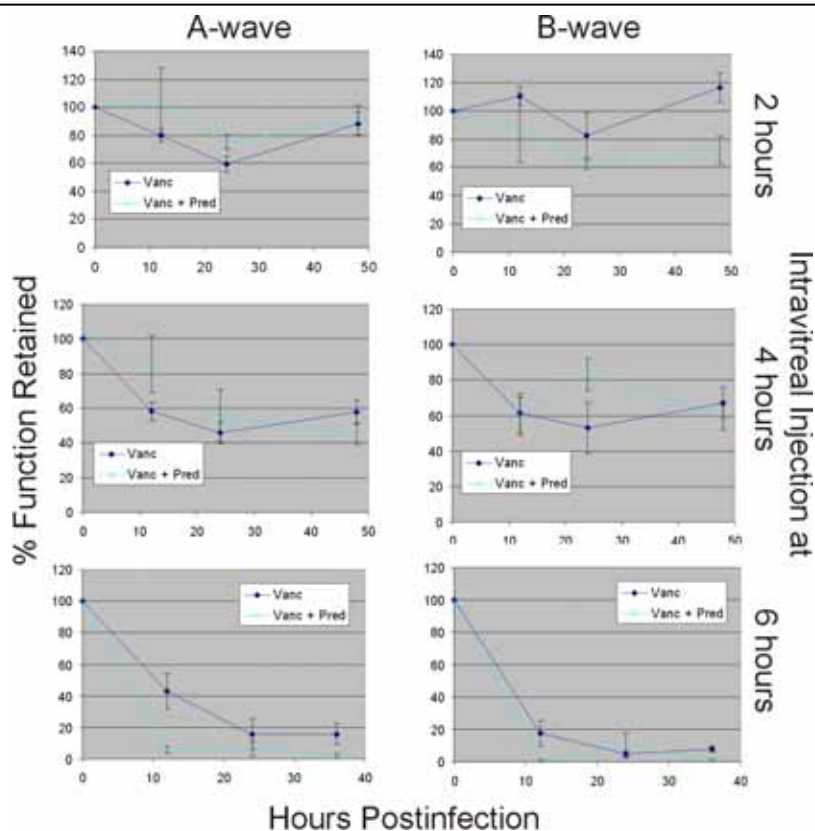
Experiments Remaining: 1) Analysis of antibiotic concentrations in eyes from the experiments described above. 2) Analysis of treatment of infection initiated by spore forms of *B. cereus*.

Relevance: These results reiterate that early intravitreal treatment of posterior segment bacterial infections is critical for salvaging not only vision, but also the architecture of the globe itself. In the battlefield where treatment delays are expected, intravitreal administration of antibiotics following post-traumatic ocular injury may pre-empt infection and improve visual outcome.

Aim 1.2 Antibiotics Plus Anti-Inflammatory Agents: Intravitreal administration of antibiotics plus anti-inflammatory agents against *B. cereus* during the early logarithmic bacterial growth stage of endophthalmitis.

Summary: In Wiskur *et al.*², we reported that intravitreal administration of dexamethasone (1.0%) with gatifloxacin

