Diagnosis and Treatment of Episcleritis

Instructor:

Len Koh, PhD, OD, FAAO

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Anterior Segment

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COURSE DESCRIPTION:

This course focuses on the clinical diagnosis and management of episcleritis. It covers the clinical features of episcleritis as compared to scleritis and other red eye conditions. Additionally, supportive and medical therapy are presented.

Course begins on Page 2
Hello, doctor. First of all, thank you for your interest in learning more about episcleritis. Whenever we hear about episcleritis we need to keep scleritis in mind, as well. Let’s start with episcleritis first in this presentation and please visit my other presentation on scleritis.

Episcleritis is defined by the abrupt onset of inflammation in the episclera of the eye. Most patients with episcleritis have a mild, isolated problem that responds readily to topical therapy alone and does not pose a threat to vision. Indeed, many patients with episcleritis require no treatment per se, since the condition typically resolves over a short course.

A small fraction of patients with episcleritis have an underlying systemic disease that signifies a serious health concern and that requires additional therapy. The slit lamp image shown in Figure 1 shows moderately injected conjunctiva in a patient with episcleritis. Note the normal vessel architecture and radial position of the episcleral vessel as indicated with the black arrow.

Another thing to note is the demographic of the patient population. A lot of times you will see more pingueculitis, or inflammation of the pinguecula, more than true episcleritis. However, as you will see in terms of management later in this presentation, there is a similar management strategy for pingueculitis and inflamed pterygium compared to how we manage episcleritis.

Before considering the criteria by which the differential diagnosis is reached it is necessary to understand the normal vascular anatomy of the outer layers of the eye. The blood vessels of the episclera are not easily seen in the uninflamed eye, but as soon as the eye becomes congested three quite separate vascular plexii become readily visible.

1. **Bulbar conjunctival plexus**
   This is the most superficial plexus of fine hair-like interlacing vessels freely moveable over the underlying structures. Overlying the episclera, the conjunctival arteries are derived from two sources: the anterior ciliary arteries at the limbus, and the palpebral branches of the ophthalmic and lacrimal arteries. When they are inflamed, the color is bright red.

2. **Episcleral plexus**
   The episcleral plexus is the layer that becomes inflamed in Episcleritis. The vessels, which are straight and radially arranged, lie in the superficial episclera (parietal layer of Tenon’s capsule) at a depth of about one quarter to one-third of the distance between the surface of the conjunctiva and sclera (Graves, 1937). The visible vessels are mainly veins, accepting the aqueous veins at intervals around the globe. These vessels are moveable over the deep layers, although not so easily as the conjunctival vessels.

In the anterior episcleral plexus (anterior to the equator and over the muscle) the vessels belong to the anterior ciliary artery; while in the posterior episcleral arterial plexus (posterior to the equator) they are derived from the arteries of the oblique muscles, the posterior ciliary arteries, and the vessels of the...
optic nerve sheaths (Hayreh and Baines, 1972). I believe that for us to understand the disease process very well, we need to have a thorough understanding of the anatomy. When inflamed, these radially arranged vessels can easily be seen, giving the eye a salmon pink color.

3. Scleral (deep episcleral) plexus
The third layer, which is the scleral plexus, is more relevant in Scleritis. This plexus consists of a rete (criss-cross) of vessels lying within the visceral layer of Tenon's capsule, closely applied to the sclera. At the limbus the superficial and deep episcleral plexii merge into one another and terminate in the superficial marginal plexii of the cornea. When congested, this layer looks bluish-red in colour and is immobile.

Thus, there are three superficial layers surrounding the eye. The most superficial, the bulbar conjunctival plexus, is affected in conjunctivitis. The episcleral plexus is affected in episcleritis, and the scleral plexus is affected in scleritis. Figure 2 depicts these layers very nicely. Remember that the sclera itself is avascular – all of these blood vessels are above the sclera.

