Central Serous Chorioretinopathy: Update on Pathophysiology and Treatment

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Abstract

Recent technological advances have led to an improved understanding of central serous chorioretinopathy (CSC): new pathophysiological insights, new imaging techniques for diagnosis and management, and new treatments. The primary role of the choroid has become more widely accepted with widespread use of indocyanine green angiography. Optical coherence tomography (OCT), and particularly enhanced depth imaging OCT, demonstrate a thickened and engorged choroid. Adaptive optics, fundus autofluorescence, multifocal electroretinography, microperimetry, and contrast sensitivity testing reveal that patients with even a mild course suffer previously undetected anatomic and functional loss. While focal laser and photodynamic therapy are the current standard of care for persistent subretinal fluid in CSC, they are not appropriate in all cases, and the optimal timing of intervention remains unclear.

Keywords
central serous chorioretinopathy; diffuse retinal pigment epitheliopathy; photodynamic therapy; corticosteroids; indocyanine green angiography; fundus autofluorescence; optical coherence tomography

I. INTRODUCTION

Central serous chorioretinopathy (CSC) is a disorder characterized by serous retinal detachment and/or retinal pigment epithelial (RPE) detachment, changes most often confined to the macula, and associated with leakage of fluid through the RPE into the subretinal space. CSC is seen frequently in most retina practices, classically in young male patients with no associated systemic conditions. CSC has been known by many names since the original description by von Graefe in 1866, and these names reflect the course of progress in our understanding of the pathogenesis of the disease. von Graefe described the disease as a recurrent central retinitis, whereas Horniker in 1922 called it capillarospastic central retinitis to reflect his belief that vasospasm was the mechanism. Other names of the 20th century include central angiospastic retinopathy and central serous retinopathy. Maumenee described fluorescein angiographic (FA) characteristics; fluorescein leakage at the level of the RPE revealed that the choroid and RPE were the primary tissues involved. Gass further characterized the angiographic findings and coined the term central serous chorioretinopathy. Since we now understand that hyperpermeability of the choroid causes
leakage through the RPE, resulting in a neurosensory retinal detachment, CSC is the preferred term. 138

A. Epidemiology

CSC has historically been viewed as primarily affecting men in their third and fourth decades, but the average age reported in recent large studies has ranged from 45 to 51 years. 200 Spaide and colleagues reported a mean of 51 years, but they observed that older patients were more likely to present with diffuse RPE loss and secondary choroidal neovascularization (CNV), suggesting that the onset of disease occurred years before presentation. Some patients are initially asymptomatic and may not be diagnosed until they develop more advanced disease. Likewise, the large retrospective case control series published by Haimovici and colleagues in 2004 included patients with evidence of chronic disease. 73 They reported a mean age of 45 years. Kitzmann and colleagues (2008) assessed for age of onset and reported a mean of 41 years. 97 Age-related macular degeneration (AMD) with choroidal neovascularization (CNV) may resemble CSC, and this must be ruled out in patients over 50.

The lone population-based study of CSC reported an annual incidence of 9.9 cases per 100,000 men and 1.7 per 100,000 women in Olmstead County, Minnesota. 97 Reported male to female ratios range from 2.7:1 to 7:1. 206 CSC is thought to be less common in African Americans than in Caucasians, Hispanics, and Asians, although this has been disputed. 44 Numerous risk factors for CSC have been reported, but the most consistent is the use of glucocorticoids. This association was suspected as early as 1966 by Jain and Singh, 86 but was first reported in detail in 1985 and 1985 by Wakakura and Ishikawa and Harada and Harada. 20,74,223 Haimovici et al reported an odds ratio of 10.3 (95% CI 4.0–26.4) for corticosteroid use in their case control study of 312 patients with CSC. 73 Tittl and colleagues reported an odds ratio of 3.17 (95% CI 1.3–7.7) in their 230 patients. 216 A smaller prospective study (38 cases) also supports the association. 58 CSC appears to be associated with elevated levels of endogenous corticosteroids, as in patients with Cushing’s syndrome. 19 Glucocorticosteroids have at times been used to treat CSC, 91,120,162 but given the strong association between CSC and steroid use, they should be avoided whenever possible. Furthermore, patients with CSC should be questioned exhaustively about all forms of steroid use to eliminate the possibility that a skin cream, joint injection, nasal spray, inhalant, or other commonly overlooked form of glucocorticoid could be a contributing factor.

Pregnancy is another recognized risk factor for CSC. Plasma cortisol levels are elevated during pregnancy, particularly during the third trimester. 42 Haimovici and colleagues had 18 pregnant patients among their 312 cases (versus just 2/312 age and gender-matched controls, P<0.0001) and calculated an odds ratio of 9.3 (95% CI 2.1–40.6). 73 Chumbley and Frank describe an otherwise healthy young woman who developed active CSC during each of four successive pregnancies, with spontaneous resolution after giving birth. 40 Pregnancy-associated CSC occurs most often in the third trimester, tends to present with distinctive white subretinal exudation, and usually resolves spontaneously after delivery. 20

The historic association between CSC and type A personality is controversial. While this is a challenging relationship to study, Yannuzzi’s study of CSC and personality types supports the association. 235 His study relied on a comparison of personality surveys of CSC patients with matched controls that predominantly had diabetic retinopathy, rhegmatogenous retinal detachment, and refractive error. Others have found use of psychotropic medication to be a risk factor, which may suggest that psychological stresses are associated with CSC. 216 Additional associations including systemic hypertension, 73,216 gastroesophageal reflux...
disease (GERD), use of alcohol or sympathomimetic agents require further confirmation. Kitzmann and colleagues small (74 eyes) case control series failed to confirm any of the above associations with CSC, including corticosteroid use.

B. Clinical Findings

CSC can occur in an acute or chronic form. The designation of chronicity in CSC is somewhat arbitrary. Some authors have defined chronicity as persistent fluid for at least six months, whereas recent clinical trials have used three months with persistent fluid. While the acute form can sometimes be recurrent, it generally resolves spontaneously with minimal sequelae. Chronic CSC, however, can result in widespread RPE damage, sometimes referred to as diffuse retinal pigment epitheliopathy (DRPE). These patients have longstanding subretinal fluid that cannot be reabsorbed efficiently because of choroidal disease and extensive dysfunction and loss of RPE. The presence of chronic fluid leads to photoreceptor death and may result in permanent visual loss. Furthermore, chronic CSC is more likely to be complicated by CNV that can cause severe visual loss. Not all patients with acute CSC go on to develop chronic disease, and the reasons for the varied courses are not well understood. There may be additional unknown differences in the pathophysiology of acute and chronic CSC.

A newer classification scheme based on the status of the retinal pigment epithelium employs the terms classic CSC and DRPE. Classic cases have minimal focal RPE damage and discrete leaks at the level of the RPE, and DRPE cases have extensive RPE damage and diffuse leakage. Additionally, a minority of patients develop the bullous variant which occurs when inferiorly gravitating fluid results in a bullous serous retinal detachment.

The hallmark of CSC is the presence of a serous detachment of the neurosensory retina in the posterior pole, sometimes associated with a serous RPE detachment. These findings are usually apparent on slit-lamp biomicroscopy, and they are easily detected and quantified with optical coherence tomography (OCT). In long-standing CSC, some eyes will develop intraretinal fluid and cystoid edema (Figure 1). The most common fluorescein angiographic pattern in CSC is a single pinpoint leak at the level of the RPE (Figure 2). Some patients will present with multiple pinpoint leaks or a smokestack fluorescein pattern (Figure 3).

