Guideline for Diagnosis and Management of Microbial Keratitis (Bacterial, Fungal, Viral and Protozoal) in Adults

Background:

Microbial keratitis is an ocular emergency and requires early detection and appropriate treatment to preserve vision. Microbial keratitis is inflammation of the cornea due to infection with bacteria, fungi, viruses or protozoa, but is rare in the absence of predisposing factors. It can be a sight threatening condition; any delays in diagnosis and management can lead to corneal scarring and poor visual outcomes. Untreated or severe keratitis can lead to corneal perforation with the potential to develop into an endophthalmitis and the possible loss of an eye [1-2].

The main risk factors for microbial keratitis are contact lens wear, ocular surface disorders and corneal trauma/surgery [3]. See Table 1 for a list of causative organisms.

Table 1: Causative organisms in microbial keratitis

Bacteria
Bacteria account for 90% of cases of microbial keratitis. The most common organisms implicated in the UK are staphylococci, streptococci and, in contact lens wearers, *Pseudomonas aeruginosa* [4]. However, other Gram negatives, particularly *Enterobacteriaceae* (*Proteus, Serratia, Klebsiella, Enterobacter, Citrobacter*) can also cause keratitis [5].

Fungi
Fungal keratitis is more common in tropical countries, particularly in rural areas, and is a relatively uncommon cause of keratitis in developed countries [6].

Amoebae
Acanthamoeba keratitis is rare in Yorkshire, but is more common in London (relative risk 6.4 in 1987-9). An increasing prevalence of soft contact lens use and lapses in contact lens care (use of tap water to rinse out contact lens case) are proposed explanations for the increasing incidence of *Acanthamoeba* infections [7].

Viruses
The most commonly implicated viruses are the adenoviruses (mostly types 8,19 and 37). Infections are usually self-limiting [8]. More serious is herpes simplex virus (HSV) keratitis, which is one of the most common infectious causes of blindness. Varicella-zoster virus (VZV) can cause significant problems if shingles affects the cornea but chicken pox rarely causes ocular problems. Shingles can cause a stromal keratitis at onset and treatment is usually systemic.

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Clinical Diagnosis:

Microbial keratitis should be suspected in any contact lens wearer with a red eye *or* any patient with predisposing factors (see table 2) and a red eye.

History: patients may describe any of the following:

- Pain – foreign body sensation
- Photophobia
- Redness
- Tearing
- Decreased visual acuity

Identify any predisposing factor(s)

Table 2. Predisposing factors for microbial keratitis
Contact lens wear (especially extended wear), and inadequate disinfection/care of lenses
corneal trauma
Previous ocular and eye lid surgery especially corneal surgery (including refractive)
Immunosuppressant drugs, both systemic and topical
Contaminated eye drop solutions
Tear film deficiency
Abnormalities of the eye lids/lashes
Blepharitis and dacryocystitis
Viral keratitis and post-herpetic corneal disease
Corneal anaesthesia and exposure
Keratoconjunctivitis sicca
Neurological damage to Vth or VIIth cranial nerves
Dermatological conditions e.g. Stevens-Johnson syndrome and ocular mucous membrane pemphigoid
Vitamin A deficiency
Bullous kerathopathy

