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Trachoma: An Update on Prevention, Diagnosis, and Treatment

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Abstract

Purpose of review—To review recent clinical and epidemiological studies regarding the prevention, diagnosis, and treatment of trachoma.

Recent Findings—Newer studies propose novel diagnostic tests that appear sensitive for the detection of ocular chlamydial infection. Immunologic studies suggest that chronic inflammation can lead to progressive scarring, even in the absence of chlamydia. Confocal microscopy can obtain accurate grading of scarring progression. Mass oral azithromycin distributions remain a mainstay of treatment; studies have assessed the appropriate frequency and duration of treatment programs. Current studies have also explored ancillary effects of azithromycin distribution on mortality and bacterial infections.

Summary—Trachoma programs have had remarkable success at reducing chlamydial infection and clinical signs of trachoma. Recent work suggests improved methods to monitor infection and scarring, and better ways to distribute treatment. While studies continue to demonstrate reduction in infection in hyperendemic areas, more work will need to be done to achieve elimination of this blinding disease.

Keywords

trachoma; chlamydia; neglected tropical disease; azithromycin; confocal microscopy

Introduction

Trachoma is the leading infectious cause of blindness worldwide, resulting from recurrent infection with ocular strains of *Chlamydia trachomatis*.[1-3]. While once widespread in Europe and the Americas, its significant decline by the end of the 20th century was attributed to improved socioeconomic conditions and hygiene. The World Health Organization (WHO) estimates that 40 million people continue to be affected by trachoma, and that 1.2 billion people worldwide live in endemic areas. Estimates from India and China

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could influence these calculations, but information from these countries is limited.[2] The economic burden is estimated to be $3-8 billion is lost in productivity annually, and the disease burden an estimated 1.3 million disability-adjusted life years.[4,5]

Recurrent inflammation of the eyelids leads to a cascade of conjunctival scarring, entropion, and inturned eyelashes (trichiasis) scratch the cornea further putting those affected at risk for secondary ulcers and eventually blindness.[2] Many feel that the prevention of blindness from trachoma may require more than just surgical campaigns and mass distribution of antibiotics, and that if underlying environmental factors that facilitate its transmission are not identified, reinfection and its clinical sequelae may continue.

The WHO Global Alliance for the Global Elimination of Trachoma (GET 2020) promotes implementation of the SAFE strategy: *S*urgery for trichiasis, *A*ntibiotic distribution, *F*acial cleanliness, and *E*nvironmental improvements.[6,7] Current WHO recommendations include mass treatment with a single dose of azithromycin to those over 6 months of age in areas where follicular trachoma prevalence is 10% or greater in children 1-9 years of age.[7,8]

Recent studies provide new insight into the diagnosis and treatment of trachoma: immunopathologic studies further elucidate etiology and clinical sequelae; new diagnostic tests such as confocal microscopy are supplementing current diagnostic criteria; mass treatment strategies are proposing effective methods for antibiotic distribution; and studies exploring the external benefits of trachoma control programs show promising effects in regards to the reduction of childhood mortality and systemic bacterial infections.

Etiology and Immunopathology of Clinical Signs

A challenge with control is that chlamydia has evolved mechanisms to evade host immune responses through intracellular invasion. Recent studies have suggested that pathways leading to clinical sequelae are related to inflammation rather than infection by *C. trachomatis* itself. An early stage involves formation of lymphoid follicles--the clinical hallmark of active trachomatous inflammation (Figure 1).[3,7,9] These follicles represent subepithelial collections of lymphoid cells with parafollicular infiltrates dominated by polymorphonuclear leucocytes, macrophages, dendritic cells, plasma cells, and B and T cells. [10] If severe enough, papillary hypertrophy obscures the deep tarsal vessels and vascular infiltrates appear in the upper cornea (pannus). Pathognomonic limbal follicles can leave shallow depressions after resolution (Herbert's pits).