Fluorescein angiography may show evidence of CSC episodes limited to the extramacular area (Figure 4) that typically go undetected as they are asymptomatic. Those presenting with DRPE have extensive RPE disease and diffuse fluorescein leakage. In long-standing CSC, findings may include RPE atrophy that exposes underlying choroidal vascular patterns, areas of RPE pigment clumping, and even bone spicules. Other important imaging findings include evidence of gravity-driven descending tracts of subretinal fluid on fluorescein angiography or fundus autofluorescence (FAF) (Figure 5). These tracts are typically hyperautofluorescent when the fluid first occurs, but then become increasingly hypoautofluorescent as RPE cells are damaged in the pathway of the fluid. On mid-phase indocyanine green (ICG) angiography, there are often plaques of hyperfluorescent inner choroidal staining both in the posterior pole and in the periphery. As shown in Figure 6, CSC often extends beyond the macula. Hence, CSC can be regarded as a disorder of the posterior pole rather than purely a maculopathy. Enhanced depth imaging (EDI) reveals a thickened choroid. These imaging findings are discussed further below.

II. PATHOPHYSIOLOGY

The pathophysiology of CSC remains poorly understood despite advances in imaging techniques and numerous studies of the disease. Clinical findings in CSC have given rise to several theories of pathogenesis, each of which may in part explain the disease process. The major theories of the pathophysiology of CSC, including etiologies originating in the
choroid, RPE, and hormonal milieu, are presented here in Part A. In Part B, there is a discussion of pathophysiological insights that have been gained through new examination and imaging technologies.

A. Theories of Pathogenesis

1. Role of the Choroid—The current understanding of the pathogenesis of CSC emphasizes the role of the choroid. The choroid is thought to be hyperpermeable in CSC, possibly as a result of stasis, ischemia, or inflammation. The staining of the inner choroid seen on mid-phase ICG angiography is the primary evidence of choroidal hyperpermeability. The primary role of the choroid is further supported by the EDI OCT finding of a thickened choroid in both eyes of patients with CSC. Interestingly, the areas of staining on ICG do not correspond with thickening on EDI OCT, and their significance remains to be fully explained.

Hyperpermeable choroidal vessels are thought to produce increased tissue hydrostatic pressure, which promotes the formation of retinal pigment epithelial detachments (PEDs), overwhelms the barrier function of the RPE, and leads to areas of fluid accumulation between the retina and the RPE. Since areas of choroidal staining are usually contiguous with foci of RPE leakage on FA, the hypothesis of a mechanistic relationship between the two findings is reasonable. Not all areas of choroidal staining are associated with RPE leaks, suggesting that in some instances the RPE may be able to withstand the stresses posed by choroidal disease.

The underlying cause of choroidal thickening on OCT and staining on ICG is not known. Theories that integrate these findings with corticosteroid use and sympathomimetic agents have been advocated. Although the connection between sympathomimetic agents and CSC is less established, their potential for effects on choroidal vessels and blood flow is clear. Corticosteroids influence the transcription of myriad genes, including those for some adrenergic receptors. Furthermore, steroids are known to potentiate vascular reactivity through a variety of pathways. CSC may result from impaired choroidal vascular autoregulation induced by steroids, catecholamines, or sympathomimetic agents. A monkey model of CSC produced by repeated intravenous administration of epinephrine (epinephrine only in one monkey, epinephrine plus steroid in a second animal) showed damage to choriocapillaris endothelium and overlying RPE. Furthermore, there was extensive fibrin leakage into Bruch membrane and fibrin clots in the choriocapillaris at the sites of endothelial cell loss. Although this model has been criticized as inducing manifestations of hypertensive disease rather than true CSC, it did produce a strikingly similar constellation of findings including serous retinal detachment and characteristic changes in fluorescein angiography.

Further evidence for choroidal vasculopathy in CSC comes from studies that indicate that areas with mid-phase inner choroidal staining also have delayed choroidal filling, suggesting choroidal lobular ischemia with associated areas of venous dilatation. Elevated serum levels of plasminogen activator inhibitor-1, an inhibitor of physiologic fibrinolysis, in CSC have led to suggestions of a thrombotic mechanism for these vascular changes.

Tittl and colleagues measured fundus pulsation amplitudes in CSC eyes and control eyes with a laser interferometer and demonstrated greater amplitudes in CSC eyes. Affected eyes were also significantly different from unaffected eyes in the same patients, while systemic parameters were similar between study subjects and controls, suggesting that the pulsatile component of choroidal blood flow is altered locally in the affected eye in CSC. In a separate study, this group demonstrated that subfoveal choroidal blood flow is
significantly greater in inactive chronic CSC patients than in controls during exercise.\textsuperscript{215} The evidence for a choroidal vasculopathy in CSC is strong, but the underlying mechanism of choroidal disease remains to be determined.

2. Role of the Retinal Pigment Epithelium—RPE dysfunction plays a significant role in the pathogenesis of CSC. This is perhaps most easily appreciated in cases of DRPE, in which widespread loss of RPE cells is apparent on clinical exam and FAF, and where the loss of RPE barrier and pumping functions in the setting of an engorged choroid results in chronic subretinal fluid. Before widespread acceptance of an underlying choroidal pathology, RPE theories of pathogenesis predominated. The focal areas of leakage through the RPE that are characteristic of classic CSC were one of the first clues to the pathogenesis of the disease. These pinpoint leaks were seen as focal defects in the RPE that were thought to be primarily responsible for the accumulation of subretinal fluid. However, Negi and Marmor showed that focal RPE defects promoted flow of fluid out of the subretinal space toward the choroid rather than vice versa.\textsuperscript{149} An alternate theory is that focal loss of polarity of RPE cells leads to active fluid pumping into the subretinal space.\textsuperscript{205}

The role of the RPE in CSC pathogenesis remains poorly understood. Perhaps the most complete theory states that increased tissue hydrostatic pressure in the choroid overwhelms the barrier function of the RPE and leads to areas of fluid accumulation between the retina and the RPE. Some refer to the pinpoint areas of leakage seen in acute CSC as micro-rips or blowouts. PEDs are common in CSC and could also represent a form of RPE decompensation in response to high choroidal hydrostatic pressure. The CSC monkey model,\textsuperscript{241} described above, and ICG findings of perfusion delays in areas of leakage indicate that local choroidal ischemia could contribute to RPE damage. Epinephrine has been associated with RPE apoptosis \textit{in vitro},\textsuperscript{195} so a direct effect unrelated to perfusion could also contribute to pathogenesis. Inflammatory and hormonal causes for focal RPE incompetence have also been suggested.\textsuperscript{62,178,239}

Spectral domain OCT studies of the RPE in CSC have shown RPE defects in the location of a fluorescein leakage in some patients.\textsuperscript{54} These studies mirror the small RPE defects found histopathologically in the monkey model.\textsuperscript{241} Many RPE defects are too small for reliable detection on OCT. Another OCT-based study of the RPE showed that RPE abnormalities are present in nearly all asymptomatic, fluid-free contralateral eyes of CSC patients.\textsuperscript{68} This suggests that RPE damage is not necessarily a late sequela of CSC, but occurs even in forma seurtes.

The success of focal photocoagulation of isolated leaks suggests that treatment at the level of the RPE may be effective in some cases.\textsuperscript{60} Pharmacologic interventions targeting the RPE (discussed further below), however, have not yet yielded a treatment breakthrough.\textsuperscript{51,164}

3. Hormonal Factors—The strong association between CSC and glucocorticosteroid use suggests a role in pathogenesis. Both serum glucocorticoid\textsuperscript{57} and serum catecholamine levels\textsuperscript{72,209} are elevated in active CSC. The complexity of corticosteroid pharmacology and the interconnected nature of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system suggest a number of possible explanations for these associations.

Glucocorticoids could potentially impact the course of the disease by affecting the choroid, Bruch’s membrane, or the RPE.\textsuperscript{20} Proposed mechanisms in the choroid include effects on vascular autoregulation via increased transcription of adrenergic receptors\textsuperscript{15,181} or potentiation of vascular reactivity,\textsuperscript{234} effects from steroid-induced systemic hypertension,\textsuperscript{216} or a prothrombotic effect.\textsuperscript{20} Corticosteroids could affect Bruch membrane via their known inhibition of collagen synthesis.\textsuperscript{152} Finally, epithelial water and ion transport are altered by
corticosteroids,\textsuperscript{16,72,182,197} and this might impair the barrier function of the RPE. Arndt and colleagues studied RPE tissue in vitro and showed that administration of hydrocortisone decreased the transepithelial membrane potential and resistance.\textsuperscript{8} In vivo, IV prednisolone reduced the rise in standing potential induced by glucose infusion.

