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Adoption of Innovation in Herpes Simplex Virus Keratitis

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Abstract: Herpes simplex keratitis, caused primarily by human herpes simplex virus type 1 (HSV-1), remains the most common infectious cause of unilateral blindness and vision impairment in the industrialized world. Major advances in the care of HSV keratitis have been driven in large part by the landmark Herpetic Eye Disease Study randomized clinical trials, which were among the first in ophthalmology to reflect emerging trial conventions, including multicenter subject enrollment, double-masking, placebo controls, and a priori sample size determinations. The results of these trials now form much of the evidence basis for the management of this disease. However, management patterns in clinical practice often deviate from evidence-based care. These perceived quality gaps have given rise to the evolving field of implementation science, which is concerned with the methods of promoting the application of evidence-based medicine within routine care. To overcome variations in the quality and consistency of care for HSV keratitis, a range of clinical- and technology-based innovations are proposed. The most pressing needs include the following: a rational and tractable disease classification scheme that provides an immediate link between the anatomical localization of disease (corneal epithelial, stromal, or endothelial) and the appropriate treatment, and the actualization of an electronic medical record system capable of providing evidence-based treatment algorithms at relevant points of care. The latter would also input data to population-wide disease registries to identify implementation-rich targets for quality improvement, education, and research. These innovations may allow us to reduce the human and economic burdens of this highly morbid, and often blinding, disease.

Key Words: herpes simplex virus, keratitis, classification, implementation, diffusion of innovations

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> "But there were also other fevers… Many had their mouths affected with aphthous ulcerations. There were also many defluxions about the genital parts, ulcerations, and boils (phymata), externally and internally, about the groins. Watery ophthalmies of chronic character, with pains and fungous excrescences of the eyelids, externally and internally, called fig, which destroyed the sight of many persons."
> —Hippocrates, Book II Section III, *Of the Epidemics* (c. 400 BCE), translated by Francis Adams[1]

Since antiquity, infections caused by the human herpes simplex virus (HSV) have presented a significant diagnostic and therapeutic challenge for physicians. The first possible descriptions of HSV infections were documented by ancient Greek scholars such as Hippocrates (c. 460 BCE to c. 375 BCE), who used the term "herpes" to describe skin lesions which would "creep" or "crawl" over affected areas.[2–4] Medical, cultural, and even political references to such orocutaneous eruptions would appear thereafter, from the Roman emperor Tiberius forbidding the act of kissing during his reign (14–37 AD)[5,6] to Shakespeare's description of lesions arising "O'er ladies' lips… with blisters plagues" in his tragedy *Romeo and Juliet*.[7] It was not until the mid to late 19th century that an infectious agent was implicated, with the work of a French dermatologist Vidal[8] demonstrating human transmission by the induction of herpetic vesicles in healthy subjects after inoculation with infected fluid. The corneal manifestations of HSV infection also gained recognition around this time,[9] with Swiss ophthalmologists Horner and Emmert describing "herpes corneal febrilis"[10,11] and "dendritic keratitis"[12] respectively, both characterized by a nonspecific prodrome of fever and coryza, followed by vision-reducing corneal disease. HSV was later successfully isolated in experimental rabbit models of herpetic keratitis performed by Löwenstein,[13] Gruter,[14] and Lipshütz.[15] These early investigations at the turn of the 20th century laid the foundation for our current understanding of HSV infections.

HSV keratitis remains a leading infectious cause of blindness worldwide.[16] Where ancient Greek physicians may have once treated ocular maledictions with bloodletting and wine to restore the capricious balance of the body's humors,[17]

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great strides have been made in establishing the evidence basis for the care of HSV keratitis. Specifically, the landmark Herpetic Eye Disease Study (HEDS), conducted from the late 1980s to the 1990s, provides guidance as to the role of antiviral therapy and topical corticosteroids in the treatment of, and prophylaxis for, the varied presentations of HSV keratitis. However, patterns of clinical care often radically diverge from what is considered "best practice."[18–20] This disparity has given rise to the field of implementation science, which is principally concerned with methods to systematically translate the evidence basis for any condition into routine care.[21,22] Using this framework, we propose a range of clinical innovations to reduce the global burden of HSV keratitis. These include the introduction of a standardized system of disease classification and the resolution of age-old "eminence-based" teachings that may conflict with current best practice. Furthermore, the actualization of a "living," machine learning–enabled electronic medical record (EMR) would support evidence-based medicine by providing clinicians with point-of-care access to validated diagnostic and management algorithms, in addition to autopopulating disease registries to identify the unmet needs in continuing medical education and research.[23] Together, the widespread adoption of these clinical innovations could change the trajectory of overall care for this ancient, highly morbid disease.