Blindness from trachoma occurs from conjunctival scarring which is attributed to recurrent infection. Subtarsal conjunctival scarring leave fibrotic bands in which scar contraction leads to entropion, trichiasis, and eventually corneal opacification.[11] Scar-tissue formation can result in loss of meibomian glands and degeneration of the tarsal plate. Dry eye can further compromise host immune responses at the ocular surface.[11,12]

New studies have demonstrated that host immunity plays a significant role in disease severity. Clinical signs are only poorly associated with documented infection.[13-15] New studies explore the relationship between adaptive immune responses and scarring, T_H1 pro-inflammatory responses, T_H2 role in fibrosis and induction of anti-inflammatory responses

through *IL-10*, and *MMP* associations with degradation of collagen and consequent chemotactic properties). [16,17]. The presumption is that increased chemokine responses lead to neutrophil activation, chemotaxis, and fibrosis. Thus, molecules such as MMPs and chemokines provide a link between inflammation and fibrosis in immunpathological consequences of trachoma. Previously, scarring complications were often ascribed to adaptive immune responses, since adults have consistently lower bacterial loads than those of children and experience short duration of infection, presumably as a result of acquired immune responses.[7,18,19]

Until recently, there has been limited information regarding fibrogenic pathways in the cicatricial stage preceding tissue damage. It has been more difficult to assess the relationship between repeated infection and progressive scaring. Burton *et al.* [16] studied conjunctival gene expression profiles among Ethiopians and found that trichiasis cases demonstrated ongoing inflammation and tissue remodeling relative to controls. In a study in The Gambia, active trachoma was associated with increased expression of profibrotic cytokines and IL17A, which is proinflammatory in both innate and adaptive immune responses.[20].

Other nonchlamydial pathogens have been are associated with clinical signs of trachoma. [17] In Tanzania, there was no association between clinically active follicular trachoma (TF) and infection, but there was a more than a four-fold relationship between TF and bacterial pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.[21] Innate proinflammatory responses (psoriasin, interleukin-1β, tumor necrosis factor alpha, defensin-β4A, chemokine ligand 5, and serum amyloid A1) were associated with nonchlamydial infection.[22] Thus proinflammatory states, possibly unrelated to chlamydial infection, can lead to the immunofibrogenic pathways and conjunctival scarring.

Conclusion

Early vaccine trials in the 1960s were inconclusive, short-lived, and possibly associated with more severe disease.[23-25] Recently, Kari *et al*. [26] reported that live-attenuated vaccination in cynomolgus macaques with a plasma-deficient strain of a *C. trachomatis* produced an anti-chlamydial immune response without production of inflammatory ocular pathology. Thus, the plasmid may play a key role in virulence, and vaccination could generate a protective immune response without induction of pro-inflammatory processes. However, upon virulent challenge, the group found no difference in ocular pathology between vaccinated and control groups, indicating that the introduction of a plasmid strain and low levels of bacterial growth are enough to sustain inflammation. Further studies of human models and the role of the plasmid in the induction of inflammation need to be performed.

Diagnosis & Treatment

Since clinical signs of trachoma are poorly correlated with actual evidence of infection, diagnostic criteria that are both sensitive and specific for infection can be further developed. The weak correlation between infection and clinical signs may be in part due to a latent phase (infection without clinical signs) and long recovery phase (with persistant clinical signs) [7,15,27]. Munoz *et al*. [28] found that high-risk clinical signs were not predictive of

infection in communities after multiple rounds of mass drug administration (MDA). Stare *et al.* [29] found that in an area of The Gambia with a 6% prevalence of follicular trachoma in children, the actual rate of infection detected by nucleic acid amplification tests (NAATs) was <1%. Recent studies continue to find that actual rates of clinical signs in children are higher than actual infection rates. [30, 31].

Accurate estimates of infection are not only important in the determination of reliable estimates for prevalence, but are also necessary to ensure that treatment control programs are cost-effective. Infection has been studied using several nucleic acid tests, most commonly with DNA-based NAATs. However, rRNA-based NAATs appear more sensitive, with comparable specificities. [27,32-34]. Latent class analysis suggests that clinical signs may be relatively sensitive, but that NAATs are far more specific. [33] Point-of-care (POC) assays of chlamydial lipopolysacchrides have yet to be found reliable in hot, humid environments [30,35].

A novel diagnostic approach to visualizing pathological changes in trachoma involve the use of *in vivo* confocal microscopy (IVCM). Hu *et al.* [36*] have applied IVCM for grading inflammatory and scarring changes. The group characterized scarring by inflammatory infiltrate density, tissue edema, and presence of dendritic cells, with good inter-observer agreement. [37] The grading system represents a novel approach to characterizing pathologic changes seen in trachoma.

In regards to treatment strategies, WHO recommends MDA in communities where follicular trachoma is >10% in children. The reemergence of infection after 1-2 rounds in hyperendemic communities has been demonstrated.[38,39] Important questions in MDA programs include how long it is necessary to treat communities and how high coverage needs to be in order to achieve elimination.