Interestingly, local ocular glucocorticoid use is usually not associated with CSC.\textsuperscript{18,82,100} Intravitreal and periocular steroid treatments are common, yet reports of CSC after local ocular steroid injections are rare; however, almost every form of exogenous glucocorticoid has been associated with exacerbation, and ocular and systemic glucocorticoids should be avoided in CSC.

CSC has not been described after treatment with sympathomimetic agents alone, so it may be that the association with elevated catecholamine levels is related to simultaneously increased levels of corticosteroids in a physiologic stress response. Furthermore, beta-blocking agents have not been effective in treating or preventing CSC.\textsuperscript{22,166}

4. \textit{H. pylori}—Several recent papers have reported an association between \textit{H. pylori} infection and CSC,\textsuperscript{3,10,41,64,135,140} and some have noted a beneficial effect in CSC in patients treated for \textit{H. pylori}.\textsuperscript{64,168} \textit{H. pylori} is a Gram-negative bacterium that causes gastritis and has also been associated with a variety of extragastric conditions, including thrombotic disease.\textsuperscript{25} Thrombotic disease is a pathway through which infection could cause CSC. Immune-mediated damage to choroidal endothelial cells resulting from molecular mimicry is one proposed mechanism.\textsuperscript{65} The largest series to date found \textit{H. pylori} infection in 31/78 (40%) French CSC patients versus a 25% infection rate in the general population (p=0.0036).\textsuperscript{3} Kitzmann and colleagues, however, found no patients with a known history of \textit{H. pylori} infection in their 74 cases.\textsuperscript{97}

A randomized, controlled trial comparing triple therapy \textit{H. pylori} treatment with observation in \textit{H. pylori}-infected acute CSC patients found that the time to fluid resorption was significantly reduced in the treatment group (9.3 vs 11.6 weeks, p=0.015).\textsuperscript{168} There was no visual acuity benefit. Follow up visits were at weeks 2, 4, 6, 8, 12 and 16. The four week interval between study visits after week 8 limits the precision of the time to resorption outcome measurements in this study. Larger studies are warranted to confirm the association between \textit{H. pylori} and CSC.

5. Genetics—A review of the CSC literature reveals numerous reports of familial CSC,\textsuperscript{5,70,119,157,161,222,224,230} Perhaps the most compelling evidence for a genetic contribution to pathogenesis comes from Weenink and colleagues\textsuperscript{224} who found CSC-like pathology in 14/27 (52%) families of chronic CSC patients. Only a small percentage of affected relatives reported symptoms.

Just one population-based prevalence study has been conducted to date, and this was in a predominantly white, American population. Nonetheless, CSC is thought to have a higher prevalence in whites, Hispanics, and Asians than in African Americans.\textsuperscript{44,138,236} Further studies of the genetics of CSC are warranted, including studies of single nucleotide polymorphisms (SNPs) that may help identify individuals at risk to allow for appropriate counseling and closer monitoring. Studies of SNPs could help identify those at greatest risk of developing CSC and may be helpful in predicting those who are more likely to progress to chronic CSC or DRPE.

6. Cytokine Analyses—Aqueous samples from CSC eyes have been analyzed for various growth factors and cytokines.\textsuperscript{114,192} Aqueous vascular endothelial growth factor (VEGF) levels are not elevated in CSC. Levels of IL-6, IL-8, and monocyte chemoattractant
protein-1 do not differ from controls, while interferon gamma and TNF-α have been undetectable in these eyes. This provides further evidence against an inflammatory etiology. Platelet-derived growth factor (PDGF) levels appear to be lower than in controls. PDGF is an RPE mitogen, and it is secreted by endothelial cells to recruit blood vessel mural cells. PDGF-related RPE dysfunction or vascular incompetence could contribute to the pathogenesis of CSC.

B. Pathophysiological Insights From New Imaging and Examination Technologies

1. Spectral Domain Optical Coherence Tomography—The first spectral domain OCT device (SD-OCT) was approved by the FDA in 2006. Since then, SD-OCT has become the standard for OCT imaging worldwide given its ability to acquire high definition images of ocular structures rapidly. While OCT allows for ready detection of known manifestations of CSC, including serous retinal detachment (Figure 7) and serous PED,144 the high resolution images have allowed for detailed study of subtle findings in CSC and have enhanced our understanding of the disease.

Perhaps the most important and clinically useful application of SD-OCT in CSC has been the ability to image the choroid with EDI OCT (Figure 7). EDI OCT can be performed with commercially available SD-OCT units. The choroid has been shown to be abnormally thick in CSC in both the affected and the fellow eye.80,130 In one study the mean age-adjusted choroidal thickness was 368 microns in CSC patients and 242 microns in controls.95 This thickening is thought to be related to choroidal vascular disease and the apparent choroidal hyperpermeability seen on ICG. Treatment response to PDT can be in part evaluated with EDI OCT, which typically shows about a 20% reduction in subfoveal choroidal thickness one year post-half fluence treatment.127,129

The thickness of the outer nuclear layer, as measured with SD-OCT, appears to correlate with acuity in CSC.133 In one study, the mean thickness was 74.6 µm in patients with resolved CSC and acuity worse than 20/20. It was 103 µm in CSC patients who saw 20/20 or better and 125 µm in normal age-matched controls. The distance from the internal limiting membrane to the external limiting membrane appears to be decreased in CSC, and this finding corresponds with outer nuclear layer thinning, possibly from photoreceptor apoptosis.132

SD-OCT has proven useful for the study of punctate precipitates and white material seen in as many as 65% of CSC eyes in the area of serous retinal detachment.101,128 These precipitates are hyperreflective on OCT and can be found both within the retina and in the subretinal space (Figure 8).134,203 The punctate precipitates and white material often occur together, suggesting that they are related substances. Numerous hypotheses about these substances are proposed: they may be accumulations of shed photoreceptor outer segments in the subretinal space, accumulations of fibrin or lipid, or macrophages clearing the subretinal space of such debris (see fundus autofluorescence section below).

OCT suggests that photoreceptor outer segments elongate in eyes with active serous detachment.132 Photoreceptor length is thought to correspond to the distance from the inner segment/outer segment (IS/OS) junction to the outermost retinal structure on SD-OCT. Outer segments may elongate on the outer surface of the detached retina when not apposed with the RPE and eventually shed into the subretinal space (Figures 9 and 10). This OCT finding is frequently present when punctate precipitates or white deposits are seen clinically.134

RPE abnormalities can also be readily imaged with SD-OCT. The area around a leak on FA frequently has a PED,54,141 sometimes with a detectable breach in the RPE layer that is believed to be the site of fluorescein transmission from the choroid. Asymptomatic
contralateral eyes, despite ostensibly normal macular raster scans, have been shown to have notable RPE abnormalities on en face RPE maps or c-scans. These RPE changes consist of multiple bumps, and they may represent early RPE decompensation.

OCT findings, particularly disruption of the IS/OS junction, correlate with acuity outcomes. Integrity of the IS/OS junction has been correlated with visual acuity in many macular diseases. Unsurprisingly, foveal thickness is less in affected eyes after resolution of fluid in chronic CSC than in fellow eyes, reflecting the risks of long term atrophy in CSC. Foveal thickness at presentation and after resolution appear to correlate with acuity outcomes. Those with more foveal thinning and atrophy have worse vision.

2. Fundus Autofluorescence—Fundus autofluorescence (FAF) is a novel imaging technique that relies on the autofluorescent properties of the breakdown products of cellular components, especially photoreceptor outer segments. While confocal systems such as the Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany) provide high resolution images by focusing on the RPE alone, non-confocal systems such as the Topcon retinal camera (Topcon Medical Systems, Oakland, New Jersey, USA) have the advantage of simultaneous imaging of the RPE and outer retina. The primary cellular breakdown product, lipofuscin, contains various fluorophores (such as the pyridinium bisretinoid A2E) that can release light when stimulated by light of specific wavelengths. Lipofuscin accumulates in RPE cells due to incomplete lysosomal degradation of photoreceptor outer segment disks. In the setting of age-related macular degeneration (AMD), hyperautofluorescence is often due to excessive accumulation of lipofuscin within the RPE, while hypoautofluorescence is frequently a result of RPE atrophy; however, the mechanisms of FAF change deserve separate consideration in the setting of CSC.