CURRENT CARE FOR HSV KERATITIS

The Human Herpes Simplex Viruses

Virus taxonomy is determined by phylogenetic comparisons of validated, whole viral genomes, and is overseen by the International Committee on Taxonomy of Viruses (ICTV).[24] In 2009, the ICTV reclassified herpesviruses into the order *Herpesvirales*,[25] comprising hundreds of closely related viruses, all sharing a double-stranded DNA genome, a 20-faceted icosahedral capsid, a surrounding proteinaceous tegument, and an external glycoprotein-laden lipid envelope.[24,26] Nine species of these viruses are known to infect humans (Fig. 1).[27–29] HSV type 1 (*human herpesvirus 1*, HSV-1) and HSV type 2 (*human herpesvirus 2*, HSV-2), of family *Herpesviridae*, subfamily *Alphaherpesvirinae*, and genus *Simplexvirus*, share 40% to 50% nucleotide sequence homology[30] and cause a wide array of diseases because of their broad tissue tropisms. These include orofacial and genital mucocutaneous infections, meningoencephalitis, varied presentations of ocular disease, and visceral invasion, the latter occurring in association with severe immune dysfunction.[31–33] The ocular manifestations of HSV include adnexal and/or anterior segment disease in the forms of blepharoconjunctivitis, keratitis, trabeculitis, and anterior uveitis, along with posterior segment disease, including acute retinal necrosis and posterior uveitis.[34,35] The morbidity and mortality associated with herpetic infections is significant and is compounded by the ability of herpes viruses to establish lifelong viral latency.[36–39] HSV-1 and HSV-2 are neurotrophic viruses, which remain dormant in sensory neurons of the dorsal root and trigeminal ganglia.[40–46] Viral reactivation can cause disease recrudescence many years after primary infection.

Epidemiology of Ocular HSV

Pooled data suggest that there are 1 to 1.5 million new[16,47,48] and 9 million recurrent cases[47,48] of ocular HSV each year worldwide, resulting in at least 40,000 cases of new-onset, severe visual disability per year.[16] However, diagnosis often relies on nonspecific clinical signs. Furthermore, heterogeneity in the study design and outcome measures, compounded by a paucity of data from low-income countries, add considerable imprecision to current global estimates. The long-held notion that ocular HSV represents the leading infectious cause of blindness in middle-to high-income countries[49] stems from epidemiological studies conducted in Denmark,[50] Croatia,[51] France,[52] and the United States,[53–55] where the reported incidence rates of total (new and recurrent) cases range from 4.1 to 31.5 per 100,000 persons per year. In the United States, much of the data derive from two retrospective cohort studies from Rochester, MN, conducted over two distinct time periods, 1950 to 1982 and 1976 to 2007.[53,54] These studies suggest a rise in the annual incidence of new ocular HSV cases from 8.4 to 11.8 per 100,000 persons per year. Extrapolating the age- and sex-adjusted incidence of 20.7 total cases per 100,000 person years,[53] as derived from the 1950 to 1982 cohort, to a US census population of 329,135,084 as of January 2020,[56] the number of new and recurrent episodes of ocular HSV now exceeds 68,000 annually. As populations age and grow, we expect the burden associated with decreased visual function, lost productivity, and need for continuing care to also increase.

Clinical Manifestations of HSV Keratitis: The Role of Classification

A simple and unambiguous disease classification system is critical to the implementation of evidence-based therapy based on stages or manifestations of the disease. HSV keratitis includes at least four distinct entities, each with its own pathophysiology and varied responses to therapeutic interventions. Historical characterizations of disease patterns observed in HSV keratitis include terms such as "dendritic,"[57–60] "geographic,"[57–60] "amoeboid ulceration,"[61–63] "interstitial,"[59,64,65] "immune stromal,"[57,58,64,65] "necrotizing,"[57,58,66–69] and "disciform,"[57–60,66,68,70,71] that are routinely used as primary classifiers of disease. Morphological descriptions can indeed be useful in generating a weighted differential diagnosis. For example, corneal epithelial ulceration with a dendritic shape and terminal bulbs at the edges most commonly represents HSV epithelial keratitis, although not always.[72–75] However, other terms are misleading and prone to inconsistent application. "Geographic" keratitis, a term applied to large areas of denuded corneal stroma resulting from HSV epithelial infection, is vague and nondescript and can lead to misdiagnosis, for example, in patients with persistent corneal epithelial defects. "Immune stromal" keratitis, used to describe corneal inflammation due to HSV in which viral replication is not a prominent feature, suggests the false narrative that other variations of HSV stromal keratitis do not involve immune activation. The characterizations of keratitis as "interstitial" or "necrotizing" are more