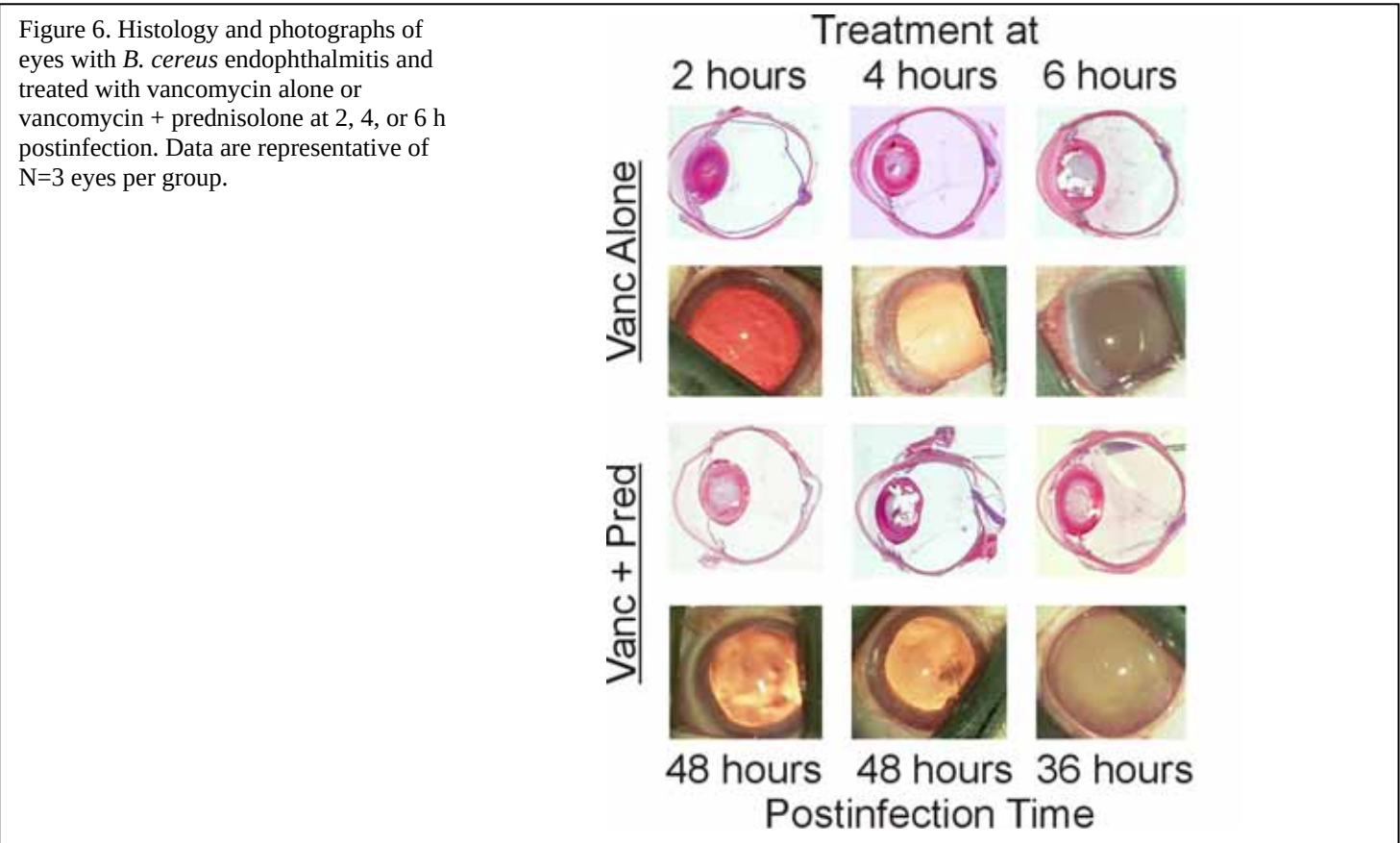
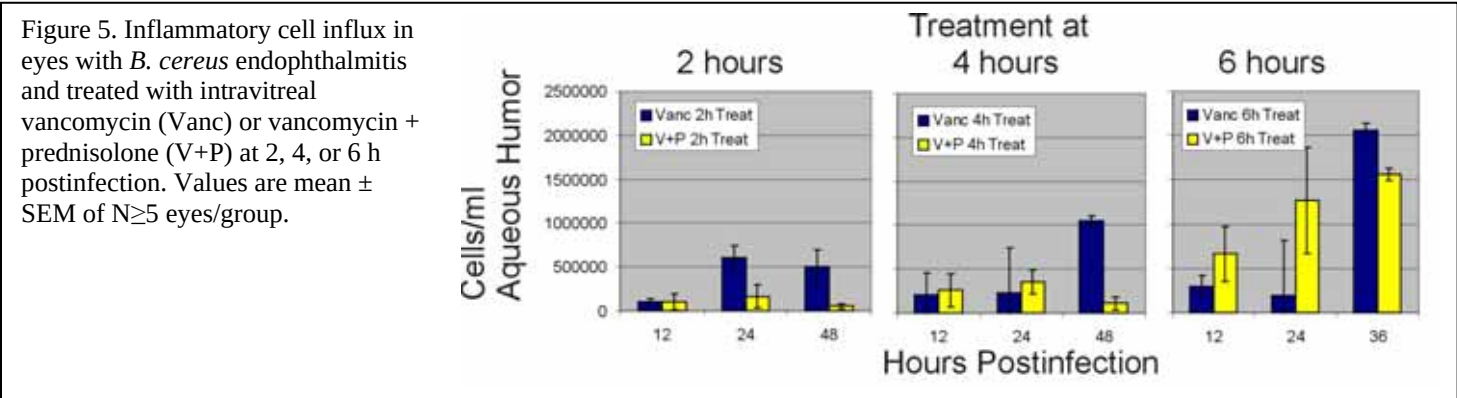
Figure 4. Retinal function analysis of eyes with *B. cereus* endophthalmitis and treated with intravitreal vancomycin (Vanc, 1.0%) or vancomycin + prednisolone acetate (Pred, 1.0%) at 2, 4, or 6 h postinfection. Values are mean $\pm$ SEM of N $\geq$ 5 eyes/group.