Autofluorescence often differs in acute versus chronic CSC. In acute CSC, there may be no FAF findings initially. Hyperautofluorescence characteristically develops within the area of subretinal fluid over months, although macular pigment may obscure FAF changes. The hyperautofluorescence tends to accumulate along the borders of the detachment, especially inferiorly and usually disappears with resolution of subretinal fluid in acute CSC. There also may be areas of hyperautofluorescence that correspond to punctate precipitates and white material seen on clinical exam (see SD-OCT section above). In chronic CSC, autofluorescence abnormalities reflect areas of chronic RPE damage or areas of active serous detachment. There are sometimes large areas of FAF changes or descending tracts consistent with past gravity-related guttering of subretinal fluid (Figure 5). FAF changes in chronic CSC have been characterized as granular or confluent hypoaurofluorescence and hyperautofluorescence. These patterns often coexist with areas with different degrees of RPE damage.

Spaide has postulated that areas of hyperautofluorescence seen in acute CSC are indicative of lipofuscin components within accumulating photoreceptor outer segments on the outer surface of the detached retina. The inability of the separated RPE to process old outer segments is thought to lead to increasing hyperautofluorescence with increased duration of serous retinal detachment. Spaide found that areas of hyperautofluorescence in CSC corresponded to areas of accumulation of material on the outer surface of the retina, as visualized with time-domain OCT. The thickness of this material was proportional to the amount of hyperautofluorescence. A more recent study using SD-OCT has proposed that these areas of thickened outer retina represent elongated photoreceptor outer segments. Accumulation of shed outer segments in subretinal fluid may explain the relative hyperautofluorescence seen at the inferior margin of serous retinal detachments.
The small granular/punctate areas of hyperautofluorescence seen in CSC correspond to the punctate subretinal white dots/precipitates seen clinically, and these may represent macrophages engorged with phagocytosed outer segments.\textsuperscript{134,203} While lipid and fibrin are proposed components of these white deposits, they do not autofluoresce and therefore do not explain the autofluorescent deposits. The punctate FAF findings correspond to hyperreflective lesions in the outer retina and subretinal space on OCT (Figure 8). Not all punctate precipitates are hyperautofluorescent, and those that do not autofluoresce may be composed of lipid or fibrin.

Accumulation of autofluorescent material in the subretinal space may contribute to RPE damage in CSC.\textsuperscript{128} A2-PE and A2E, autofluorescent byproducts of visual cycle proteins, have been shown to promote production of reactive oxygen species that would impact nearby RPE cells and photoreceptors.\textsuperscript{92}

In DRPE, advanced and irreversible FAF changes predominate. FAF changes highlight areas of RPE damage. Imamura and colleagues grouped significant hypoautofluorescence findings into three categories: granular hypoautofluorescence, confluent hypoautofluorescence, and descending tracts.\textsuperscript{81} In their large cohort, they found equal incidences of descending tracts from the macula and from the optic nerve head (9.1\% for each). OCT studies have shown that areas of hypoautofluorescence correlate with RPE atrophy and associated atrophy of the outer retina.\textsuperscript{203} The granular pattern of hypoautofluorescence appears to signify incomplete loss of RPE tissue.

While FAF imaging has shed light on the pathophysiology of CSC, this imaging modality has functional utility as well. Spaide and colleagues reported that normalized central macular FAF predicts visual acuity.\textsuperscript{203} Decreased central macular autofluorescence was associated with decreased visual acuity. In the largest retrospective cohort examining the correlation between FAF and visual acuity, both granular and confluent patterns of hypoautofluorescence were found to be strongly correlated with visual function.\textsuperscript{81} In that study, hyperautofluorescence did not reach a statistically significant correlation with acuity in multivariate prediction analyses.

Infrared (IR) and near infrared autofluorescence has been investigated in CSC.\textsuperscript{177} Sekiryu and colleagues also looked at the short-wave autofluorescent properties in CSC eyes. Areas of simultaneous punctate hyper-IR autofluorescence and hyper-short wave autofluorescence in CSC eyes are believed to signify RPE hyperplastic clumps, since hyper-IR autofluorescence may come from melanin while hyper-short wave autofluorescence appears to be associated with lipofuscin fluorophores. RPE clumping in these areas is consistent with OCT findings. Study of these modalities is in an early stage, and the significance of the findings at new wavelengths has yet to be fully elucidated.

3. Multifocal Electroretinography (mERG)—Studies using mERG indicate that there is more widespread retinal dysfunction in CSC than is appreciated on clinical exam. Marmor and Tan were among the first to investigate mERG in CSC, and they argued that mERG depression may extend beyond the border of observed serous detachment and could also be found in fellow eyes.\textsuperscript{126,147} Vajaranant and colleagues, however, found that mERG changes predominantly corresponded with areas of clinically apparent disease.\textsuperscript{219} mERG amplitudes improve markedly after resolution of subretinal fluid, but do not return to normal levels.\textsuperscript{38,210,211}

Multifocal ERG findings tend to correlate with function. Correlation between acuity, first order amplitudes, and implicit times has been documented.\textsuperscript{107,240} Implicit times in the paracentral rings correlate with OCT findings as well, including macular volume, area of

\textit{Surv Ophthalmol}. Author manuscript; available in PMC 2014 March 01.
subretinal fluid, and thickness of subretinal fluid. Given that mfERG correlates with activity and function in CSC, mfERG is a reasonable modality for documenting disease course and has been used as a primary outcome measure in a study of half dose verteporfin PDT for acute CSC. Significant improvements in OCT findings and vision at twelve months correlated with mfERG amplitude ratios.229

4. Microperimetry—Microperimetry allows for functional testing of different points in the macula, thereby providing more information about the health of the macula as a whole than visual acuity alone. Microperimetric data in CSC appears to correlate well with anatomic findings (Figure 11).

Ojima and colleagues compared microperimetry with SD-OCT and found that retinal sensitivity in areas of RPE irregularity or IS/OS disruption is significantly decreased.155 Microperimetry findings have also been successfully correlated with mfERG implicit times and visual acuity.94

Retinal sensitivity as measured with a microperimeter improves with treatment and with resolution of subretinal fluid.55,173,187 Sensitivity generally does not return to normal levels after resolution of subretinal fluid, even in patients with 20/20 visual acuity.159 This highlights the need to balance the risks and benefits of early treatment in eyes with persistent subretinal fluid.

5. Adaptive Optics—Adaptive optics (AO) is a technology that corrects for the optical aberrations of an eye and thereby allows for imaging of individual photoreceptors. A wavefront sensor detects higher order aberrations in the optical system, and a deformable mirror or another form of phase modulator corrects the aberrations.158 Ooto and colleagues have investigated CSC eyes with an AO scanning laser ophthalmoscope (SLO) device.158 They examined eyes with resolved subretinal fluid; most of their patients had acute CSC that resolved spontaneously. Eyes with resolved CSC had fewer cones per square millimeter than controls (31,290 +/- 14,300 at 0.2 mm from the fovea versus 67,900 +/- 9120 in controls).

They documented this dramatic loss of photoreceptors in a cohort where most patients (29/45) had 20/20 or better visual acuity. In fact, the cone density in CSC eyes with preserved IS/OS junctions was significantly less than controls (42,380 +/- 6,390 versus 67,900 +/- 9120 in controls). Cone density at 0.2 mm from the fovea correlated with visual acuity and also with OCT findings. CSC eyes with intact IS/OS junctions had greater average cone densities than CSC eyes with IS/OS junction gaps on OCT. There was no difference in cone density between eyes treated with PDT or focal laser and untreated eyes. The loss of photoreceptors, even in eyes with relatively good acuity, underscores the frequently subclinical functional loss that patients can experience after even a single episode of CSC.