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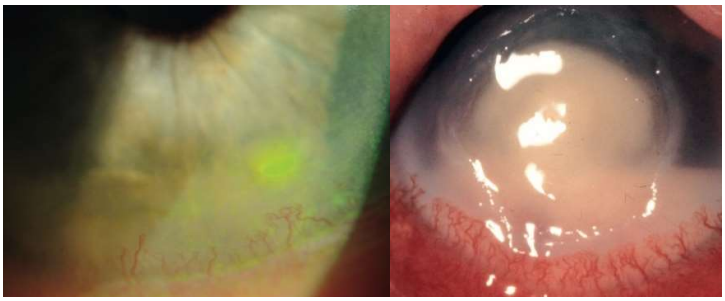
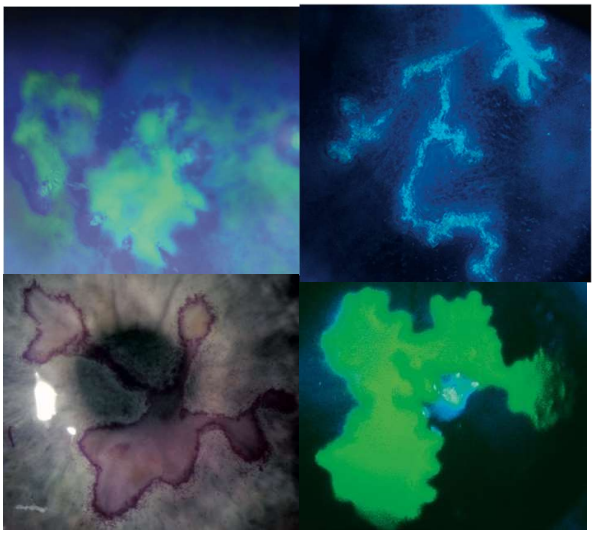
Examination

- Assess visual acuity
- Perform slit lamp examination

Clinical features of bacterial, viral, fungal and acanthamoeba keratitis

Table 3: Clinical features of bacterial, viral, fungal and acanthamoeba keratitis

Photos courtesy of Kanski Clinical Ophthalmology.

Bacterial	 The characteristic lesion of bacterial keratitis is a corneal epithelial defect with associated suppurative infiltrate into the stroma. This may be accompanied by a hypopyon.
Herpes simplex	 The first symptoms of herpes simplex infection are usually irritation, photophobia and tearing. As corneal anaesthesia usually occurs early in the course of the infection the symptoms

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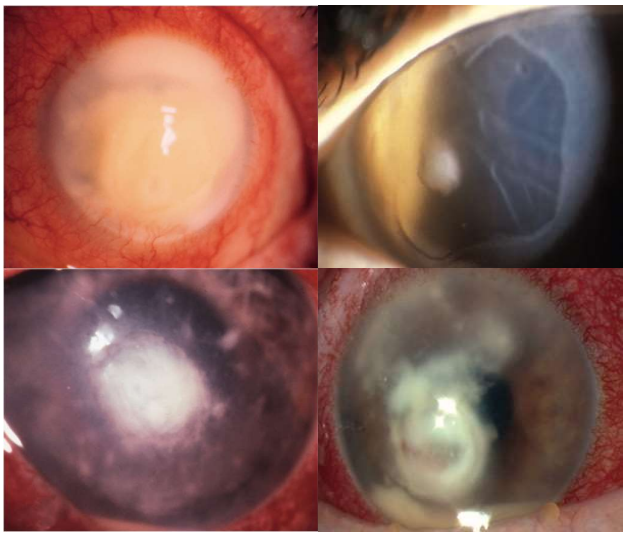
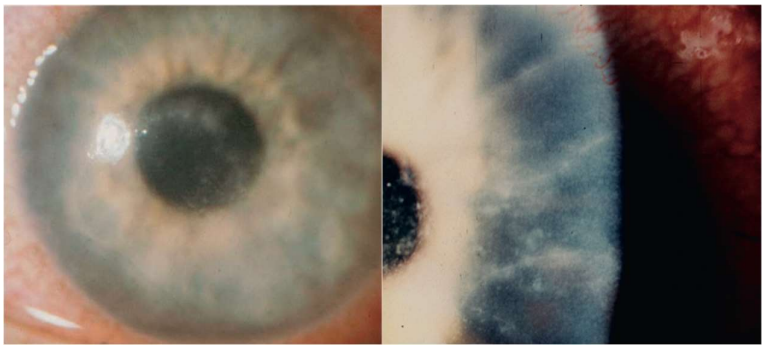
	may be minimal. The most characteristic lesion is a dendritic ulcer but this can develop into a geographic ulcer or stromal keratitis.
Fungal	 Fungal keratitis should be suspected in the presence of risk factors (long term topical steroid use, immunocompromised patient). This can present as multifocal corneal infiltrates +/- hypopyon. The clinical presentation of fungal keratitis is insidious and slowly-progressive ulceration of the cornea with variable degrees of inflammation and pain. Characteristic features include feathery edges to the ulcer, a dry grey elevated infiltrate and satellite lesions [9].
Acanthamoeba	