(0.3%) or vancomycin (1.0%) did not limit inflammation or improve the outcome of infection compared with treatments with antibiotics alone. The present studies analyzed the effectiveness of prednisolone acetate in improving the outcome of experimental *B. cereus* endophthalmitis.

Experimental Design Summary: Eyes were intravitreally infected with 100 CFU *B. cereus*. 0.1 mL of vancomycin (1.0%) or a combination of vancomycin and prednisolone acetate (1.0%) were intravitreally injected at either 2, 4, or 6 h postinfection. Eyes were analyzed at 12, 24, and 36 or 48 h postinfection by bacterial quantitation, electroretinography, inflammatory cell quantitation, and histology (N≥5 eyes per group).

Progress To Date: Vancomycin treatments sterilized all eyes, except vancomycin administered at 6 h, as previously described.² Retinal function analysis is summarized in Figure 4. In general, administration of vancomycin + prednisolone was not effective in reducing retinal function loss compared to the use of vancomycin alone. However, treatment with vancomycin + prednisolone did reduce inflammatory cell influx compared to that of vancomycin alone (Figure 5). For 2 h treatment, differences in inflammation between treatment groups were noted at 24 and 48 h, while treatment at 4 h or 6 h resulted in differences at the latest time point only. The only potential difference observed between the treatment groups



was in anterior segment inflammation observed via histology (Figure 6). This observation correlates with less inflammatory cell counts in eyes treated with vancomycin + prednisolone (Figure 5). There were no observable differences between treatment groups upon gross clinical examination (Figure 6).

Data Not Shown: Bacterial counts (discussed in *Progress to Date*) and histology sections and photographs of eyes from each treatment group at all endpoints.

Experiments Remaining: 1) A control group of treatment of infection with prednisolone alone is needed to complete the study. 2) Analysis of antibiotic concentrations in eyes from the experiments described above. 3) Comparison of treatment with gatifloxacin alone or gatifloxacin + prednisolone in experiments similar to those described in Aim 1.2.

Relevance: Although the administration of prednisolone acetate with vancomycin improved inflammation during infection, loss of retinal function was similar to that of eyes treated with vancomycin alone during infection. These results suggest that, like our recent findings² of lack of benefit of antibiotics in conjunction with dexamethasone, prednisolone acetate does not improve the therapeutic outcome of *B. cereus* endophthalmitis when combined with vancomycin. Further studies are needed to determine whether the combination of gatifloxacin and prednisolone improves therapeutic outcome.

Aim 1.3 Antibiotics Plus Surgery: The effect of vitrectomy plus intravitreal antibiotics against *B. cereus* during the late logarithmic bacterial growth stage of endophthalmitis.

Summary: As noted in the experiments above, treatment at 6 h postinfection resulted in loss of retinal function, but ocular architecture remained intact. Histology and photographs depicted the severe degree of inflammation in these eyes (Figure 6). In clinical cases of this severity, vitrectomy is used to remove posterior segment debris in order to potentially salvage vision. This Aim was proposed to analyze the effectiveness of vitrectomy used in conjunction with antibiotics for treatment of late-stage *B. cereus* endophthalmitis.

Progress To Date: These studies have not yet begun.

Aim 2: Non-Conventional Therapeutics. We hypothesized that blocking toxin activity, bacterial migration within the eye, and/or influx of inflammatory cells during *B. cereus* endophthalmitis will attenuate intraocular virulence and improve the therapeutic outcome of disease.

Aim 2.1 Blocking Toxin Activity: Intravitreal administration of anti-toxin raised to *B. cereus* toxins plus antibiotics against *B. cereus* during the early logarithmic bacterial growth stage of endophthalmitis.