Episcleritis is commonly categorized into 2 subgroups: diffuse episcleritis and focal or nodular episcleritis. Slit lamp views show moderately injected conjunctivitis. Note the normal vessel architecture and the radial position of the episcleral vessels in Figure 1 (diffuse episcleritis) and Figure 3 (nodular episcleritis).

Episcleritis inflammation is usually sectorial in nature, confined to carefully delimited portions of the episclera. However, more diffuse episcleral involvement can occur, as seen in Figure 1.

What is the epidemiology of episcleritis? Does it affect more males? More females? Patients older or younger than 40 years old? Or is it more common in our patients over the age of 60 – our geriatric population?

There was a study published in Ophthalmology journal in 2012. [Ophthal 2012] Fifty-nine of the patients with episcleritis (69.4%) had simple episcleritis compared to 26 (30.6%) who had nodular episcleritis. Thus, the diffuse form is more common than the nodular form. Also the nodular form tended to be more severe. Episcleritis did not progress to scleritis in these patients.

In terms of gender, approximately 70 percent of cases of episcleritis occur in females [1]. Thus, women tend to be affected more, which also holds for scleritis, as well. It occurs most frequently in young and middle-aged adults, but may affect all age groups. The mean age of patients with episcleritis was 47.4 years (range, 10–80 years; P0.0001; Table 1).

Disease association is relatively rare for episcleritis, and is much more common in scleritis, as you will see if you view my presentation of Scleritis. The vast majority of episcleritis cases are isolated and are not associated with a known underlying systemic immune-mediated disorders (unlike scleritis, with which the association is much higher). However, episcleritis may be associated with a number of systemic diseases.
Simple episcleritis is observed in association with seronegative spondyloarthropathies, sharing common clinical characteristics of back pain, uveitis, GI symptoms, and rashes. A clinical pearl here is that if you see a patient with episcleritis, you want to ask about these common clinical characteristics. Ask if the patient has back pain, evaluate for uveitis, ask the patient if they have any GI disease such as Crohn’s or Ulcerative Colitis, IBD, etc. Check for any rashes around the face, neck, or extremities. Examples of seronegative spondyloarthropathies include ankylosing spondylitis, reactive arthritis (Reiter Syndrome), and psoriatic arthritis. We also know that ankylosing spondylitis is closely associated with uveitis, especially the HLA-B27 group of diseases.

Inflammatory bowel disease, and certain forms of vasculitis, particularly those associated with antineutrophil cytoplasmic antibodies (ANCA) have also been linked to episcleritis. ANCA–associated small-vessel vasculitis includes microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome. We will talk a little bit more about this small-vessel vasculitis in the Scleritis presentation.

Nodular episcleritis is most frequently idiopathic, but may be associated with any of the rheumatic conditions, particularly rheumatoid arthritis. Rheumatoid arthritis accounts for approximately 6% of all cases of episcleritis, but only a small minority of patients with rheumatoid arthritis develop episcleritis. Even though it is rare that episcleritis is associated with systemic disease, if you have recurrent episcleritis in a patient, keep some of this in mind.

Some reports suggest a possible link between use of the bisphosphonate drugs, risedronate and pamidronate, and Episcleritis [4,5]. These drugs are commonly used in osteoarthritis. The common suffix for this class of drugs is –dronate. However, a clear cause-and-effect relationship has not been established. Reported occurrence rates are generally less than 1%. Another clinical pearl here is that if you see a patient with conjunctivitis or episcleritis, also check in terms of medications they are on to rule out the possibility of medication-induced episcleritis.

In terms of pathogenesis, Episcleritis is a clinical diagnosis that can be produced by a variety of systemic immune and nonimmune mechanisms that incite inflammation. (Table 2) A common cause of episcleritis that has no associated systemic manifestation is dry eye syndrome that is not linked to Sjögren's syndrome. This is especially relevant if you have a patient with pingueculitis or inflamed pterygium. Usually the triggering factor is that they have a dry ocular surface that leads to inflammation – be that inflammation in the form of pingueculitis, inflamed pterygium, or episcleritis.