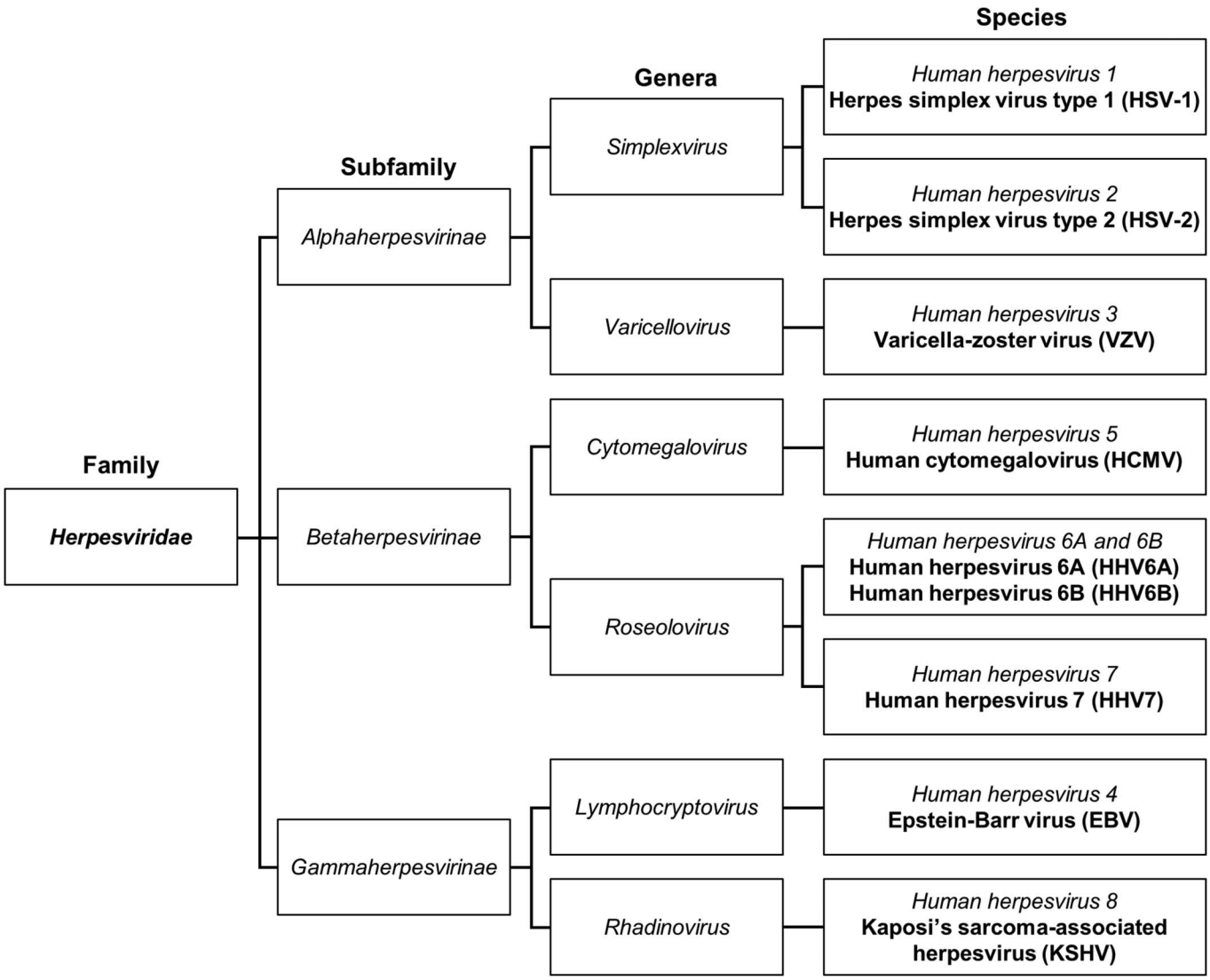

FIGURE 1. Taxonomy of the family *Herpesviridae*, as determined by the International Committee on Taxonomy of Viruses and based on phylogenetic analysis of whole viral genomes.[24] This truncated chart only includes the 9 species of human herpesviruses. Among these, HSV-1 and HSV-2, representing the subfamily *Alphaherpesvirinae* and genus *Simplexvirus*, are indistinguishably associated with keratitis. The third human herpesvirus in this subfamily, varicella-zoster virus, of the genus *Varicellovirus*, is another cause of corneal infection.

appropriately applied to tissue biopsies examined by histopathology. In Japan, "disciform" keratitis is considered a type of stromal keratitis.[76] In the United States, the term typically refers to endothelial keratitis but has also been applied to stromal keratitis presenting with round or oval infiltrates.[66,68] In addition, "disciform" does not capture other patterns of endothelial disease (eg, diffuse and linear) that have the same pathogenesis and treatment. Unfortunately, much of the HSV keratitis lexicon has been formally codified in the International Classification of Diseases. Confusion in diagnostic terminology may contribute to misapplications of therapy, lost opportunities to treat the disease in its earliest stages, and even frank medical errors.

A comprehensive classification scheme based on the anatomical layer of the cornea most prominently involved—epithelium, stroma, or endothelium—is an easily implemented clinical innovation (Fig. 2) that enables anyone experienced in slit-lamp examination to easily synthesize the clinical signs and pathognomonic features associated with HSV keratitis. Implicit to this classification is that identification of the corneal layer most clearly involved correlates well with the unique pathogenic mechanisms that in turn mandate specific therapeutic measures. With standardized nomenclature, this system also provides a logical approach to understanding the epidemiology and natural history of the disease. As such, it has broad applications, from aiding the conduct of systematic reviews and meta-analyses to allowing clinicians to properly counsel patients regarding prognosis. HSV epithelial keratitis, typically a self-limiting process, results from the cytopathic effects of corneal epithelial