III. TREATMENT

Acute CSC is typically a self-limited process.98 Recovery of visual acuity typically occurs within one to four months, coinciding with reattachment of the neurosensory retina, with few recognized visual sequelae.98,148,239 Recurrences are common, however, occurring in approximately 30–50% of patients by one year.121 Patients with frequent recurrences or chronic neurosensory retinal detachment may develop RPE atrophy and neurosensory retinal changes that result in permanent loss of visual function, including visual acuity, color vision, and contrast sensitivity.14,23,50,103,122 Although the terms classic CSC and DRPE seem to be more helpful in determining treatment approaches, the terms acute and chronic (fluid persisting >3 months) will be used in this discussion.
Observation is the standard initial management in most cases of acute or classic CSC, but there are instances when treatment may be desirable. These include cases of CSC with persistent macular subretinal fluid or reduced visual acuity, cases in which rapid recovery of vision is required for vocational or other reasons, and also where untreated CSC has previously resulted in a poor visual outcome in the fellow eye. Treatment should also be considered in patients who experience multiple recurrences.

The aims of treatment of CSC are to induce reattachment of the neurosensory retina, improve or preserve visual acuity, and prevent recurrences. It is important to consider the temporal course of the fluid and the RPE status when choosing among different treatment options. Treatment of DRPE cases may not offer significant visual benefit if RPE atrophy and photoreceptor damage is extensive, but may prevent further toxicity to the photoreceptors in the setting of chronic fluid. CNV can arise in the setting of CSC and requires rapid detection and treatment. Retinal hemorrhage and lipid in conjunction with subretinal fluid suggest CNV may be present. Diagnostic fluorescein or indocyanine green angiography can confirm the presence of CNV.

Only limited randomized clinical trials evaluating CSC treatment modalities have been performed, but they are critical for guiding evidence-based treatment. Non-randomized trials are less helpful for providing definitive data regarding efficacy given the waxing and waning course of CSC. Several pilot studies provide insight about the feasibility of larger trials. In the following discussion the quality of the evidence for a particular intervention is rated as good, fair, or poor based on the U.S. Preventive Task Force definitions (Table 1).1

A. Observation and Risk Factor modification (Quality of Evidence – Fair)

Management of classic CSC usually involves careful observation with risk factor modification. In most cases, a three month period is acceptable to allow subretinal fluid to resolve spontaneously.98,236 Visual acuity characteristically returns to normal after a first episode.

Risk factor modification most frequently consists of discontinuing corticosteroid use (see section below). Other risk factor modifications have been proposed. As CSC has been associated with high baseline cortisol levels and Type A personalities, it has been suggested that activities to reduce overall stress levels may be of benefit; however, their utility has not been established.61,75,139,198,213,216,231

Obstructive sleep apnea has been associated with CSC, possibly because some patients with sleep apnea have higher basal levels of endogenous catecholamines.99,111 Interestingly, one report demonstrated a rapid (one week) resolution in a patient with bilateral CSC after starting treatment with a continuous positive airway pressure machine.85

Use of 5-phosphodiesterase inhibitors (eg., sildenafil and tadalafil) has been associated with CSC.4,52 Although some improved after stopping such medications, the only large study of this association, a case control study with 577 cases, failed to confirm an association.53

B. Discontinuation of Steroids (Quality of Evidence – Good)

Given the association between steroid use and CSC, discontinuation of such treatment when practical is warranted to aid resolution of CSC and prevent complications of chronic disease.32,73 In 1966 Jain and Singh described a case of CSC that resolved after stopping oral steroids prescribed to treat Reiter syndrome.86 Several subsequent case reports demonstrated a link between reduction or discontinuation of systemic corticosteroids and resolution of CSC.2,112,166,223,227 The largest series to date was a noncomparative case series of 24 eyes with CSC, most of which were initially misdiagnosed and therefore
inappropriately on systemic steroids. Nearly 90% had resolution of subretinal fluid and RPE leaks after discontinuation of steroids, with approximately 14% of eyes requiring adjunctive laser photocoagulation.\(^{189}\)

Although there are no randomized trials of steroid discontinuation for CSC, a consensus has developed about the role of corticosteroids in CSC based on epidemiologic data (discussed previously), case series, and challenge/re-challenge reports. Further study in the form of large clinical trials are unlikely.

For patients using glucocorticosteroids, consultation with the prescribing physician is necessary to manage discontinuation or taper of these medications.\(^{87, 112}\) Steroid-sparing agents may be of utility in patients requiring long-term immunomodulation. Nasal sprays,\(^{71}\) joint injections,\(^{6, 12, 90, 143}\) and steroid skin creams\(^{47, 48, 89}\) have been associated with disease, and we routinely counsel patients to discontinue such medications if medically possible.

C. Helicobacter Pylori Treatment (Quality of Evidence – Poor)

As discussed above, Helicobacter pylori (\(H.\) pylori) infection has recently been implicated in the pathophysiology of CSC\(^{3, 64, 135}\). Some, therefore, have recommended testing and treatment of concomitant H. pylori infection in patients with CSC.\(^{65}\) The first report suggesting a relationship between H. pylori infection and CSC was a case report that described a patient with chronic recurrent CSC that seemed to wax and wane with infection and re-treatment.\(^{64}\) The one, randomized, unmasked trial of H. pylori treatment is discussed above.\(^{168}\).

D. Anti-glucocorticosteroids (Quality of Evidence – Poor)

Patients with CSC commonly have elevated levels of serum cortisol,\(^{57, 72, 244}\) resulting in trials of medications targeting cortisol pathways.\(^{87}\) This includes ketoconazole, mifepristone (RU486), finasteride, rifampin, and anti-adrenergics. There have been no randomized, controlled trials of these medications for CSC.

Ketoconazole, an anti-fungal agent, has been investigated by two groups as a treatment for CSC.\(^{66, 137}\) Ketoconazole interferes with endogenous glucocorticoid production in part by inhibiting the conversion of 11\(\beta\)-deoxycortisol to cortisol. Golshahi and colleagues retrospectively investigated ketoconazole (200 mg daily) in patients with new onset subretinal fluid, either as a first episode or a recurrence. They compared 15 study patients to 15 historical controls and found no difference between the two groups in terms of visual acuity or OCT parameters. Meyerle and colleagues prospectively studied five patients with chronic CSC in an uncontrolled pilot study. They used a higher dose (600 mg daily) and showed reduced serum cortisol levels, stable acuity, and anatomic improvement at 8 weeks.

Nielsen and colleagues investigate oral mifepristone, an abortefacient with glucocorticoid receptor antagonist properties in 16 chronic CSC subjects.\(^{150}\) Some patients responded well to the treatment, but the overall results were mixed. Seven subjects (44%) gained 5 or more letters after 12 weeks of treatment, and 7 subjects had improved OCT findings.