Immune mechanisms causing episcleritis may involve acute type 1 hypersensitivity responses caused by IgE mediated degranulation of tissue mast cells. At this point, it has some associations with allergies, as well, so if a patient has allergies in their history, they may be prone to

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<th>Table 1</th>
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<tr>
<td><strong>Simple Episcleritis</strong></td>
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<tr>
<td>Seronegative spondyloarthritides</td>
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<td>Inflammatory bowel disease (IBD)</td>
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<td>ANCA-associated vasculitis</td>
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<th>Table 2</th>
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<td><strong>Non-immune</strong></td>
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<td>Dry eye syndrome</td>
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episcleritis. If your patient has some type of atopic history, they also have an increased risk of developing episcleritis, as well. It can also be induced by immune complex-mediated reactions (type III hypersensitivity), as occurs in some vasculitic diseases, and by systemic infections, such as syphilis or tuberculosis. In granulomatous diseases, the pathophysiology of episcleritis is thought to be mediated by a type IV delayed-type hypersensitivity response, but the underlying antigens are unknown.

In summary, in pathogenesis, be sure to check for dry eye syndrome. This can lead to exacerbation of a pinguecula or pterygium, or a flare of episcleritis as a possible immune-related mechanism in terms of all types of hypersensitivities, with the exception of Type II. Also keep infections like syphilis or tuberculosis in mind, as well.

Regarding symptoms, in simple scleritis, eye redness is the chief complaint with acute onset (~30 min). The appearance can be either diffuse or sectorial. Pain is mild or absent, rarely severe. If you see severe pain, you need to think about more of a severe condition like scleritis rather than episcleritis. Sensations of heat or a pricking pain (rather than the boring pain which you may see in scleritis) may present in an episcleritis patient. The pain tends to be localized to eye, but may radiate to forehead. Lid edema is rare. Symptoms peak at ~ 12 hours and resolve over several days. Recurrence of episcleritis is common, and attacks may be bilateral or jump from eye to eye.

For nodular episcleritis, the patient will have eye redness that slowly spreads. Discomfort increases as redness worsens. There will be a subacute onset that progressively worsens over several days. Usually, first noticed by the patient upon waking.

Table 3: Symptoms

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<th>Simple episcleritis</th>
<th>Nodular episcleritis</th>
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<tr>
<td>Acute onset</td>
<td>Slow onset</td>
</tr>
<tr>
<td>Mild or no pain</td>
<td>Increasing discomfort</td>
</tr>
<tr>
<td>Heat, pricking</td>
<td>Worsens over several days</td>
</tr>
<tr>
<td>Resolves over several days</td>
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<tr>
<td>Recurrence is common</td>
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Table 4: Exam findings

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<tr>
<th>Simple episcleritis</th>
<th>Nodular episcleritis</th>
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<tbody>
<tr>
<td>Diffuse edema</td>
<td>Localized edema with vascular congestion</td>
</tr>
<tr>
<td>Mild flush to brick red</td>
<td>Tender, mobile nodule(s)</td>
</tr>
<tr>
<td></td>
<td>Interpalpebral fissure</td>
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</tbody>
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Exam findings in simple episcleritis will show engorged episcleral vessels. However, normal vessel architecture and radial position are still present.

Diffuse edema will be found in the episcleral tissues. You may also see gray deposits which can appear yellow under red-free light if present. One key thing in terms of a clinical examination is that you can use red-free light to examine a patient with episcleritis, scleritis, pingueculitis or even an inflamed pterygium. The appearance in daylight will be a mild flush to brick red, which can be either diffuse or sectorial.

Whereas with nodular episcleritis you get localized edema with vascular congestion. It could be a single or multiple, tender, mobile, non-necrotic nodule(s). It could be one nodule or multiple nodules. The nodule(s) almost always presents in the interpalpebral fissure. As we know, one very good way to differentiate between episcleritis and scleritis is to use a vasoconstrictor such as 2.5% or 10% phenylephrine drops allow visualization of sclera because of general blanching.