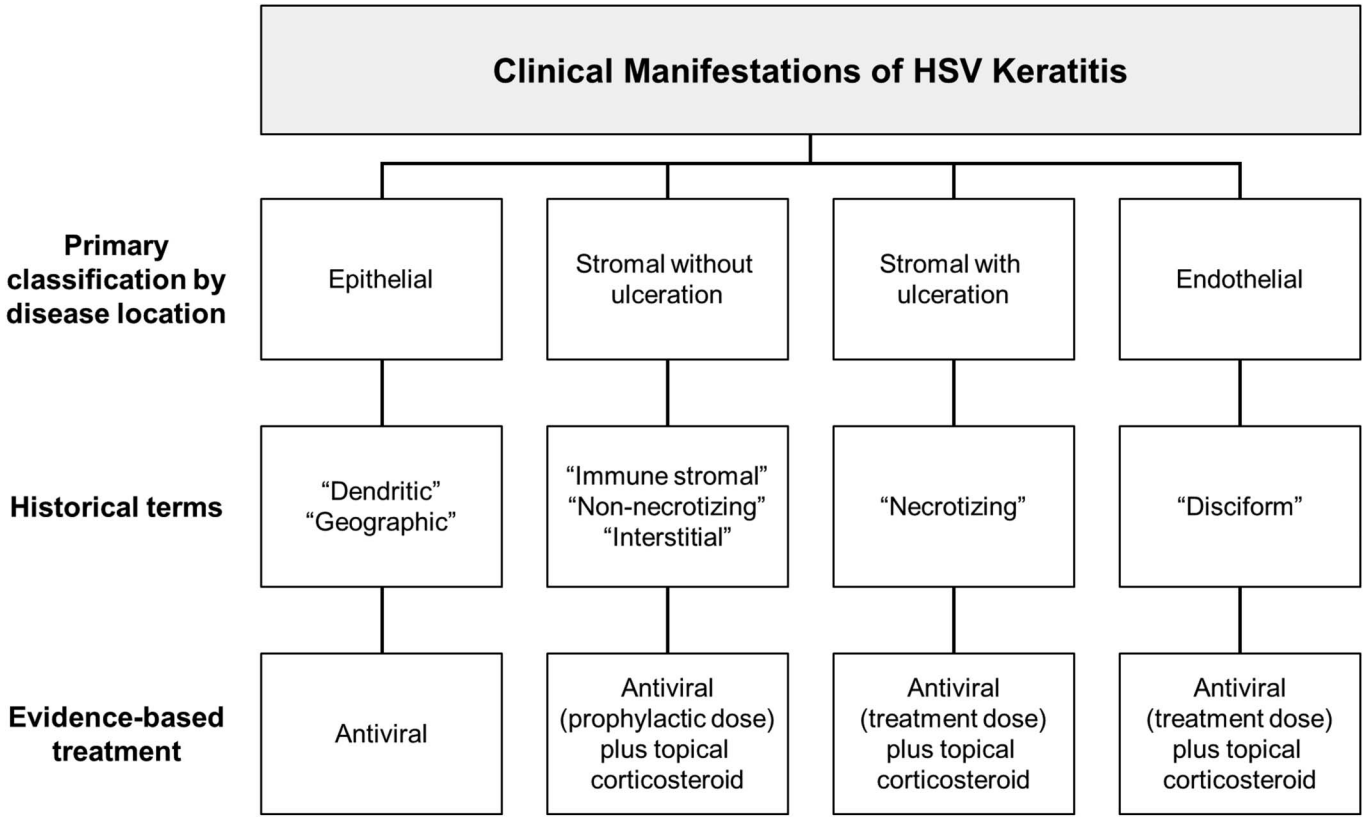

FIGURE 2. Overview of clinical manifestations and management of HSV keratitis, classified by anatomical localization. For full treatment recommendations, see *Herpes Simplex Keratitis: A Treatment Guideline* (2014) by White and Chodosh[47] as published by the American Academy of Ophthalmology.

infection and cell death. The condition is characterized by the presence of an epithelial ulcer with raised grey edges, typically with a leafy, branching appearance (dendrite), although larger (geographic) ulcers may bare the epithelial basement membrane (Fig. 3). Stromal keratitis occurs either with or without epithelial ulceration. Stromal keratitis without ulceration, the more common form, is often described as "nonnecrotizing," "immune-stromal," and "interstitial." Focal, multifocal, or diffuse HSV-related stromal inflammation with intact epithelium is believed to represent immunopathology in the relative absence of viral replication.[71,77–82] Stromal keratitis with overlying epithelial ulceration, most likely the result of stromal HSV reactivation,[83–85] is characterized by severe, "necrotizing" inflammation and a proclivity for scar formation and progressive neovascularization. Finally, endothelial "disciform" keratitis is believed to result from infection of the corneal endothelium.[86–88] This form of keratitis is typically associated with a distinct area of corneal edema with underlying keratic precipitates, although diffuse and linear patterns can also occur. The remaining, uninvolved cornea is characteristically clear. This clinical picture is not to be confused with anterior uveitis associated with secondary keratic precipitates, which, unlike endothelial keratitis, is distinguished by a pronounced anterior chamber reaction. Although all forms of HSV keratitis are commonly recurrent, the risk is greatest in stromal keratitis, which is the most likely to result in corneal scarring, thinning, and neovascularization.[89,90]

Treatment of HSV Keratitis

Before the discovery of specific antiviral agents, ophthalmologists treated HSV keratitis with a wide range of approaches, including manual debridement, chemical cautery, photoreactive dyes, surgery, antiseptics, and antibiotics.[91] More extreme treatments included intramuscular injections of placental extract,[92] subconjunctival injections of autologous blood,[93] snake venom,[94] and radiotherapy.[95] In 1962, Kaufman et al demonstrated the first evidence of clinical benefit for the newly synthesized antiviral, idoxuridine, first in rabbits[96] and then in humans.[97] Small, uncontrolled studies followed investigating other antiviral agents such as trifluridine, vidarabine, and acyclovir, mostly in the care of HSV epithelial keratitis.[35,98] Treatments for HSV keratitis evolved concurrently with advances in the conduct of randomized clinical trials (RCTs) during the 1980s. Emerging trial conventions, emphasizing the importance of methodologic rigor, included the designation of control and/or placebo groups, explicit specification of recruitment criteria, masking, and pretrial determinations of sample size requirements. The National Institutes of Health-funded, placebo-controlled, double-masked, multicenter HEDS RCTs,[99] completed in the 1990s, were the first in HSV keratitis to

