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Microbial keratitis

Microbial keratitis is infection of the cornea that can be caused by a range of non-viral pathogens. The causative organisms include bacteria, protists (e.g. acanthamoeba), and fungi (yeasts, moulds and microsporidia). It is characterised by an acute or sub-acute onset of pain, conjunctival injection, and corneal ulceration with a stromal inflammatory infiltrate. Depending on the size and location of the ulcer, vision may be impaired.

Epidemiology

There are large regional differences in the relative prevalence of each of these causative organisms determined by climate and socio-economic factors. In tropical countries fungal corneal infection, often associated with agricultural injury, is a major cause for preventable corneal blindness. In temperate countries, such as the UK, bacterial keratitis is the most common cause, although cases of acanthamoeba, fungus and microsporidium keratitis occur.[1] Mixed infections causing keratitis can confuse the clinical picture and make management more difficult. The majority of cases have a clearly identifiable risk factor for infection and in the UK contact lens wear is now the most important risk for all forms of microbial keratitis. Other important risk factors are ocular surface disease, trauma, surgery, and the use of topical steroid. Importantly, risk factors for infection change over time (e.g. increased popularity of contact lens wear and refractive surgery) and monitoring for changing patterns of disease and sensitivity profiles is essential. Guidelines for the management of microbial keratitis need to informed by local patterns of infection and antimicrobial sensitivities. Although treatment guidelines are often based on laboratory sensitivity data the relevance of in vitro sensitivity disc diffusion results to clinical outcomes is uncertain.[2] Sensitivity testing for acanthamoeba is not generally available and fungal sensitivity testing is only performed in the National Fungal Reference Laboratory (Tel: 0117 9285030).

Diagnosis

A careful history should be taken to identify potential risk factors for infection, particularly a history of recent contact lens wear or foreign travel. Poor lens hygiene, swimming, showering and face washing in contact lenses, or corneal trauma involving contaminated water or soil are especial risks for acanthamoeba infection. Clinical signs do not reliably distinguish different organisms. Some features such as a gradual onset of symptoms may raise the suspicion of an atypical cause, while perineural infiltrates are a frequent feature of early acanthamoeba infection, and raised slough and serrated infiltrate margins suggest fungal disease.

Wherever possible, the nature of the causative organism should be investigated by the collection of samples for microscopy, culture and sensitivity testing using a validated protocol. It is not necessary to stop antibiotics prior to taking samples for culture. Multiple samples should be taken from the edges of the ulcer using a disposable needle or blade following the instillation of a non-preserved topical anaesthetic. As a minimum, samples should be placed on a glass slide for gram stain examination and also plated directly onto blood agar and a nutrient broth for bacteria. The use of transport media is not recommended The laboratory should be asked to give antibiotic sensitivities to agents that are available for topical ophthalmic use.

If acanthamoeba infection is suspected an epithelial biopsy should be plated directly onto non-nutrient agar and an additional sample sent in formalin for histopathology Yeasts and filamentary fungi will grow slowly on blood agar, however, isolation is enhanced if additional samples are plated directly onto Sabouraud dextrose agar. If contact lenses and lens care solutions are available they should also be sent for culture.

Confocal microscopy of the cornea is an important diagnostic aid to help make a rapid diagnosis of acanthamoeba or fungus infection. Bacteria and microsporidium are too small to be resolved by this technique. Polymerase chain reaction (PCR) to detect acanthamoeba and fungal DNA is not yet generally available in the UK, although this also promises to be useful (see *www.micropathology.com*).

Management of Microbial Keratitis:

Approximately 5% of new cases of microbial keratitis in the UK are caused by fungus or acanthamoeba and priority should be given to identifying these cases early. Cases with a history or signs suggestive of acanthamoeba or fungus

infection should have smears and cultures, and preferably be referred to a unit where confocal microscopy is available. Appropriate treatment for these pathogens should be started immediately. Topical steroid should not be used until the nature of the infection is confirmed, and then only in conjunction with an effective antimicrobial.

Bacterial keratitis: Initial treatment should be with a broad-spectrum antibiotic to cover both Gram-positive and Gram-negative pathogens. Topical fluoroquinolones (e.g. ofloxacin, levofloxacin or moxifloxacin) are well tolerated and effective in the UK. Dual therapy with fortified 5% cefuroxime and 1.5% gentamicin is also effective but less well tolerated. Prolonged use of a fortified aminoglycoside such as gentamicin is toxic and may delay epithelial recovery or cause epithelial necrosis. The topical therapy may subsequently be modified according to the results of in-vitro bacterial sensitivity. Treatment needs to be intensive for the first few days to achieve therapeutic tissue concentrations and rapid control of the infection, with the frequency being reduced in line with the clinical response. Oral antibiotic is not indicated unless there is a risk of endophthalmitis or bacterial scleritis. Topical steroid is not usually part of an initial treatment regimen.[3]