Usually with episcleritis, visual acuity, intraocular structures, and sclera are all unaffected.
Episcleritis is only one of many potential causes of a red eye. So what are the differential diagnosis possibilities for episcleritis? Other disorders that may cause this syndrome include subconjunctival hemorrhage, conjunctivitis, blepharitis, keratitis, scleritis, acute anterior uveitis, and acute angle-closure glaucoma. The closest one, most similar to episcleritis would be scleritis, followed by acute anterior uveitis because you may have diffuse injection.

Episcleritis must also be distinguished from conjunctivitis, a much more common cause of a red eye. Patients with all types of conjunctivitis (bacterial, viral, allergic) complain of morning crusting and daytime redness and discharge. The key thing here is discharge – usually if you have discharge, you are more likely dealing with conjunctivitis because episcleritis does not come with discharge.

In conjunctivitis, the erythema or injection of the eye is diffuse, involving the bulbar (globe) conjunctiva for 360 degrees as well as the palpebral or tarsal conjunctiva (the mucous membrane on the inner surface of the lids). If the conjunctival injection is localized rather than diffuse, then episcleritis is more likely. Again, discharge and diffuse injection 360 degrees is more likely to point to conjunctivitis rather than episcleritis. Viral conjunctivitis typically presents as injection, watery or mucoserous discharge, and a burning, sandy, or gritty feeling in one eye.

The episclera is a thin and highly vascular connective tissue that lies beneath the conjunctiva but is superficial to the sclera. Episcleritis must be distinguished from scleritis, a potentially dangerous cause of a red eye. In contrast to episcleritis, which is characteristically associated with bright red episcleral discoloration and not with pain, classic cases of scleritis present with intense ocular boring pain, photophobia, and a deep-red or purplish scleral hue. In addition, in episcleritis, there is no edema or thinning of the sclera. Such changes in the sclera are readily visible with the aid of a slit-lamp biomicroscope.

In cases that are not classic, the distinction between these two disorders may be difficult on gross (unmagnified) physical examination alone. In such cases, the application of phenylephrine eye drops leads to swift, transient resolution of episcleral redness, permitting more careful evaluation of the underlying sclera. In difficult cases, 2.5% or 10% phenylephrine will need about 10 to 15 minutes for the medication to work and give you the best differentiation.

### Table 5: Scleritis versus Episcleritis

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<tr>
<th>Clinical Features</th>
<th>Episcleritis</th>
<th>Scleritis</th>
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<tbody>
<tr>
<td>In daylight</td>
<td>Salmon pink</td>
<td>Purple/grey choroid</td>
</tr>
<tr>
<td>Slit-lamp (red-free)</td>
<td>Yellow patch</td>
<td>Scleral edema, vessels, avascular patches</td>
</tr>
<tr>
<td>10% Phenylephrine</td>
<td>More constriction</td>
<td>Minimal constriction</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Mild or no pain</td>
<td>Severe pain, photophobia</td>
</tr>
<tr>
<td>Scleral edema</td>
<td>No</td>
<td>Yes, or thinning</td>
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Table 5 shows some clinical information and examination tips. For example, to differentiate episcleritis from scleritis, you can look at the conditions in normal daylight and episcleritis will be salmon-pink while episcleritis will appear purple-grey. In terms of slit lamp if you flip in the red-free filter, you will see more yellow patches in episcleritis whereas in scleritis you will see scleral edema, and maybe avascular patches in the area that are more prone to thinning. Symptoms of episcleritis usually involve mild to no
pain while in scleritis you have severe pain or a boring pain, with photophobia. Usually with episcleritis there is no scleral edema which you do have in scleritis, in addition to in some cases you also have thinning of the sclera.

For diagnosis in a patient with a first episode of episcleritis, the only type of evaluation required in addition to a complete eye examination is a thorough history and physical examination. If the general history and physical examination are normal, the patient should be reassured that the disorder is probably benign and that additional investigations are needed only if episcleritis recurs or new symptoms develop.