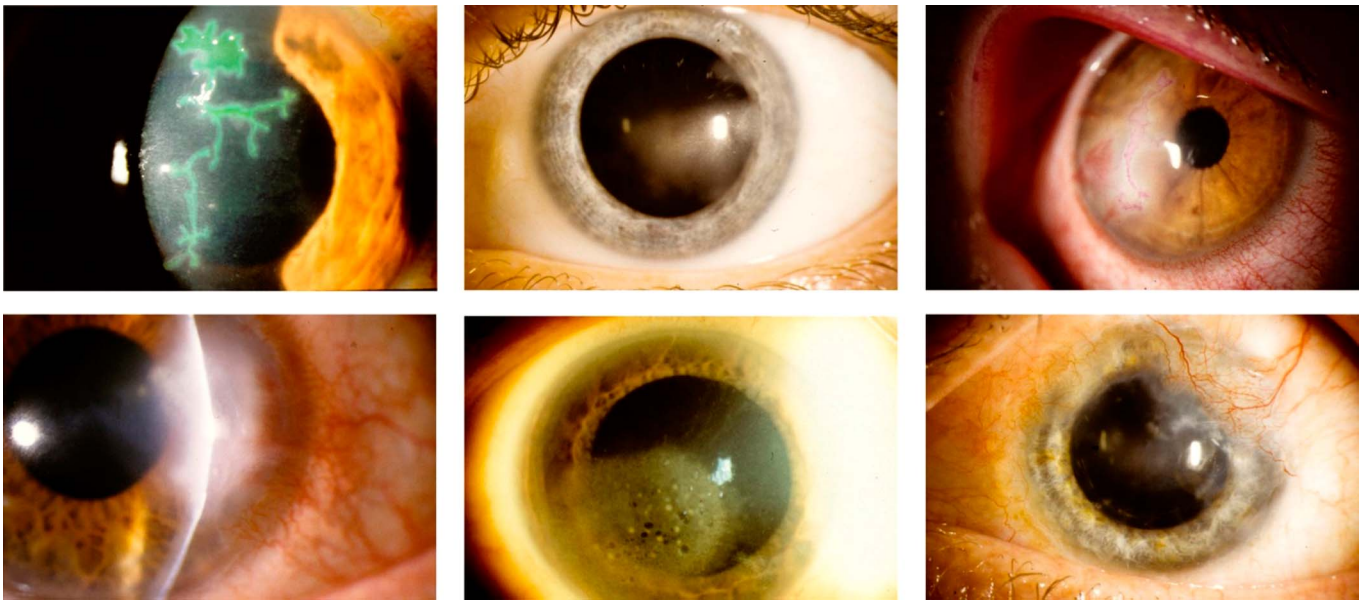

FIGURE 3. Clinical photography of varying manifestations of HSV keratitis. Top row: epithelial keratitis with pathognomonic dendritic ulcer, visualized with lissamine green staining (left); stromal keratitis without ulceration (middle); mixed epithelial and stromal keratitis, visualized with rose bengal dye staining (right). Bottom row: stromal keratitis with ulceration (left); endothelial keratitis (middle); chronic, scarring stromal keratitis with limbal neovascularization (right). (The full color version of this figure is available at www.corneajrnl.com.)

include a priori power-based calculations for enrollment targets.[100] The so-called HEDS-I[101] included the Herpes Stromal Keratitis Not on Steroid (HEDS-SKN),[102] Herpes Stromal Keratitis on Steroid Treatment (HEDS-SKS),[103] and the HSV Iridocyclitis Receiving Topical Steroids (HEDS-IRT)[104] trials. HEDS-II[105] consisted of the HSV Epithelial Keratitis (HEDS-EKT)[106] and Acyclovir Prevention (HEDS-APT) trials.[107] A third study, the Ocular HSV Recurrence Factor Study (HEDS-RFS), was a questionnaire-based study that investigated precipitating factors for recurrence.[108] The HEDS trials formed the evidence basis for the publication of a treatment guideline by White and Chodosh[47] in 2014 (https://www.aao.org/clinical-statement/herpes-simplex-virus-keratitis-treatment-guideline).

Treatment of HSV Epithelial Keratitis

The use of antiviral therapy for HSV epithelial keratitis is supported by decades of clinical trial data. In the United States, Food and Drug Administration–approved topical antiviral formulations include trifluridine solution (1%), ganciclovir gel (0.15%), and a newly available acyclovir ointment (3%), whereas systemic formulations include acyclovir, valacyclovir, and famciclovir. Treatments that have been superseded include antivirals that are no longer manufactured, such as idoxuridine and vidarabine, or those that are effective but associated with unacceptable systemic toxicity, including oral valganciclovir, foscarnet, and cidofovir.[47] The effectiveness of antiviral therapy for HSV epithelial keratitis was confirmed in an updated Cochrane systematic review and meta-analysis conducted by Wilhelmus, which included 137 randomized studies involving 8333 eyes.[98] This study confirmed that the earliest antivirals, idoxuridine and vidarabine, were superior to controls, and that vidarabine, trifluridine, acyclovir, and brivudine were superior to idoxuridine in 2-week healing rates.[98] Comparisons of topical ganciclovir to topical acyclovir in 28 studies involving 2062 eyes showed a modest advantage of ganciclovir in healing rates (relative risk: 1.34, 95% confidence interval [CI]: 1.20–1.51), although study heterogeneity and publication bias may have confounded this finding. Taken as a whole, the literature suggests that topical trifluridine, acyclovir, and ganciclovir are, at a minimum, not inferior to each other in the treatment of HSV epithelial keratitis.