West *et al.*, [40*] evaluated 71 previously hyper-endemic communities in Tanzania after 3-7 years of annual treatment, where MDA coverage was >50%. They found: i) a linear relationship between prevalence of clinical trachoma and years of treatment; ii) greater than 7 years of annual treatment would be needed to reach a prevalence of <5%; and iii) no communities after 3 years of treatment had achieved the WHO target of <5% prevalence of follicular trachoma. This suggest that in hyperendemic regions the effect of consecutive, long-term programs are still required.

It seems likely that the frequency of treatment may also influence the rate of elimination. Gebre *et al.*[41*] compared the effect of annual versus biannual mass distribution of azithromycin in 24 Ethiopian subdistricts where coverage was >80% and prevalence of infection was near 40% at baseline. The prevalence of infection was similar at 42-month follow up. However, elimination was more rapid in biannually treated groups with prevalence of infection lower at 12, 24, & 36 months in the biannually treated groups. In comparison to West et al. [40], this study population had higher antibiotic coverage (>80% vs >50%). Given that biannual treatment may expedite elimination efforts, current and future studies can explore the frequency, duration of treatment, and coverage estimates needed to achieve elimination as they relate to prevalence in endemic areas.

Determination of effective community-based strategies is integral to ensure efficient elimination efforts. Recent studies have demonstrated that after multiple rounds of treatment the following are not associated with more infection: living with an untreated infant (azithromycin is not approved for children<6 months)[42], non-participation[43], household density, and lack of antibiotic use in the past 3 months.[44] Ayele *et al.* [44] found that infection was associated with missing prior antibiotic treatments, having a sibling with ocular chlamydia, and living in a larger community. Studies such as these provide insight into why targeted strategies are reasonable in endemic communities.

Azithromycin has been the drug of choice for trachoma due to its safety profile in children, efficacy as a single oral dose (20 mg/1kg), long half-life in tissues, and efficacy against intra-cellular bacteria such as *C. trachomatis*. Although tetracyclines can be used to treat infection, oral use is contraindicated in children, and poor compliance has been demonstrated with topical tetracycline ointment.[45] Erythromycin, requires a longer course, and sulfonamides are associated with more severe side effects such as Stevens-Johnson syndrome. [1]

The majority of azithromycin distribution studies report no serious adverse events [41]. In a cluster-randomized clinical trial in Ethiopia, two surveillance rounds reported adverse events in 4.9-7.0% of children, with complaints primarily of abdominal pain and vomiting.[46] These rates are consistent to western populations taking single high dose azithromycin.[47]

Surgery to avert complications from trichiasis and environmental improvements to prevent transmission have been extensively studied. Bilamellar tarsal rotation has demonstrated mixed outcomes.[48] Surgery can clearly correct trichiasis and prevent blinding complications.[6,48,49] Yet, coverage in programs has been low, attrition of surgeons has been consistently high,[50] acceptance of surgery can be poor, and recurrence can be frequent.[51]

The WHO currently warrants tarsal rotation surgery for individuals with a single trichiatic lash. However, new studies suggest that not all trichiasis is associated with clinically significant entropion. Rajak *et al* [52] studied 2,256 individuals with trachomatous trichiasis (TT) in Ethiopia and found that over half presented with little evidence of entropion. Rather, trichiasis was attributed often to metaplastic or misdirected eyelashes. The same group found that epilation was associated with less central corneal opacity, suggesting that this may be a viable option for mild TT cases and individuals with barriers to acceptance of surgery.[53] In a large randomized controlled trial, Rajak *et al.* found no evidence that use of absorbable sutures was associated with a lower prevalence of trichiasis recurrence than silk sutures. [54*]

The challenges in surgical interventions can be ascribed to the need for sufficient and sustainable health systems in workforce training and in management of infrastructure. Habtamu *et al*. [50] found that high attrition of surgeons and low surgical productivity at outreach campaigns were associated with lack of support, shortage of consumables, and equipment. Fifty-nine percent of surgeons who received extensive training had switched

jobs during study. Thus, health systems infrastructure and management of supply chains could be further examined in future studies.

Beyond Trachoma: Positive Externalities and Integrated Studies

While antibiotic resistance has been demonstrated in previous studies, mathematical models using longitudinal data from trachoma trials have described that such resistance tends to drop after distribution is stopped, even with an initial rise in resistance. Maher *et al*.[55] specifically examined the fitness cost of antibiotic resistance in *S. pneumoniae*, and found that antibiotic resistance has a selective disadvantage in the absence of antimicrobial drugs of approximately 12-14%.