More extensive evaluation is required in patients with recurrent episcleritis, evidence of other ocular disease, or abnormal findings on the general history and physical examination. Both routine and specialized serologic assays are important in the evaluation of patients suspected of having an underlying rheumatic or infectious illness.

What are the basic lab workups? CBC, Serum Chemistry, Urinalysis, ESR, and CRP are all good basic lab workups if you have a patient with recurrent episcleritis or some other ocular complications. The following routine tests should be sent for all patients who are suspected, based upon their medical history or other systemic features, of having a systemic disease as the cause of their episcleritis:

- Complete blood count (CBC) – Patients with systemic conditions frequently have abnormalities of the white blood cell count, platelet count, or hematocrit.
- Serum chemistry profile – This should include creatinine, blood urea nitrogen, electrolytes, albumin, total protein, and aminotransferases.
- Urinalysis with microscopy – Urinalysis with microscopic examination of the urine sediment is essential to excluding glomerulonephritis and other renal disorders.
- Acute phase reactants – Patients with episcleritis associated with a systemic illness, but not those with isolated disease, are likely to have extremely high acute phase reactant levels. Both the erythrocyte sedimentation rate and serum C-reactive protein should be measured.

An exhaustive systemic immunological workup is not warranted unless either the medical history or review of systems are suggestive of a non-ocular immune-based disorder; or unless the patient has recurrent episcleritis, which is associated with an increased chance of an associated systemic disease.

A more extensive lab workup can be done for a more severe case that is suspected to have a systemic association. Blood tests targeted to specific systemic inflammatory diseases associated with episcleritis include:

- Rheumatoid factor – A positive rheumatoid factor assay is a nonspecific result, but extremely high titers of rheumatoid factor are usually found in the setting of rheumatoid vasculitis.
- Antibodies to cyclic citrullinated peptides – Antibodies to cyclic citrullinated peptides (anti-CCP antibodies) have a high specificity for rheumatoid arthritis.
- Antineutrophil cytoplasmic antibodies – Antineutrophil cytoplasmic antibody (ANCA) assays are positive in most patients with granulomatosis with polyangiitis (Wegener’s) or microscopic polyangiitis and in a smaller proportion of patients with the Churg-Strauss syndrome. Patients with inflammatory bowel disease may also have ANCA.

If an immunofluorescence assay for ANCA is positive in either a cytoplasmic or perinuclear pattern (ie, CANCA or P-ANCA), then further investigation through specific enzyme
immunoassays is important. Among the vasculitides, only antibodies to proteinase-3 (C-ANCA) or myeloperoxidase (one of a variety of PANCAs) have specific associations with granulomatosis with polyangiitis (Wegener’s), microscopic polyangiitis, and the Churg-Strauss syndrome. Patients with inflammatory bowel disease typically have P-ANCAs that are directed against non-myeloperoxidase antigens, assays for which are not widely clinically available.

- Antinuclear antibody testing – Antinuclear antibody (ANA) testing is useful for the exclusion of connective tissue diseases related to systemic lupus erythematosus. A strongly positive ANA assay should be followed by a rheumatology consultation and possibly by additional serologic testing to determine the specific disease responsible for the ANA positivity. The additional testing may include serum complement levels (C3, C4), antibodies to double-stranded DNA, and antibodies to the Ro, La, Sm, or RNP antigens.
- Chest imaging — A chest x-ray should be performed in patients suspected of having a systemic condition. Any abnormality detected on chest x-ray should be defined more completely by a computed tomography (CT) scan of the chest.
- Other testing — Additional specialized testing, such as endoscopic procedures to exclude inflammatory bowel disease in a patient with severe episcleritis, is mandated only if there are non-ocular comorbidities or elements in the medical history and physical examination suggestive of a particular condition.