The off-label use of oral antivirals—which are at least as effective as their topical counterparts[35,98,109,110]—is preferred by many corneal specialists.[19] Oral acyclovir, the most commonly used antiviral for ocular HSV, has good ocular penetration[111] and is well tolerated and safe,[112,113] although dose adjustment is required in moderate-to-severe renal impairment and in the elderly.[114] By contrast, topical antivirals are limited by poor intraocular bioavailability[115] and side effects such as ocular surface toxicity,[116–118] allergic reactions, and punctal and nasolacrimal duct stenosis.[119] One report suggested an association between trifluridine and corneal epithelial dysplasia.[120] Although topical and oral antivirals are independently effective in HSV keratitis, there is insufficient and conflicting evidence for combining modalities to accelerate healing.[106,121] Finally, nonspecific therapies are only minimally effective at best. For example, manual debridement alone has been shown to be inadequate.[122–124] Topical administration of the experimental biologic agent interferon has only a modest benefit over placebo, and its addition to specific antiviral therapy does not alter recovery time.[98] Corticosteroids are contraindicated in HSV epithelial keratitis, and when used can cause prolonged infection and

conversion of a dendritic epithelial ulcer to that of a larger "geographic" morphology.

Treatment of HSV Stromal Keratitis

The preferred treatment for HSV stromal keratitis is an oral antiviral agent combined with a topical corticosteroid, the latter tapered over a period greater than 10 weeks.[47] Stromal keratitis with intact epithelium can be treated with prophylactic doses of antiviral medication, whereas ulcerating disease often requires therapeutic doses from its early stages. Although the requirement for antiviral therapy in HSV stromal keratitis has never been disputed, historically the role of topical corticosteroids was controversial. The introduction of corticosteroids to ophthalmology in the 1950s led to two opposing schools of thought regarding their use in herpetic eye disease, now known as the decades-long "Steroid Wars."[125,126] The "West-Coast" school, led by Thygeson and Hogan at the Proctor Foundation and the University of California, San Francisco, expressed severe reservations regarding the use of corticosteroids for any indication involving HSV keratitis.[127–129] The "East-Coast" school, led by Kaufman, Laibson, and Pavan-Langston, among others, advocated for their use in select circumstances, including HSV stromal and endothelial disease.[130,131] The lack of clear clinical guidance led to the initiation of HEDS-SKN, which commenced in 1989. This trial randomized 106 patients with active HSV stromal keratitis, all treated with topical trifluridine at baseline, to the addition of either 1% prednisolone sodium phosphate or placebo, tapered over a 10-week period.[102] Over 90% of participants had stromal keratitis without epithelial ulceration. The main outcome measure was time to treatment failure, defined as the worsening of stromal inflammation or development of uveitis at any visit, no change in stromal inflammation within 2 weeks of treatment commencement, or the occurrence of an adverse event. By the end of treatment, 26% of the corticosteroid group and 73% of the placebo group had failed treatment. The median time to treatment failure was far longer in the corticosteroid group (98 days, 95% CI: 81 to >120 days) than that in the placebo group (17 days, 95% CI: 14–27 days). Those treated with prednisolone had a shorter median time to clinical resolution (26 days, 95% CI: 14–49 vs. 72 days, 95% CI: 44–123). These unequivocal results, obtained during an interim analysis commissioned by the study's Data and Safety Monitoring Board, led to the early termination of enrollment well short of the initial recruitment target of 178 participants. Of note, the proportion of participants who later reached a study endpoint, as determined at 16 weeks after initiation of the study drug, that is, 6 weeks after tapering off prednisolone or placebo, increased to 49% in the corticosteroid group and 76% in the placebo group. This suggested that a 10-week tapered course of topical corticosteroid was insufficient, leaving patients susceptible to early disease recurrence immediately after drug cessation.

Treatment of HSV Endothelial Keratitis

HSV endothelial keratitis is relatively uncommon and was not directly addressed by the HEDS trials. The current evidence basis for its management is limited to a few, relatively small studies conducted in the 1980s and 1990s.[113,118,132–134] Three RCTs showed that in patients treated with 3% topical acyclovir at baseline, the addition of topical betamethasone at concentrations ranging from 0.01% to 0.1% resulted in more rapid resolution compared with the addition of placebo.[118,132,133] An open-label RCT later demonstrated that either oral or topical acyclovir, when added to 0.05% topical prednisolone, resulted in similar mean healing times (25.9 days vs. 25.3 days).[134] However, oral treatment was associated with faster resolution of symptoms than topical treatment, with a greater degree of visual recovery.[134] Therefore, existing evidence supports a combination of an oral antiviral and a topical corticosteroid for the management of HSV endothelial keratitis. Oral antiviral agents penetrate the aqueous humor at therapeutic levels,[111] and because HSV endothelial keratitis likely involves viral replication in the posterior cornea,[86–88] agents with adequate anterior chamber penetration are preferred. Among the available topical antivirals in the United States, only acyclovir reliably achieves therapeutic levels within the aqueous humor.[115,135,136]