Summary: We reported that toxin production in the eye during *B. cereus* endophthalmitis was responsible for the majority of retinal function loss during progressive infection.^{5,6} Others have reported that antisera raised to another ocular pathogen, *Staphylococcus aureus*, was effective in abrogating the effects of toxins during experimental endophthalmitis caused by that organism.^{7,8} We proposed a similar approach for treating *B. cereus* – combining anti-*B. cereus* toxin antisera with antibiotics during treatment at the early stages of infection when toxins are produced. The key is to kill the organism and arrest toxin activity.

Progress to date: We are presently raising polyclonal antibody to *B. cereus* toxins for administration with antibiotics during experimental *B. cereus* endophthalmitis. *In vivo* testing has not yet begun.

Aim 2.2 Blocking Bacterial Migration: Intravitreal administration of anti-flagellar antibody raised to *B. cereus* flagella plus antibiotics against *B. cereus* during the early logarithmic bacterial growth stage of endophthalmitis.

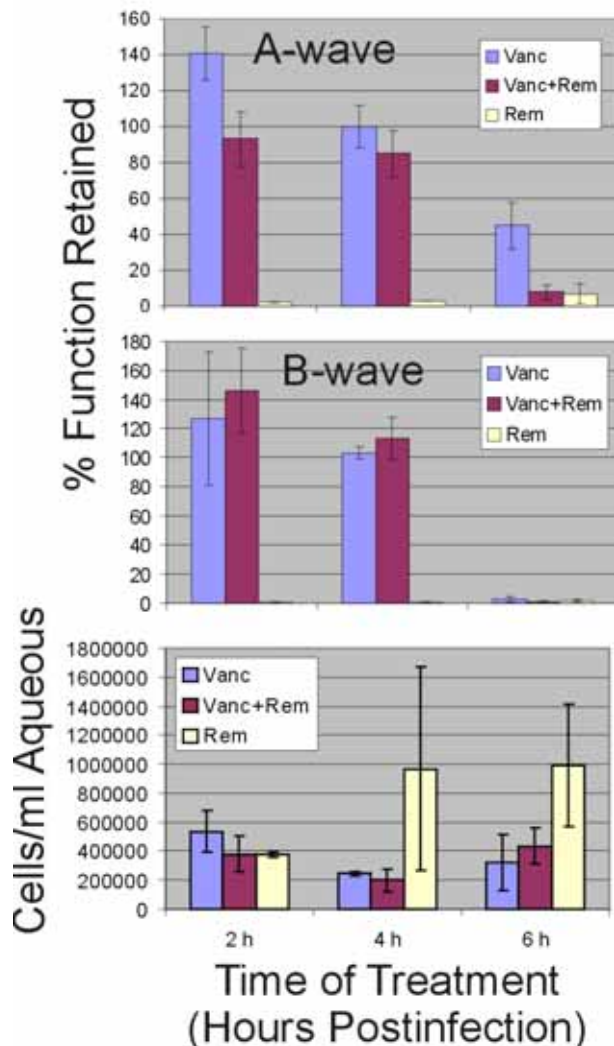
Summary: We reported that *B. cereus* migration throughout the eye was important to the virulence of the organism.^{6,9} In an approach similar to that in Aim 2.1, we proposed to combine anti-*B. cereus* flagella antisera with antibiotics during treatment at the early stages of infection when bacteria are moving within the posterior segment of the eye. The key is to prevent migration of the organism into niches where they may circumvent antibiotic action while also killing the organisms.

Progress To Date: We are presently purifying *B. cereus* flagella for use in generating polyclonal antibody for administration with antibiotics during experimental *B. cereus* endophthalmitis. *In vivo* testing has not yet begun.

Aim 2.3 Blocking Intraocular Influx of Inflammatory Cells: Intravitreal administration of anti-TNF α plus antibiotics against *B. cereus* during the early logarithmic bacterial growth stage of endophthalmitis.

Summary: We reported that TNF α is one of the pro-inflammatory cytokines synthesized in the eye during *B. cereus* endophthalmitis.¹⁰ Using transgenic mice deficient in TNF α , we identified this cytokine as being important in recruitment of inflammatory cells into the eye during *B. cereus* endophthalmitis.¹¹ Pilot experiments in mice demonstrated that anti-TNF α reduced the inflammatory cell load when administered intravitreally alone at the time of infection, but the reduction was only 40% at 10 h postinfection. We proposed to analyze whether anti-TNF α combined with antibiotics effectively reduced inflammation and sterilized the eye during the early stages of *B. cereus* endophthalmitis.

