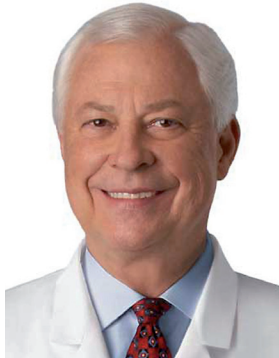


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## INTERVIEW

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“I would say that one of the biggest challenges [for clinical research into blepharitis treatment] is that there is a very heterogeneous population and in doing a clinical trial one wants to enter patients that are as homogenous in their expression of disease and underlying pathophysiological mechanisms as possible.”

# Update from recent blepharitis clinical trials: interview with James McCulley

James McCulley\*

**McCulley speaks to Alice O’Hare, Commissioning Editor, about clinical research into blepharitis treatment.**

James McCulley is Professor and Chairman of the Department of Ophthalmology at University of Texas Southwestern and is currently entering his 32nd year of chairmanship. He is a recognized expert in cornea, external disease, keratorefractive and cataract surgery. His research interests include more than 25 years of NEI/NIH supported evaluation into the pathophysiology and therapy of chronic blepharitis and associated ‘dry eyes.’ This work not only has led to understanding of chronic blepharitis but to a very thorough understanding of the lipid layer of the tear film. His work has allowed the development of a model for the structure of the lipid layer of the tear film and has led to the identification of the biochemical abnormality accounting for the ‘evaporative dry eye’. McCulley has published over 260 articles in peerreviewed literature. He also has received distinguished alumnus awards from Texas Christian University (TX, USA), his undergraduate university; Washington University Medical School (MO, USA) and the Harvard Department of Ophthalmology/Massachusetts Eye and Ear Infirmary (MA, USA) where he did his residency and fellowship. McCulley also serves as an Examiner for the American Board of Ophthalmology, and has the lead role in the establishment of a partnership with Prevent Blindness TX to reestablish on an annual basis the ‘Eye Ball’ in Dallas (TX, USA). He has served on multiple local, state and national boards, and been an invited speaker at multiple locations, nationally and internationally.

Q For our nonspecialist readers, can you please define what blepharitis is and what the present treatments are for this condition?

Blepharitis refers to inflammation in the eyelids. It has many, many different expressions of disease. The treatments vary tremendously, depending on the underlying cause of the blepharitis.

Q What are the limitations of the current treatment options for blepharitis?

Well, when one talks about blepharitis, for purposes of discussion and for understanding pathophysiology one really has to divide it into acute and chronic. Acute is going to mean principally infectious or allergic and then chronic can have an infectious component to it; however, it can also be frequently associated with other skin diseases such as seborrheic blepharitis, associated seborrheic

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dermatitis and acnerosacea, and there can be chronic atopic disease as well.

Therefore, the limitations for acute blepharitis are going to be identifying the underlying cause and directly treating that, with the hope and plan for cure. The various types of chronic blepharitis in general do not have a cure. So the major limitation there is that we have to find therapy initially to bring the disease under control, and then define the minimum amount of safe chronic therapy to maintain control.

Q For the blepharitis that we can cure, what would you say are the most promising novel agents to fight this condition?

Well, getting back to the kinds that we can cure – the principally acute therapy – and the antibiotics for the infectious type (which is mainly going to be *Staphylococcus*-caused disease) we have good antibiotics currently available to us to treat the condition. So I do not foresee any exciting new antibiotics for acute blepharitis. For the acute allergic type of blepharitis, it is typically self-limited, but we do have various products such as steroids and nonsteroidal anti-inflammatory drugs that we have available to us to treat the condition.

Q What clinical research in this field are you currently involved in?

In terms of the acute therapies, the most recent research that I have been involved with has been related to the potential role of fourth-generation fluoroquinolones as an added agent that can be of benefit to us in the acute infectious types of blepharitis. The potential major advantage to them is that they are more effective against methicillin-resistant *Staphylococcus aureus* than many of the previous antibiotics that we have had available to us.

More recently there have been some other agents or combinations that have come out that have been antibiotic–steroid combinations; for example, tobramycin and dexamethasone preparation (Tobradex ST™). Another that has come along recently is azithromycin, which is a macrolide, which has not only an antimicrobial component, but also the molecule has anti-inflammatory characteristics. So those are the two more recent approaches.

Q What advantages and disadvantages do these novel agents present?

The disadvantage to the Tobradex is that it is a steroid. When treating significant acute blepharitis I have no problem with trying to decrease the inflammation with a steroid combination so long as the combination is not

used for more than 2 weeks. If therapy is still needed after that, then I would recommend a switch to an antibiotic alone.

The disadvantage to the azithromycin is that the sensitivity patterns for the bacteria are not terribly good, relative to the azithromycin; that is, there is significant *in vitro* resistance to this antibiotic. So the principle benefit is the anti-inflammatory component – it does not have any bad side effects with long-term use, but it does not have as an effective antimicrobial characteristic.

Q In one blepharitis clinical trial, the efficacy of two antibiotics are compared [101]. Improvements in the patients' conditions are evaluated by microbiological evidence. What would you say are the advantages and disadvantages of measuring antimicrobial activity *in vitro*?