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	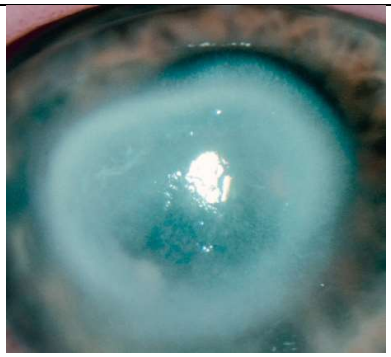 Clinical features of acanthamoeba keratitis are variable and patients can range from being asymptomatic to reporting severe pain (which can be disproportate to mild clinical findings). There may be epithelial ridges, dendritites/pseudodendrites. stromal infiltrates (which can progress to a ring), perineural infiltrates and reduced corneal sensation. Diagnosis of *Acanthamoeba* infection is difficult and often delayed or misdiagnosed as herpes simplex. **Never diagnose HSV keratitis in a contact lens wearer without attempting to culture *Acanthamoeba* keratitis.**

Initial investigations

- A corneal scrape should be performed on corneal ulcers in which any of the following features are present:
  - Central ulcer (within 3mm of the visual axis)
  - Ulcer greater than 1mm in diameter
  - Anterior chamber reaction
  - Failure of previous antimicrobial therapy
  -
- For contact lens associated keratitis, the contact lenses and contact lens case should be sent for culture. Patients must be advised that the cases will not be returned.
- Corneal scrapings should be taken before antimicrobial therapy is started
- If the patient is not responding to treatment at 48 hours and no organism has been cultured, consider stopping topical antibiotics for 12-24 hours and then re-sampling, this should be done in conjunction with a consultant ophthalmologist.
- A corneal biopsy should be sent for culture if debridement is required or if there is no response to treatment.

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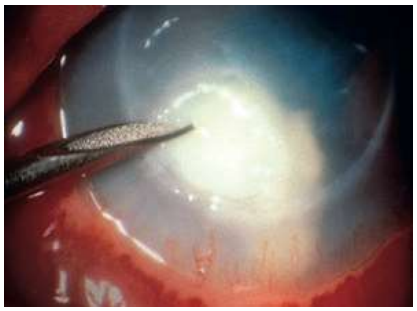
How to perform a corneal scrape

Attaining the sample:

1. Wash hands
2. Instil preservative free topical anaesthetic and perform scrape at the slit lamp, prior to use of fluorescein.
3. Use a 25 gauge needle or no. 15 blade; utiilising a new needle or blade for each sample. Bending the tip of the needle against the inside of its sheath to create a spoon shape can be helpful to retain a good size sample but can make it very difficult to inoculate the plates.

   Be very careful to avoid contamination of needles/swabs/plates/bottles with fingers and avoid contamination of the needle against the conjunctiva and lids.

4. Scrape both the base and the leading edge of the ulcer



Innoculating culture media:

5. Samples should be obtained in the following order of priority and sent to the laboratory:
   - Glass slide
   - Blood agar plate x 2 (aerobic and anaerobic)
   - Chocolate agar plate
   - Sabouraud agar

Gently smear material on the surface of agar in C-streaks, as shown below, taking care not to puncture the surface of the agar.