Retinal function and inflammatory cells in eyes with *B. cereus* endophthalmitis and treated with intravitreal vancomycin (Vanc), vancomycin + anti-TNF α (Vanc + Rem), or anti-TNF α alone (Rem) at 2, 4, or 6 h postinfection. Values are mean $\pm$ SEM of N $\geq$ 3 eyes/group.



Experimental Design Summary: Eyes were intravitreally infected with 100 CFU *B. cereus*. 0.1 mL of vancomycin (1.0%), a combination of vancomycin and anti-TNF α (Remicade, 0.5 ng), or anti-TNF α alone were intravitreally injected at either 2, 4, or 6 h postinfection. Eyes were analyzed at 12 h postinfection by electroretinography and inflammatory cell quantitation (N $\geq$ 3 eyes per group).

Progress To Date: Analysis of retinal function and inflammatory cell influx is presented in Figure 7. Overall, the combination of anti-TNF α + vancomycin did not improve B-wave function loss or extent of infiltrating inflammatory cells compared to vancomycin alone. To date, eyes have been analyzed at 12 h only. Treatment with anti-TNF α (Remicade) alone resulted in near complete retinal function loss and significant inflammation, as expected when antibiotics are absent.

Experiments Remaining: 1) Continuation of these experiments with analysis of bacterial growth, histology and antibiotic concentrations 12 h, and analysis of all parameters at 24 and 36 h postinfection. N values must also be increased for some data points.

Relevance: We found that intravitreal administration of anti-TNF α (Remicade) to mouse eyes did not significantly reduce inflammation or alter function loss during *B. cereus* endophthalmitis. To date, no studies have analyzed the value of cytokine blockade in the treatment of intraocular infection, but studies do describe the use of anti-TNF α drugs in treating

intraocular inflammation during uveitis.¹²⁻¹⁴ Our preliminary results demonstrate that anti-TNF α blocking, even in the early stages of infection, may not improve the outcome of inflammation or infection. This is not surprising considering our findings of the production of additional chemotactic cytokines in the eye during experimental endophthalmitis in the mouse.¹¹ However, it is of interest to determine whether inflammation is kept at bay by anti-TNF α at a time past the 12 h time point.

KEY RESEARCH ACCOMPLISHMENTS

- We demonstrated that early and aggressive (i.e. intravitreal) antibiotic treatment of intraocular infection is critical in salvaging vision.
- Delayed treatment (i.e. at 6 h postinfection) does not prevent significant vision loss but does arrest deterioration of the globe itself.
- Addition of prednisolone acetate to vancomycin in the treatment of *B. cereus* endophthalmitis does not improve retinal function loss but slightly dampens inflammation during infection.
- Adjunct use of anti-TNF α may not alter the outcome of infection, but further studies are needed to determine whether inflammation is altered during infection.

REPORTABLE OUTCOMES

There are no reportable outcomes to date. We plan to submit the results of Aims 1.1 and 1.2 to the Association for Research in Vision and Ophthalmology (ARVO) 2009 Annual Meeting (deadline December 2008) and prepare a manuscript containing this data for submission to *Investigative Ophthalmology and Visual Science*. The results of the studies of Aim 2.3 can also be submitted to the ARVO meeting if completed before the deadline.

CONCLUSIONS

Early and aggressive (i.e. intravitreal) administration of antibiotics are key to preventing significant vision loss and loss of the eye itself following penetrating injury and potential intraocular infection. The importance of these studies lies in identifying the timing in which an eye can be salvaged, even though sight may be lost. On the battlefield, as well as during accidental trauma, the timing from injury to treatment is critical, as is the type of treatment administered. Numerous studies have demonstrated that for posterior segment infections, systemic and/or topical antibiotic treatment is relatively useless (reviewed in reference 15). We demonstrated that intravitreal administration of antibiotics (with or without anti-inflammatory drugs) salvages vision if given early and can rescue the eye if treatment is delayed. Although our work analyzes treatment of *B. cereus* endophthalmitis – the most devastating form of bacterial endophthalmitis – the results of these studies can be extrapolated toward treatment of infections with other vicious pathogens such as *Staphylococcus aureus* or *Streptococcus pneumoniae*, where courses of infection are slower but infection outcomes are just as devastating. The use of anti-inflammatory agents to alter inflammation remains controversial, and our results of prednisolone acetate/vancomycin or anti-TNF α /vancomycin administration do not help to clarify the issue. Future work should involve analyzing use of prednisolone acetate/gatifloxacin to identify any therapeutic improvements with this combination.

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