Acanthamoeba keratitis: Treatment is directed at killing the amoebic cysts as opposed to the more sensitive trophozoites. Biguanides are the treatment of choice because they have the best cysticidal effect of the available agents. There is no proven benefit of the use of Polyhexanide (PHMB) 0.02% over chlorhexidine 0.02%, and although dual therapy with a second agent such as hexamidine or brolene is common, there is no published trial data to support this strategy. If there is a poor initial response higher concentrations of both PHMB (0.06%) and chlorhexidine (0.2%) are available. The host response is thought to be important in elimination of acanthamoeba infection and the early use of topical steroid may delay recovery and adversely affect outcome. Topical steroid may be indicated later if there is progressive vascularisation, stromal melt, scleritis or marked anterior uveitis. Oral non-steroidal agents (e.g. flurbiprofen 50mg TDS) can help control pain and immunosuppression should be considered if there is an associated scleritis.[5]

Fungal keratitis: Evidence from a large randomised controlled trial supports the initial use of topical natamycin 5% for suspected filamentary fungal infections.[4]

Alternatives if this is not available are topical chlorhexidine 0.2% or topical voriconazole 0.1%. If yeast is identified treatment should include topical amphotericin 0.015%. Although the use of an intrastromal injection of voriconazole has been suggested as a means of achieving high tissue concentrations this may increase the risk of perforation. The addition of oral antifungal treatment with voriconazole or Itraconazole is indicated if there is evidence of deep corneal invasion or intraocular spread, or if there is spread of the infection to the limbus. Topical steroid should not be used during treatment of fungal infection. Excisional keratoplasty has an important role for control of progressive filamentary fungal keratitis, aiming for an excision into 2mm of clear tissue. Topical ciclosporin or systemic immunosuppression may be required to control severe inflammation after keratoplasty.

Microsporidium keratitis: This is rare but may be seen in patients who have acquired their disease overseas, particularly following visits to Hong Kong, Singapore and other South-East Asian areas. The organism does not grow in culture and the diagnosis is confirmed by histological examination of an epithelial biopsy. In the majority of cases disease is limited to the epithelium where the appearance can mimic acanthamoeba infection. Epithelial disease is managed by epithelial debridement and the use of a topical fluoroquinolone.

Progressive disease: Microbial keratitis may pose a significant therapeutic challenge, particularly if initial cultures are negative. Even in specialist units cultures are negative in 30 to 40% of cases of acanthamoeba despite the presence of clinically characteristic appearances. Filamentary fungi spread deep within the cornea and superficial biopsies may be negative. Suspect unusual pathogens (e.g. Mycobacterium, Nocardia), particularly if there has been laser refractive surgery or foreign travel. Re-culture onto selective media such as Lowenstein Jensen medium, Sabouraud agar and non-nutrient agar. A corneal biopsy (for culture and histopathology) may be necessary, particularly in cases where the infection is focused in the deeper part of the cornea. Confocal microscopy examination or tissue for PCR examination may also prove informative. Strategies for the culture of unusual pathogens, as well as treatment, should be discussed with a microbiologist.

Unfortunately, even with early diagnosis and apparently appropriate therapy a proportion of cases with acanthamoeba or fungal infection will inexorably deteriorate. The reasons why some cases do not respond to therapy despite in vitro susceptibility of the pathogen to treatment are unclear. Better therapeutic agents are required.

Recommendations

- There should be improved efforts to educate the public of the infection risks associated with cosmetic contact lens wear.
- Acanthamoeba infection should be considered in ALL cases of epithelial or anterior stromal keratitis in patients who have worn cosmetic contact lenses. Do NOT make a diagnosis of herpes simplex infection in a contact lens wearer until acanthamoeba infection has been excluded.
- Do not treat contact lens associated keratitis with topical chloramphenicol. The most common bacterial pathogen for contact lens associated keratitis is Pseudomonas aeruginosa, which is resistant to chloramphenicol.[6]
- Referral pathways for obtaining a confocal microscopic examination should be identified, with prompt referral.
- PCR should be introduced as a diagnostic aid for suspected acanthamoeba or fungal infections.

Figure

Severe microbial keratitis in a soft contact lens wearer. Early isolation of the pathogen and effective treatment are essential.

Table

Suggested primary topical treatments for microbial keratitis

Pathogen	Primary treatment	Alternative
Bacteria	Fluoroquinolone e.g. moxifloxacin	Cefuroxime 5% and Gentamicin 1.5%
Acanthamoeba	Polyhexanine 0.02% or Chlorhexadine 0.02%	Hexamadine Brolene
Fungi	Natamycin 5%	Chlorhexidine 0.2% Voriconazole 1%

For references see Collge website