Prophylaxis for HSV Keratitis

Two arms of the HEDS trials addressed the issue of prophylaxis against recurrence of HSV keratitis. In the HEDS-EKT study, 287 patients with acute HSV epithelial keratitis were treated with topical trifluridine at baseline and randomized to either a 3-week course of concomitant oral acyclovir (400 mg 5 times a day) or placebo.[106] At the end of a 12-month follow-up period, no difference was observed between treatment groups in the proportion of patients who later, after the resolution of epithelial keratitis, developed stromal keratitis or iritis (11% vs. 10%). This study demonstrated that oral acyclovir given briefly during an episode of HSV epithelial keratitis does not prevent later stromal keratitis or iritis. The subsequent HEDS-APT study randomly assigned 703 patients with a history of ocular HSV in the preceding year to a 12-month course of prophylactic oral acyclovir (400 mg) or placebo twice daily. All participants were followed up for 6 months after the cessation of treatment, resulting in a total trial duration of 18 months.[41] Study participants on oral acyclovir had a significantly reduced cumulative probability of ocular HSV recurrence compared with placebo (19% vs. 32%, $P < 0.001$). The benefit of oral acyclovir was specific to stromal keratitis, as was shown in a subgroup analysis of the 337 participants who had a history of at least one previous episode of stromal keratitis. Importantly, the prophylactic benefit of oral acyclovir was in effect only when taking the drug; the risk of recurrent stromal keratitis returned to baseline immediately after drug cessation. HEDS-APT did not determine whether prophylaxis beyond 12 months would have successfully reduced recurrences after treatment cessation. Existing data suggest that oral prophylaxis should be considered on an indefinite or long-term basis for high-risk patients, including those with a history of recurrences, atopy,[137–139] a corneal allograft in the setting of previous ocular HSV,[140–143] or immune compromise.[144–146] It is also reasonable to prescribe oral antiviral prophylaxis to patients before scheduled ocular surgery including photorefractive procedures[147,148] whenever there is a known history of HSV

keratitis, and to maintain prophylaxis until topical corticosteroids are tapered successfully.

IMPLEMENTATION GAPS IN EVIDENCE-BASED CARE

Dissemination and implementation science is the study of methods that promote the systematic translation of evidence-informed practices within a field of interest.[149–152] In medicine, the extent to which clinical care is informed by evidence-based medicine—that is, the conscious and discerning use of clinical trial data, systematic reviews, meta-analyses, and clinical practice guidelines—has become an area of intense scholarship.[153–156] "Quality gaps"[157] and implementation stasis in medicine are not new phenomena, with even the most transformative of medical innovations (eg, penicillin, smallpox vaccination, and hand hygiene) not entering routine patient care until many years after their discovery.[158] Empirically, it has been estimated that a "17-year odyssey"[159] elapses between the publication of original clinical research and the incorporation of their findings into standard care.[160] In part, this is because of the growing recognition that RCTs, the gold standard of medical evidence, are conducted under carefully controlled "experimental" conditions that do not entirely replicate real-life settings. The exclusion of various groups of study participants, often for purely practical reasons, can limit the generalizability of trial results[161] as can recruitment criteria for entities such as HSV keratitis, which are diagnosed according to the clinical criteria alone.[102] Other factors that contribute to implementation inertia include the time required to "deimplement"[162,163] nonevidence-based practices and often the need to establish the appropriate health infrastructure to deliver such care. Overall, clinicians are slow to adopt evidence-based recommendations.[164,165]

The roots of medical implementation research are found in social and behavioral science, including the literature surrounding the diffusion of innovations. Proponents of diffusion theory study the factors that determine the rate at which innovations are adopted within a specified community,[166,167] which classically approximates a sigmoid curve.[166,168,169] In its initial phases, the innovation typically fails to gain traction apart from a few early adopters. Further implementation is only achieved with time, attrition, and sustained behavioral and systemic changes.[170] In ophthalmology, practice patterns in the care of HSV keratitis are highly variable. This was demonstrated by a 2010 survey of 595 US-based eye care providers, including optometrists, comprehensive ophthalmologists, and cornea specialists, who were asked to identify their preferred treatment choices for the following three uncomplicated cases of HSV keratitis: epithelial, stromal, and a repeated stromal recurrence.[19] Although more than 95% of respondents correctly selected a topical or oral antiviral agent for the treatment of epithelial keratitis, only 82% of cornea-trained ophthalmologists elected to treat stromal keratitis correctly with a combination of antiviral and topical corticosteroid therapy. For the prevention of stromal recurrences, 12 years after publication of HEDS-APT, only 62% of corneal specialists correctly elected to prescribe a prophylactic oral antiviral agent. Such disparities in the care of HSV keratitis are not unique to the United States,[52,171–173] suggesting an overall lack of adoption of HEDS-derived recommendations.

Historically, medical practitioners have drawn on "eminence-based"[174–176] or "tradition-based"[177,178] teachings to guide patient care, leaning on the authority, experience, and wisdom of senior physicians and leading experts. However, the development of the modern RCT, comparative effectiveness research,[179] and evidence-based medicine has shifted the emphasis to data-driven clinical decision-making. Despite this change in medical culture, eminence- and evidence-based medicine can be complementary.[180,181] Clinical medicine and its evidence basis are replete with knowledge gaps, and there are perfectly sound clinical, logistical, and/or ethical reasons why an RCT cannot or should not be pursued for a particular clinical question. It is the physicians' training and clinical acumen that enable them to meaningfully engage with medical evidence so that treatment plans can be tailored according to patient demographics, comorbidities, financial means, health priorities, and individual preferences.[155,182] However, the failure to distinguish those nonevidence-based elements of clinical practice, passed down to students by eminent teachers and repeated without interrogation, prevents us from asking the right questions and slows progress toward more effective treatments.