Finasteride, which is FDA-approved for benign prostatic hypertrophy (BPH) and male-pattern hair loss, is a 5-alpha-reductase inhibitor. 5-alpha-reductase converts testosterone to the potent androgen dihydrotestosterone (DHT). Given the overwhelmingly male demographics of CSC and its relationship to steroid hormones, this oral anti-androgen treatment has been investigated in CSC. In a pilot study of 5 patients with chronic CSC, the central subfield macular thickness, subretinal fluid volume, and serum DHT declined.\(^{51}\) The changes in center-subfield macular thickness and subretinal fluid volume paralleled serum DHT concentrations. Interestingly, subretinal fluid volume worsened in four out of five...
participants following discontinuation of finasteride. Three out of these four participants qualified for repeat finasteride treatment according to the investigational protocol, and when finasteride was re-instituted all of these participants experienced a reduction in subretinal fluid volume. A phase II, randomized trial sponsored by the National Eye Institute will provide more definitive data. Rifampin, another oral agent that proposed as a treatment of CSC, is thought to suppress endogenous glucocorticoid production, but has only been investigated in a small series.\textsuperscript{169,207}

The rationale for adrenergic blockade to treat CSC is that CSC patients seem to have high serum catecholamine levels. Glucocorticosteroid use may affect adrenergic pathways by increasing expression of adrenergic receptors.\textsuperscript{69,181} Furthermore, Yoshioka’s monkey model suggest that inhibition of adrenergic receptors, particularly alpha receptors, prevents development of experimental CSC.\textsuperscript{243} Beta-blocking agents have therefore been investigated for CSC, but have not proven effective.\textsuperscript{22,166} There is one early report of prompt resolution of chronic CSC with an alpha blocking agent, but this has not been confirmed.\textsuperscript{76}

E. \textbf{Carbonic Anhydrase Inhibitors (Quality of Evidence \textendash Poor)}

Oral acetazolamide has been investigated as a treatment for CSC on the basis that inhibition of carbonic anhydrase IV in the RPE seems to promote resorption of subretinal fluid and retinal adhesion.\textsuperscript{43,208,228} The only clinical study to date investigating acetazolamide is a comparative, non-randomized, cohort study of 15 patients with acute CSC treated with acetazolamide compared to seven controls.\textsuperscript{164} Patients treated with acetazolamide had faster subjective improvements and resorption of subretinal fluid, with a mean time to resolution of 3.3 ± 1.1 weeks in the treatment group and 7.7 ± 1.5 weeks in the control group (\(P < 0.0001\)). There was no detectable difference in final visual acuity or recurrence rates between the two groups.

F. \textbf{Anti-VEGF Agents (Quality of Evidence \textendash Poor)}

Anti-VEGF agents are not considered first-line treatments for either acute or chronic CSC, but several small trials have yielded suggestive results. Although VEGF levels are not elevated in aqueous samples from CSC eyes,\textsuperscript{114,192} some have hypothesized that hypoxic conditions in the choroid or RPE could lead to compartmentalized VEGF expression not detected in aqueous samples. Given this hypothesis and the remarkable success of these drugs in other disorders, numerous small trials have been undertaken.

1. \textbf{Randomized, Controlled Trials}—There are two small, randomized trials of anti-VEGF agents for CSC. The first was a trial of a single 1.25 mg bevacizumab injection in eyes with subretinal fluid for less than three months, most of which were experiencing recurrences. There was no difference in the clinical course of the 12 study eyes and the 12 controls.\textsuperscript{115} They did not report time to resolution of subretinal fluid, and the single injection design may be a limitation.

Bae and colleagues compared half-fluence PDT to intravitreal ranibizumab (0.5 mg) in a randomized trial of 16 eyes with chronic CSC (defined as recurrent CSC or persistent fluid for greater than six months).\textsuperscript{11} Visual acuity improved in both groups, but only two of 8 eyes in the ranibizumab group became fluid free after three months of treatment versus 6 of 8 PDT-treated eyes. These findings in this small study suggest that half-fluence PDT may be superior to intravitreal ranibizumab as a treatment for chronic CSC and requires further investigation.
2. Other Studies—Many uncontrolled studies report favorable results for intravitreal bevacizumab in CSC, \(^7,8,10,11,18,117,118,183,188,217\) and some comparative studies suggest a need for further study. \(^9,109,115\) Artunay and colleagues conducted a prospective, controlled, open-label, nonrandomized, trial of a single 2.5 mg intravitreal bevacizumab injection in thirty previously untreated eyes with chronic CSC. \(^9\) Treated eyes had a significantly better rate of stability or improvement in acuity (15/15 vs. 10/15 at 6 months) and a significantly higher rate of fluid resolution. A retrospective study comparing as needed bevacizumab injections to PDT for chronic CSC revealed similar improvements in acuity, greater foveal thinning in PDT eyes, and more fluid recurrence in injected eyes. \(^109\) The largest series published to date of intravitreal bevacizumab treatment for CSC included mostly patients having a first episode of CSC with a mean duration of about four months. \(^117\) Most patients (82.5%) had resolution of subretinal fluid with one or two injections. Classic CSC has a largely favorable natural history, so the lack of controls in this study is significant. An uncontrolled series of ten acute CSC eyes showed favorable anatomical and visual results. \(^188\)

Anti-VEGF agents have a clearer role in eyes with CSC-related CNV. Intravitreal bevacizumab has been used successfully for CNV of diverse etiologies, \(^67\) and several reports confirm its utility for CSC-related CNV. \(^34,123,145,165\) Similarly, ranibizumab appears to be effective in the treatment of CSC-related CNV. \(^31,102\)

G. Aspirin (Quality of Evidence – Poor)

Previous work has shown that patients with CSC demonstrate increased levels of plasminogen activator inhibitor compared to controls. \(^79,232\) This finding has led to a hypothesis that hypercoagulability plays a role in CSC pathogenesis. A study by Caccavale and colleagues investigated an aspirin regimen (100mg daily for 1 month followed by 100mg on alternating days for 5 months) in 109 patients. \(^27\) In this non-randomized, open label case series, aspirin appeared to hasten recovery of acuity, reduce the rate of recurrence, and result in a slightly better visual outcome (logMAR +0.07 +/- 0.13 or Snellen 20/23 versus +0.17 +/- 0.13 or 20/30, \(P<0.0001\) at 2 years) in a comparison with a historical control group.

H. Laser Photocoagulation (Quality of Evidence – Good)

Focal laser photocoagulation is commonly used to expedite the absorption of subretinal fluid in acute and chronic CSC. Some reports indicate that laser treatment is associated with a decreased rate of recurrences, but this remains controversial (see below). Typically, laser burns are applied to areas of focal leakage that have been identified on FA as the principal sources of subretinal fluid. The mechanism of subretinal fluid resolution after laser photocoagulation treatment is not known; photocoagulation may seal focal defects in the RPE monolayer, promote a healing response and recruitment of healthy RPE cells, or directly stimulate pumping function of RPE cells near the leak. Although the first reports of thermal laser for acute CSC described the use of the xenon laser, the argon laser is used more commonly. \(^142\)

1. Randomized, Controlled Trials—Leaver and Williams in 1979 reported faster resolution of subretinal fluid (6 vs. 16 weeks, \(P<0.001\)) in eyes treated with focal argon laser photocoagulation to the leakage site. \(^108\) This randomized trial included 70 eyes with subfoveal fluid and acuity of 6/12 or better. No duration of disease was stipulated, although minimal apparent RPE disease was required. They did not find a visual acuity benefit in the treatment group at six months.
Robertson and Ilstrup studied 42 eyes with “recent onset” CSC in a randomized, controlled trial comparing argon laser photocoagulation of the leakage site (“direct”) to sham treatment or treatment away from the leakage site (“indirect”). Just seven eyes underwent direct treatment, but they had a shorter duration of neurosensory retinal detachment (6 +/- 2.2 weeks) compared to the control groups (13.2 +/- 6.1 weeks for indirect and 16.3 weeks +/- 6.3 weeks for sham). Direct laser was not, however, directly compared with sham as direct laser was only given to eyes with extramacular leakage sites. No recurrences occurred over the 18 month follow-up period in the direct treatment eyes.

2. Other Studies—Burumcek and colleagues conducted a non-randomized study of laser versus observation in 45 eyes. They found a shorter time to fluid resolution and fewer recurrences in the laser group than in an untreated comparison group. They also reported a better final visual acuity in the treated group over almost 5 years of follow-up.

While the time to fluid absorption is consistently less in laser trials, reported recurrence rates after focal laser have varied. Ficker and colleagues reported the long-term follow-up of the Leaver and Williams study. While just 44 eyes were available for long-term analysis, follow-up ranged from 6.4 years to 12.1 years. Recurrence rates were similar between the two groups (53% of controls and 44% of treated eyes, P=0.79). Final acuity and color discrimination were also similar. Two treated eyes developed extrafoveal CNV at the treatment site, but both eyes maintained excellent vision without further treatment for CNV. Drawbacks of this study include the number of patients lost to follow-up and limited power.