Well, the *in vitro* correlation of antibiotic effectiveness to *in vivo* effectiveness is not always directly tied to one another, that is, *in vitro* sensitivity patterns do not always correlate with clinical response. The agents, just as I have indicated with the macrolides, have other mechanisms of action other than antimicrobial. Also, the *in vitro* determination of sensitivity is based on achievable serum levels and we can get much higher concentrations with topical applications. So it is of use, but it is less than ideally predictive.

Q What would you say are the advantages and disadvantages of measuring microbial response *in vivo*?

I think it doesn't hurt to determine what one has done with the bacterial flora – how effective one has been in decreasing or eradicating the presumed pathogen in question. But the most important thing is clinical outcome.

Q Other outcome measures, such as tear production, are discussed in blepharitis trials. How is blepharitis linked to tear production?

If you start to talk about the role of, or the impact of, blepharitis on the tears, it is principally going to be in the chronic type of blepharitis, not the acute. In chronic blepharitis, there can be alterations (principally in the lipid layer) although there can also be associations with aqueous efficiency and presumably the alterations in aqueous efficiency come from long-term inflammation that then has an innocent bystander negative effect on the lacrimal and accessory lacrimal glands. However, in the principle type of chronic blepharitis that affects the tear film, it is thought to be an alteration (either

qualitatively and/or quantitatively) of the meibomian secretions, which are the source of the lipid layer of the tear film. This may result in increased evaporation of the aqueous tears. Therefore, outcome measures relating to the production of tears are more likely to be used in the assessment of chronic blepharitis.

Q Chronic blepharitis can lead to other ophthalmological complications, such as dry eye. How are these complications caused by blepharitis?

These are known as associated secondary effects. Another way of dividing blepharitis (I have already stated one, which is acute vs chronic), is infectious versus non-infectious. So the acute is mostly going to be infectious, although it can include allergy. And the chronic is typically not going to be infectious, although it can have an infectious component to it.

Another approach is to divide blepharitis anatomically – anterior blepharitis, which is on the external part of the lid, or posterior blepharitis, which is principally on the posterior lid involving the meibomian glands. It is this gland that produces the lipid layer, and when that is perturbed, one has what we currently (by popular agreement) call an evaporative dry eye. The lipid layer of the tear cell inhibits the aqueous tears (the watery tears) from evaporating, and if it is defective, then excessive evaporation occurs and there is drying of the ocular surface.

Q How do these complications affect trial recruitment to blepharitis trials?

One has to determine whether there is associated meibomian gland disease with the blepharitis, or whether there is no evidence of meibomian gland abnormality. And if one does not differentiate, then one ends up in a clinical trial entering a very heterogeneous group of patients. Some of the anterior blepharitis can also be chronic, such as seborrheic blepharitis, and they may or may not have associated posterior lid changes with them. Now, one has to be certain to get as homogeneous a patient population as possible, otherwise the outcome data is going to be tremendously confounded.

Q Do you believe this is being taken into account in the design of current blepharitis clinical trials?

I can see evidence in clinical trials in the last 5–10 years that I have participated in, that they have both been effectively and noneffectively taken into consideration. The ones that have not effectively taken it into consideration typically have resulted in poor success of the trial.

Q Published in 2011, one study has suggested that the prevalence and severity of blepharitis is higher in patients suffering from age-related macular degeneration [1]. Do you believe this has implications on age-related macular degeneration trials?

No, I do not. The pathophysiological mechanisms involved in these two diseases is really very, very different, and I doubt very seriously that there is a correlation between the two. My best assessment of this would be that one is obviously dealing with an older patient group with age-related macular degeneration, and chronic blepharitis with associated dry eye is much more common in an older population, so I think it is probably more age related than any correlation between, or association directly between the two disease processes.

Q In a paper published in 2000, you suggested that to improve blepharitis treatment, specific microbial abnormalities/inflammatory processes should be addressed and targeted [2]; do you believe this has been addressed in the last 12 years?

I think in general it has been recognized and accepted. What we looked for in many of the different types of chronic blepharitis (in chronic posterior blepharitis) was the possibility of a particular pathogen associated with disease. We found no identifiable single pathogen, so we then looked to see if there might be a common pathway shared by multiple different bacteria that could contribute to disease. What we found indeed was that *S. aureus*, coagulase-negative staphylococci and *Propionibacterium acne*, which are all commonly found in the lid flora, produce lipolytic enzymes. These then break down the lipids that are being made by the meibomian glands, and this lipid breakdown can contribute to disease.

Q What would you say are the biggest challenges we now face for clinical research into blepharitis treatment?

I would say that one of the biggest challenges is that there is a very heterogeneous population and in doing a clinical trial one wants to enter patients that are as homogenous in their expression of disease and underlying pathophysiological mechanisms as possible. That can be very difficult with this group of patients, because in the general population of patients with chronic blepharitis it is a very heterogeneous group of patients.

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### Financial & competing interests disclosure

*J McCulley is a consultant to Alcon Laboratories. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

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#### ■ Website

- 101 ClinicalTrial.gov identifier: NCT01478256.  
[www.clinicaltrials.gov/ct2/show/NCT01478256](http://www.clinicaltrials.gov/ct2/show/NCT01478256)