ADOPTION OF INNOVATION IN HSV KERATITIS

Myths in the Care of HSV Keratitis

Without acknowledgment, eminence-based teachings can prolong clinical myths, which can compromise the quality of patient care. As discussed earlier, historical classification systems for HSV keratitis obfuscate clinical trial outcomes, render treatment guidelines more difficult to interpret, and therefore do not offer a tractable link between clinical diagnosis and the appropriate evidence-based management. Another common pitfall is the incomplete reading of published evidence. For example, in the HEDS-SKN trial,[102] topical prednisolone and placebo were tapered over 10 weeks, after which a high proportion of participants experienced worsening disease. However, it would be a misapplication of the trial results to conclude that topical corticosteroids were ineffective. Rather, the trial indicated that there are subsets of patients with active stromal keratitis who may need a prolonged or indefinite taper of topical corticosteroids.[183] Similarly, it would be a misinterpretation of the HEDS-APT[41] study to surmise that 12 months of treatment, the designated length of oral acyclovir or placebo, were sufficient for longer-term prophylaxis. In the 6 months after treatment cessation, study subjects experienced recurrences at similar rates regardless of their previously assigned treatment, suggesting that there are select patients with a history of HSV stromal keratitis who may require indefinite prophylaxis. Competent and nuanced medical practice should not be "ritualistic"[177]; the delivery of personalized care requires systematic engagement with the literature, hierarchical

appraisal of studies that vary in strength,[184] and thoughtful application of clinical practice guidelines.[164,185]

Clinical Equipoise

The recognition of eminence-based teachings in medicine may also highlight examples of clinical equipoise within physician practice. This principle refers to the circumstances where there may be genuine uncertainty regarding the efficacy of treatment modalities for a given condition.[186–188] Equipoise is the primary philosophical, ethical, and clinical reasoning on which appropriately designed RCTs are conducted. Although the HEDS trials directly addressed many of the clinical controversies once present in the eye care community, significant questions remain. For instance, the optimal treatments for HSV stromal keratitis with ulceration and HSV endothelial keratitis, both uncommon entities, were not effectively addressed by the HEDS trials. Any approach to their treatment is therefore eminence-based at best. In addition, the finer details of antiviral prophylaxis have not been resolved. Although the HEDS-APT trial showed that 400 mg of acyclovir administered twice daily is effective in reducing the rate of recurrence of HSV stromal keratitis, it is not known whether an increased dose would be more effective, whether other oral antivirals such as valacyclovir and famciclovir are superior to acyclovir, or whether a long-term, low-frequency topical corticosteroid has any additional role in prophylaxis.[19]

The Promise of a Diversified Electronic Medical Record

Mechanisms to better implement evidence-based medical innovations range from improving access to digitalized forms of continuing medical education,[189] to offering financial incentives for following predetermined algorithms of care,[190–192] and to restrictions on the scope of practice by training and professional degree.[193] However, one technological innovation with the potential to dramatically improve health care is a diversified, "smart" EMR. Originally touted as the panacea to the limitations of the study record-keeping,[194] the principal benefits of current EMR systems include improved efficiency in billing and better cross-institutional access to legible medical records within increasingly large healthcare systems. However, despite billions of dollars in investment,[195] poor intersystem compatibility continues to hamper longitudinal health record-keeping and the centralized coordination of multidisciplinary care across disparate healthcare networks.[196] With counterintuitive workflows, overabundance of clinically irrelevant tools, and excessive alert systems, current EMR applications often distract physicians from patient care and contribute to physician burnout and dissatisfaction.[197,198] In a 2018 survey of over 500 primary care physicians conducted by Stanford Medical School, only 8% of respondents reported that they found *clinical value* in their EMR.[199]

A reenvisioned EMR would incorporate artificial intelligence and machine learning to provide enhanced physical and laboratory examination cues to the physician, generate data-driven and ranked differential diagnosis lists, and offer point-of-care access to validated clinical algorithms.[200] Automated input of patient data to Health Insurance Portability and Accountability Act-compliant registries, such as the eye disease registry, Intelligent Research in Sight (IRIS),[201] would permit data mining heuristics.[202,203] This could guide research in previously inconceivable ways, well beyond binary decision-making to questions of disease epidemiology, quality improvement, and utilization management. This "smart" EMR would facilitate comparative effectiveness research and provide postmarketing surveillance of evidence-based interventions, enabling continuous fine-tuning of best care. When confronted with diagnostic or therapeutic dilemmas for which evidence is scarce or unavailable, this EMR would enable physicians to guide treatment with real-time analyses of pooled patient data stratified by relevant clinical variables.[204] A diversified EMR would also allow researchers to answer questions of clinical equipoise with data from sample sizes far larger than RCTs could ever enroll, providing a powerful complement to traditional study designs.

CONCLUSION

A common misconception in medicine is that the mere existence of an evidence basis inevitably translates into improvements in clinical practice. However, it has been shown repeatedly that a passive approach to the adoption of new evidence is rarely sufficient. For HSV keratitis, current gaps in care are addressed only in part by the uptake of a classification of HSV keratitis based on anatomical localization. A closer review of eminence-based patterns of treatment can assist in dispelling the persistent myths that currently impact patient care, and enable us to identify examples of clinical equipoise for future clinical trials. Furthermore, an EMR that functions beyond its record-keeping role to provide immediate access to validated management algorithms in real time, while also serving as a source of data for population-wide disease studies, is needed to improve the implementation of evidence-based care into routine practice. The more rapid adoption of clinical innovations in HSV keratitis will enable the delivery of the highest quality of care, and reduce the complications and morbidity associated with this age-old blinding disorder.

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