Despite the risk of adverse events and concerns regarding antibiotic resistance associated with antibiotic research, new studies have explored additive benefits trachoma control programs. Previously, azithromycin has been shown to be effective against upper respiratory infections, diarrhea, and malaria.[56,57] Recent studies have suggested associations with mortality prevention, diarrhea, and acute lower respiratory infection.[57-59] In a cohort of 35,502 individuals > 1 and 5,507 children ages 1-5 in 24 communities in Ethiopia, Keenan *et al*. [58*] found that all-cause mortality (OR=0.35, 95% CI=0.17-0.74) and infectious childhood mortality (OR=0.20, 95% CI=0.07-0.58) were associated with oral azithromycin treatment, even when compared to members of the same household who had not been treated. Coles *et al.* [59] studied 1,036 children in 8 rural communities in Tanzania and found that a single dose of azithromycin reduced the risk of acute lower respiratory infection (ALRI) by 38%. Notably, *S. pneumoniae*, *H. Influenzae* b, and *S. aureus* are common causes of ALRI in sub-saharan Africa, where greater than half of ALRI mortalities occur. [60,61] In the same cohort, the group found that treatment was also associated with 39% and 24% percent lower risk of diarrhea at 0-1 and 1-3 months follow-up, respectively.[62] Overall, ancillary effects of oral azithromycin may outweigh the risks associated with adverse events and antibiotic resistance. Future studies may focus on integrated monitoring and treatment strategies in order to understand how mass antibiotic administration can be optimized in communities.

Environmental and Social Studies

The WHO's goal is to control infection to a low enough level that resulting blindness is not a public health concern. Recent evidence from the Gambia has shown that infection in once hyper-endemic areas has dropped to well below 1%. [29] Infection rates have dramatically fallen over the past decade in hyperendemic areas. For example, a survey of 14 villages in Northern Sudan estimated a drop in prevalence of clinical signs from 47% to to 5-9% in 11 districts.[63] Similarly, a recent national survey described that the Sichuan province in China has also seen dramatic reduction in prevalence.[64] However, elimination efforts have been slower in remote Aboriginal communities.[65]

Mathematical models suggest that complete elimination of infection is possible, perhaps even more possible than previously thought. A mathematical model [66] demonstrated that large-scale elimination may be an achievable goal in hyper-endemic regions, even with

incomplete coverage. Return of infection is sufficiently slow that surveillance could be effective in stopping re-emergence.[67,68]

In a cross-sectional study of 8358 children aged 1-9 years across Ethiopia, Roba *et al*. [69] found that all indicators for the SAFE strategy, except for surgery, showed a statistically significant effect. Other recent studies have shown risk factors such as water, flies, lack of latrines, face washing less than once per day, and lack of access to safe water sources (within 30 minutes of walking distance) to be associated with active clinical trachoma. [7,69-72]. Studies have associated some of the following risk factors clinically active trachoma: living in indigenous, mobile communities[73], isolated households whose distance is > 1400 meters from social gathering sites[74], and hot temperatures[75].Contrary to previous findings, new studies in Ethiopia were unable to demonstrate an association between latrine promotion and infection or mortality. [76,77].

Conclusion

As trachoma elimination nears, research will require more accurate diagnosis of infection and monitoring of clinical sequelae (Table 1). NAATs and confocal microscopy can assist in accurate diagnosis of infection and scarring, respectively. Recent research suggests ancillary benefits from mass antibiotic distributions, including possible reductions in infectious diseases and even childhood mortality. Integrating trachoma programs with other neglected tropical diseases may prove cost-effective, since close to 95% of drug distribution costs have been attributed to recurring costs (personnel, travel, etc.)[78]. However, overlap between diseases would need to be considered to ensure effective integration.[75,79] Perhaps the most important finding in the past few years is that trachoma elimination is possible, even in areas that had previously been severely affected.

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Key Points

- Nonchlamydial bacterial pathogens have been closely associated with clinical signs of trachoma, suggesting that fibrogenic pathways may be a factor of both adaptive and innate immune responses.
- Clinical signs may be present despite no identification of *C. trachomatis*, suggesting that complications may be a consequence of chronic inflammation rather than direct infection.
- *In vivo* confocal microscopy has been used to propose a grading system for trachoma based on inflammatory and scarring changes.
- Mass single-dose oral azithromycin treatment remains the WHO-recommended treatment in districts with greater than 10% prevalence of active clinical signs in children ages 1-9 years; at least 3 years of annual treatment is needed in moderately endemic areas. Biannual treatment may expedite elimination efforts.
- Trachoma programs have been associated with reduction in mortality, diarrhea, and upper respiratory infections.