How is episcleritis managed? Episcleritis is not sight-threatening and, in most patients, is an episodic, self-limited process. When patients come see us, they expect a prescription rather than to be told that the condition will resolve on its own. We can prescribe a topical lubricant 4-6x per day, or we can also prescribe a mild NSAID or mild steroid for inflamed pterygium, pingueculitis or episcleritis. Symptomatic relief should be the goal of the therapy. For the achievement of symptomatic relief, there are four levels of therapy. For some of these treatment modalities, a handful of randomized clinical trials have been performed.

- Topical lubricants — The initial management of episcleritis consists of the application of topical lubricants. Any over-the-counter preparation of artificial tears will suffice, provided it is used four to six times daily. If more frequent use is required, we suggest the use of preparations that do not contain preservatives in order to avoid preservative-induced toxicity. Such preservative-free preparations can be used as frequently as required and for as long as the patient remains symptomatic. We recommend artificial tear preparations that do not contain preservatives, such as Refresh Plus or Bion Tears (Grade 1B).
- Topical nonsteroidal antiinflammatory drugs (NSAIDs) – We suggest topical diclofenac (Volteran) four times daily (Grade 2C).
- Topical glucocorticoids – We suggest either fluorometholone acetate (0.1%) or prednisolone acetate (1%) (Grade 1B). Both of these medications are applied four times daily.
- Oral NSAIDs – For patients with severe episcleritis, we suggest indomethacin (Grade 2C). This medication is usually prescribed as 25 mg taken by mouth three times daily.

These treatments, as I mentioned earlier in this presentation, can also be considered for inflamed pterygium or inflamed pinguecula, as well as for episcleritis. I tend to go with the topical steroid like
FML or Pred Forte, depending on the severity of the symptoms and ocular signs. Remember to also supplement with the artificial tears. If you use artificial tears more than 4-6x per day, be sure to go with a preservative-free preparation of artificial tears to prevent preservative toxicity.

Regarding prognosis, although episcleritis does not produce significant ocular complications and does not impair vision, mild complications including corneal infiltrates and low-grade uveitis occur rarely. Small peripheral corneal infiltrates, visible only with the slit-lamp biomicroscope, are a rare occurrence. These infiltrates represent inflammation within the stroma of the cornea. The changes are small, localized, non-progressive and do not affect vision. Patients with significant limbal or corneal inflammation should be followed more carefully to ensure that they do not progress to frank scleritis.

Some patients develop transient low-grade anterior uveitis with severe attacks [3]. The onset of photophobia, pain, and decreased vision should alert the clinician that uveitis has complicated a case. These patients may benefit from a short course of topical glucocorticoids.

Regarding recurrence, 2/3 of the patients had recurrences up to 6 years after the onset of the disease, but after this the recurrence rate fell. (The study followed patients for up to 8 years.) This recurrence could be bilateral, unilateral, or jump from one eye to the other. Of the 159 patients with episcleritis and the 207 patients with scleritis, 146 (91%) and 186 (90%), respectively, have been followed-up during a period of between one and eight years (mean 5-8 years). Two-thirds of the patients had recurrences up to six years after the onset of the disease, but after this the recurrence rate fell. It is important to follow up those patients with necrotizing disease because the disease can continue to progress when they are symptom-free, and they may require continuous treatment even when the disease is quiescent.

In conclusion, most patients with episcleritis have a mild, isolated problem that responds to topical therapy alone and that does not pose a threat to vision. However, a minority have an underlying systemic disease that signifies a serious health concern and that requires additional therapy. In some patients, episcleritis is an early presentation of a more severe and destructive ocular immune problem such as scleritis. Accurate distinction between episcleritis and scleritis is critical. The topic of scleritis is covered in another presentation.

Thank you very much for your attention.

**Corresponding author:**
Len Koh, PhD, OD, FAAO
Pacific University College of Optometry
2043 College Way, UC Box A134
Forest Grove, OR 97116-1797
lenvkoh@pacificu.edu

**Address questions about Pacific’s Web CE to:**
James Kundart, OD Med FAAO FCOVD-A
Kundart@pacificu.edu