Brancato and colleagues reported a comparative series of 87 eyes with a mean of about eight years follow-up. The recurrence rate in the treated group was 40.5%, and in control eyes it was 42%. A retrospective study of 157 cases by Gilbert and colleagues also found no difference in long-term outcomes with laser.

For chronic CSC, laser treatment to areas of leakage may decrease the amount of subretinal fluid. Yannuzzi and colleagues reported an uncontrolled series of 18 DRPE eyes treated with grid laser in areas of leakage, finding high rates of resolution of macular detachment and vision stability. These findings have not been confirmed in controlled studies, and there is some concern that grid laser to areas of damaged RPE may further impair RPE function. Focal laser does not appear to have a role in CSC with bullous serous detachment.

Some general guidelines should be followed when planning laser treatment for CSC. Leakage sites should be greater than 375 µm from the fovea, and treatment should be performed with reference to a current FA. Other considerations include the duration of the attack (as fluid often resolves spontaneously), status of the fellow eye, and the patient’s life circumstances and desire for treatment. Treatment sites need to be monitored long-term for CNV. Leakage not amenable to laser, including subfoveal leaks and diffuse leakage, may be amenable to other treatment modalities (see below).

I. Photodynamic Therapy (Quality of Evidence – Good)

Verteporfin photodynamic therapy (PDT) has shown promise for not only promoting resolution of acute CSC but also preventing recurrences. Studies in chronic disease have yielded favorable results as well. The ICG finding of mid-phase hyperfluorescent choroidal plaques consistent with choroidal hyperpermeability suggests that treatment targeted at the choroidal vasculature might address the root cause of the disease. Treatment successes in early reports in 2003 using standard, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) protocol PDT led to larger studies of standard PDT and eventually to numerous studies of reduced fluence PDT for CSC.
1. Randomized, Controlled Trial—Chan and colleagues performed a randomized, double-masked, controlled trial of half dose PDT versus placebo in 63 eyes with acute CSC.35 Participants had a baseline acuity of 20/200 or better and a duration of subretinal fluid of less than three months. All participants were experiencing either a first or second episode, and pregnant patients and those with exogenous corticosteroid exposure were excluded. In this report, 37 of 39 (94.9%) patients in the PDT group did not have subretinal fluid on OCT at one year compared to only 11 of 21 (57.9%) in the placebo group ($P=0.001$), suggesting that half dose PDT may be preferable to observation even in acute cases. Visual acuity was stable or improved in all patients in the PDT group compared to 78.9% of those in the placebo group. Although this is not a sufficient sample size to establish safety in this patient population, no adverse events occurred. Wu and colleagues reported mfERG results from a subset of the same study.229 Amongst 34 eligible eyes in the substudy, the P1 amplitudes in rings one and two were significantly greater in treated eyes ($P = 0.030$ and $P = 0.018$). N1 amplitudes were not significantly different.

2. Other Studies—The largest series of standard fluence PDT to date suggest a beneficial treatment effect. Yannuzzi and colleagues used ICG-guided PDT in 20 eyes with chronic CSC, and treatment led to complete resolution of macular detachment in 60% of eyes, with stable or improved vision in all eyes over 6.8 months follow-up.238 Ruiz-Moreno and colleagues have reported a series of 82 eyes with chronic CSC treated with standard PDT.180 All 82 eyes had complete resolution of subretinal fluid. Thirteen were treated more than once. There was a statistically significant improvement in acuity for the cohort (mean gain of 1.9 +/− 2.4 Snellen lines). Two patients developed CNV in the follow-up period, and nine eyes developed RPE hyperplasia at the treatment site. Moon and colleagues treated 41 eyes, mostly with persistent first episodes of CSC, with standard PDT and found 88% fluid resolution at 4–6 weeks.146 They compared PDT-treated eyes with a retrospective control group of eyes treated with focal laser for extrafoveal leaks. There was a significantly greater rate of foveal RPE atrophy in the PDT group. In some eyes, foveal RPE atrophy was progressive after PDT and associated with vision loss. Ozment and colleagues demonstrated that fundus autofluorescence intensity increased following standard PDT and returned to baseline when subretinal fluid resolved.160

Risks of PDT include choroidal ischemia, RPE atrophy, and iatrogenic CNV.104,106,170,171,226 RPE rip has also been reported after PDT for CSC.93 The risks of PDT are thought to be decreased when reduced fluence PDT is used. Reduced fluence treatment involves decreasing the laser treatment time, lowering power to reduce energy output, or altering the interval between infusion and laser treatment. Reduced dose PDT, as in the randomized trial above, is also used. Several groups have evaluated the utility of reduced fluence PDT, and two have compared full fluence to half fluence. Reibaldi and colleagues treated 19 eyes with chronic CSC with standard fluence PDT and 23 with half fluence.172 They found no difference in the rate of vision improvement or fluid resolution. One eye in the standard group developed CNV in the follow-up period, and eight had severe choriocapillaris non-perfusion in the treated area. These complications did not occur in the low fluence group. Shin and colleagues retrospectively reported similar results in 67 eyes, and the half fluence group avoided the choriocapillaris hyperperfusion and retinal atrophy seen in the standard treatment group.191 Numerous other small trials of reduced dose or reduced fluence PDT have found favorable results.7,116,179,193

PDT has been shown to induce choroidal vascular remodeling and thinning of treated choroid.131,184 In CSC, even half-fluence PDT has been shown to reduce choroidal vascular congestion and decrease subfoveal choroidal thickness.127,129 Mid-phase ICG plaques, suggestive of choroidal hyperpermeability, disappear after treatment with PDT but not after successful treatment with focal laser. Microperimetry studies indicate functional benefit in
CSC eyes treated with half-fluence PDT, even when no visual acuity improvement has occurred.\textsuperscript{46,55,187}

Maruko and colleagues report a case of excessive iatrogenic choroidal thinning after half fluence PDT in an elderly patient who went from 321 µm pre-treatment to 64 µm at twelve months.\textsuperscript{129} Visual acuity nonetheless improved over the same period. Elderly patients may be at risk for severe choroidal thinning with PDT.\textsuperscript{125}

Zhao and colleagues tested various verteporfin doses in the treatment of acute CSC and concluded that a 30% dose may be optimal.\textsuperscript{245} Patients treated with 30–70% doses (5 patients) had complete resolution of fluid, while 10% and 20% doses (3 patients) required re-treatment. An additional seven patients had successful anatomic resolution with 30% dosing. These findings require confirmation in larger trials.

Although PDT has mainly been used to treat acute or chronic subretinal fluid from CSC, PDT has also been described in the treatment of PED. To date there are two case reports describing PDT for chronic PED.\textsuperscript{37} Chang and colleagues describe a case of a chronic PED without concomitant subretinal fluid in a patient with 20/50 vision.\textsuperscript{37} After full fluence PDT the PED resolved with recovery of vision to 20/20 at 14 weeks post-PDT. However, caution must be exercised in the setting of large PEDs as there is a risk of RPE rip.

Performing PDT in CSC eyes often involves ICG angiogram guidance. Areas of presumed choroidal hyperpermeability (hyperfluorescent plaques on mid-phase ICG) are identified and treated with a spot size large enough to cover the plaque when practical. If there is diffuse involvement of the posterior pole, the spot is moved during the treatment to cover more territory. Areas of severe RPE loss should be avoided given past reports of RPE atrophy with PDT treatment. The absence of characteristic plaques on ICG may predict a poor response to PDT.\textsuperscript{84} Use of FA guidance rather than ICG guidance for PDT has been reported in a small series with favorable results.\textsuperscript{105}

**J. Diode Micropulse Laser (Quality of Evidence – Poor)**

Diode micropulse laser treatment targets a series of ultrashort 810 nm laser pulses at the tissue of interest.\textsuperscript{196} These repetitive bursts allow for lower total energy use, and they help minimize damage to surrounding tissues from harmful thermal effects. In CSC the laser targets focal leaks at the level of the RPE. Retina-sparing photocoagulation is of particular interest in CSC given the frequent proximity of leaks to the fovea. One of the challenges of diode micropulse laser treatment is that no visible burn is created, and the surgeon is not able to visually confirm laser uptake. Ricci and colleagues have attempted to overcome this drawback with ICG-guided diode laser treatment.\textsuperscript{174,175}

1. **Randomized, Controlled Trial**—Verma and colleagues randomized acute CSC patients with a single focal leak to diode micropulse laser or standard argon laser photocoagulation.\textsuperscript{220} All 30 eyes had resolution of fluid and similar final visual acuities at twelve weeks, but the diode group had significantly better final contrast sensitivity. Patients reported no persistent scotomata (versus 3/15 with a persistent scotoma in the argon group). The primary outcome measure for this study is not specified.