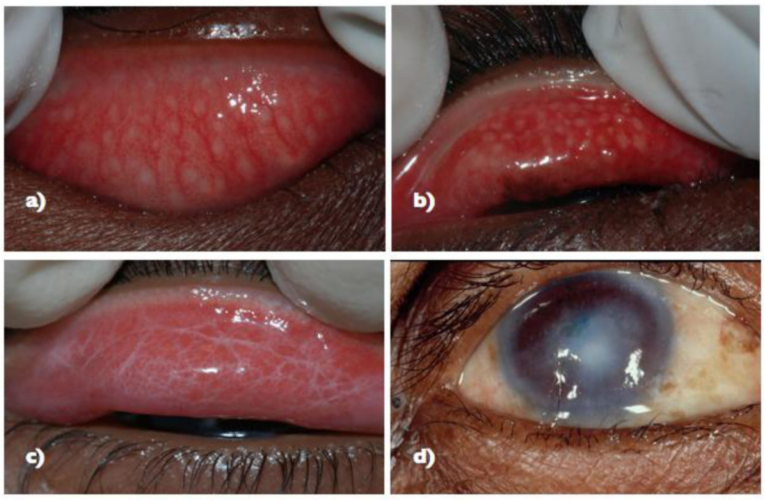

Figure 1.

Clinical features of Trachoma Based on the WHO clinical grading scheme[9]

a) Follicular Trachoma (FT) with follicles ≥ 0.5mm

b) Active trachoma characterized by TF and intense trachoma

c) Tarsal congunctival scarring (trachomatous scarring, TS)

d) Corneal opacification (CO) over the pupil with trachomatous trichiasis

Table 1

Selection of recent trachoma studies

	Studies	Findings	Implications
			Etiology of clinical sequelae
Immunopathology	Burton *et al.*[16] Burton *et al.*[20]	• Patients with trichiasis are likely to have ongoing inflammation. • Active trachoma is associated with expression of profibrotic cytokines and proinflammatory interleukins.	• Clinical complications may be attributed to chronic inflammation. • Repeated infection can facilitate fibrogenic pathways.
Non-chlamydial pathogens	Hu *et al.*[17] Burton *et al.*[21]	• Non-chlamydial bacterial pathogens are more likely to be associated with clinically active trachoma than actual infection by C.trachomatis.	• Proinflammatory states after infection by *C.trachomatis* can lead to immunofibrogenic pathways facilitating scar formation.
			Diagnosis & Monitoring
Clinical signs	Munoz *et al.*[28] Stare *et al.*[29] Michel *et al.*[30]	• Clinical signs are weakly correlated to actual infection. • Slow resolution of symptoms after infection is common.	• More studies are needed to better characterize clinical sequelae as they relate to infection.
Confocal microscopy	Hu *et al.*[36], [37]	• Confocal microscopy can visualize cellular and tissue changes in patients with trachoma. • A grading scheme has been developed to characterize inflammatory and scarring changes to monitor disease progression.	• Confocal microscopy can be used to monitor cicatricial changes
RNA-based nucleic acid amplification tests (NAATs)	Keenan *et al.*[32]	• RNA-based NAATs are more sensitive than DNA-based NAATs in detecting *C. trachomatis* infection.	• More sensitive laboratory testing for chlamydia is now available
Point-of-care tests	Michel *et al.* [30] Hardin-Esch *et al.*[35]	• POC tests have low reliability in hot, humid environments.	• Further development of POC tests need to be explored before their acceptance.
			Treatment Strategies
Frequency and length of antibiotic distribution	West *et al.*[40] Gebre *et al.*[41]	• In hyperendemic communities, >3 years of annual treatment is needed to achieve <5% prevalence. • Biannual treatment may expedite elimination efforts, but does not affect prevalence after a few years.	• Mass distribution of antibiotics over a number of years can significantly reduce prevalence of infection. • Biannual treatment may not be necessary.
Surgery	Rajak *et al.*[52-54] Habtamu *et al.*[50]	• Patients with trichiasis may frequently present with little evidence of entropion.	• More surgical studies are needed to determine effective surgical

	Studies	Findings	Implications
		• Surgeon attrition is high and surgical programs continue to face obstacles in infrastructure.	interventions and infrastructure.
Ancillary benefits of antibiotic programs	Keenan *et al.*[58] Coles *et al.*[59] Coles *et al.*[62]	• MDAs may significantly reduce all-cause mortality. • A single dose of azithromycin may reduce acute lower respiratory infection and reduce a child's risk of diarrhea.	• Anciallary benefits of azithromycin likely exist. • New avenues for integrated studies can be explored.