2. **Other Studies**—Diode laser for CSC was first described by Bandello and colleagues in 2003, who treated five patients who had complete fluid resolution within one month.\textsuperscript{13} Subsequently, Chen and colleagues reported a series of 26 eyes in which 14 of 15 eyes with focal leaks had fluid resolution, and just 5 of 11 eyes with diffuse leakage cleared all fluid.\textsuperscript{39}
The ICG-assisted technique of Ricci and colleagues deserves separate mention because it is thought to benefit from RPE uptake of the ICG molecule, which has an absorption peak at 805–810 nm. The 810 nm diode laser energy would therefore be absorbed by ICG molecules, allowing for a more targeted treatment. Furthermore, post-operative imaging with an ICG filter allows for confirmation that the laser spots have treated the desired area. Ricci and colleagues have reported a series of seven eyes with persistent subretinal fluid, all of which were fluid free at one year post-treatment.

K. Transpupillary Thermotherapy (TTT) (Quality of Evidence – Poor)

TTT is a long-pulse, low-energy, 810 nm near-infrared laser used in the treatment of choroidal tumours. TTT is purported to induce choroidal vascular thrombosis by raising the temperature of the choroid. Some authors argue that TTT offers an option for treatment in cases where the site of focal leakage is juxtafoveal and therefore unsafe to treat with thermal laser. The utility of TTT in treating chronic CSC has been investigated in a handful of small studies.

Wei and colleagues were the first to report the use of TTT for CSC, describing the complete resolution of subretinal fluid four weeks after TTT in a case of chronic CSC with no observed visual improvement. In a case series of 14 patients with chronic, macula-involving CSC, Hussain and colleagues reported resolution of subretinal fluid on OCT in 64% of eyes at one month and 79% at two and three months, with approximately 50% demonstrating three lines of visual gain and 86% achieving 20/40 vision or better.

In the largest study to date, Shukla and colleagues investigated TTT in chronic CSC. In this unmasked, nonrandomized, prospective cohort study, 25 eyes were treated with TTT (with a spot diameter of 0.5mm for 60 seconds) and were compared to an unmatched control group of 15 eyes which were observed. In the group treated with TTT, 84% experienced complete resolution of neurosensory retinal detachment and focal leakage on FA at one month, rising to 96% at three months. One patient developed CNV. Visual acuity improved by one line or more in 92% of cases compared to 33% of the control group, with 88% of TTT treated eyes attaining 20/30 vision or better. At baseline, controls had a longer duration of disease, and the outcomes of controls were likely negatively impacted by this difference. Given the lack of well-controlled, long-term studies demonstrating safety and efficacy of TTT, the precise role for TTT in the management of CSC remains to be defined.

IV. CONCLUSION

Recent technological advances have fostered collaborative efforts leading to a greater understanding of the pathogenesis of CSC. Advances in imaging techniques have not only resulted in more accurate phenotyping essential for diagnosis and management, but have also provided the foundation for the development of new treatments. Gass was ahead of his time when he emphasized the primary role of the choroid, as opposed to the retina, in CSC and coined the term central serous chorioretinopathy. Today, choroidal disease in CSC is widely accepted with widespread use of ICG angiography. OCT, and particularly EDI OCT, has confirmed his hypothesis by implicating a thickened and engorged choroid. Fundus autofluorescence (FAF) has also established a critical role for diagnosis and monitoring, and provided pathophysiological insights.

The application of adaptive optics, mfERG, microperimetry, and contrast sensitivity testing demonstrates that patients with even a mild course suffer significant anatomic and functional loss that was previously undetected. While focal laser and PDT are the current standard of care for persistent subretinal fluid in CSC, these treatments are not appropriate in all cases and the optimal timing of intervention with these modalities remains unclear. Recent
imaging findings illustrating subclinical damage put a new onus on the ophthalmic community to develop treatments that are effective at the earliest sign of disease to prevent photoreceptor damage.

V. METHOD OF LITERATURE SEARCH

In preparing this review, we conducted a systematic review of the literature using PubMed® databases with the following search terms: “central serous retinopathy,” “central serous chorioretinopathy,” and “central serous.” We included case reports only if they contributed new information about characteristics, diagnosis, or treatment of the disease.

REFERENCES


Figure 1.
Cystoid macular edema in end-stage CSC. (A) Time-domain OCT of an eye with CSC and subretinal fluid (between arrows). Best-corrected visual acuity is 20/40. (B) SD-OCT of the same eye four years later, now with cystoid macular edema (arrows), subretinal fluid, and best-corrected visual acuity of 20/400. The eye had not responded to two PDT treatments, multiple anti-VEGF injections, and a trial of oral acetazolamide. CNV had been ruled out with fluorescein angiography and indocyanine green angiography. (C) SD-OCT of the same eye one month later. Macular atrophy is apparent after spontaneous resolution of cystoid edema. Best-corrected visual acuity is 20/500.
Figure 2.
Fluorescein angiogram demonstrating a single pinpoint leak at twenty seconds (A) and ten minutes (B).
Figure 3.
Fluorescein angiogram showing a smokestack leakage pattern at thirty seconds, two minutes, and five minutes.
Figure 4.
Fluorescein angiogram of an asymptomatic eye with extramacular evidence of CSC.
Figure 5.
Fundus autofluorescence (FAF) of a descending tract in CSC. The marked hypoautofluorescence suggests chronic disease and irreversible RPE damage. There is also a hyperfluorescent ring superiorly due to a retinal pigment epithelial detachment.
Figure 6.
Numerous hyperfluorescent plaques on mid-phase indocyanine green (ICG) angiography demonstrating inner choroidal staining.
Figure 7.
(A) Enhanced depth imaging (EDI) OCT of an area with CSC-related subretinal fluid. The choroid is abnormally thick (502 microns). (B) Corresponding FAF in which a line shows the location of the EDI OCT. Note central hypoautofluorescence and surrounding hyperautofluorescence suggestive of RPE damage.
Figure 8.
Punctate hyperautofluorescence resulting in a granular appearance on FAF (A, arrow) often corresponds to hyperreflective lesions in the outer retina (B, arrow) and subretinal space on OCT. They have been hypothesized to be macrophages engorged with phagocytosed outer segments.
Figure 9.
SD-OCT of a fovea-involving a serous retinal detachment in a patient with acute CSC. Note the lack of significant reflective debris on the outer retina or in the subretinal space.
(A) SD-OCT from the initial visit of a patient who had symptoms of CSC for ten months. Note the accumulation of material on the outer retina (arrow). This accumulation is thought to represent shed photoreceptor outer segments, engorged macrophages, and other inflammatory debris such as fibrin. (B) SD-OCT of the same eye two months later showing that the accumulation of this material has increased (arrow), perhaps due to elongation of outer segments.

Figure 10.
Figure 11.
(A) Fundus autofluorescence (FAF) showing several paramacular areas of autofluorescence abnormalities. The hypoautofluorescent descending tract inferotemporal to the macula represents the area of greatest RPE damage. (B) A microperimetry pattern used to study the inferior macula and mid-periphery shows decreased sensitivity in the areas of autofluorescence abnormality, with a particularly dense scotoma in the area of the descending tract seen in (A). Units are decibels.
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<tr>
<th>Quality of Evidence, U.S. Preventive Services Task Force Definitions</th>
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<tr>
<td><strong>Good</strong> Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes</td>
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<tr>
<td><strong>Fair</strong> Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes</td>
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<td><strong>Poor</strong> Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.</td>
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