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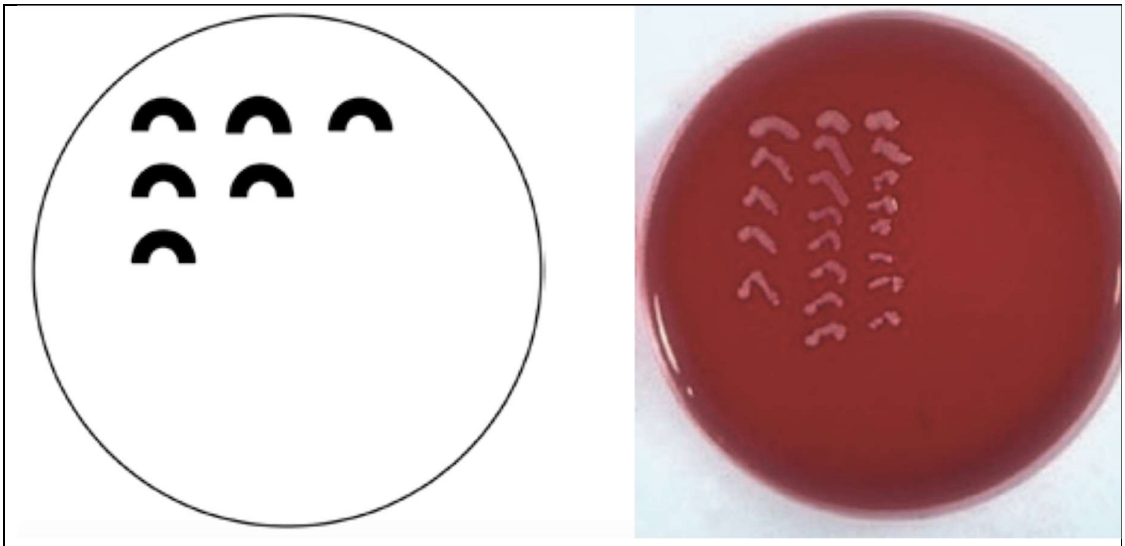
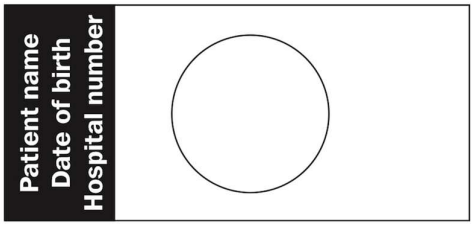


6. Sellotape the lid of the plate to the base around the perimeter.
7. When transferring tissue to the glass slide, place the specimen within a pre-marked circle and handwrite the patient's details on that side of the slide, as shown below. Leave to air dry. Then place in slide box or tape another slide on top to sandwich the smear.



Images courtesy of Leck A., (2015) How to take a corneal scrape. CEH; 28(89)

If acanthamoeba keratitis is suspected, before any scraping, use green needle to obtain a scroll of epithelium and place the sample in c. 1ml volume of saline. A minims vial or universal container is fine (both can be labelled with a patient sticker). Only penetrate the epithelium try and remove as much epithelium as possible (removes cysts). Do not breach Bowmans. The sample request must clearly state that acanthamoeba keratitis is suspected and sent for acanthoemeba PCR , the microbiology staff at HDFT should be informed that the specimen is on its way.

Label all specimens clearly with name and hospital number or date of birth. State current or previous antibiotic regimen clearly on the microbiology form along with what samples obtained.

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8. Contact lenses, lens case and contact lens solutions should be sent to the laboratory for microscopy and culture for bacteria and fungi. If required, they can be sent to Leeds for amoebae (sent by HDH Microbiology).
9. Document the size and nature of the corneal ulcer before and after scraping.

Microbiological processing of corneal scrapes:

1. Glass slides: for Gram stain. Other stains (e.g. PAS for fungi and amoeba, Ziel-Nielsen for atypical mycobacteria, modified Ziel-Nielsen for nocardia) will be performed on specific request by Leeds (sent by HDH Microbiology).

2. Blood agar: most ocular pathogens including aerobes, anaerobes and fungi

3. Sabouraud's agar: fungi

4. Epithelial biopsy: acanthamoeba.

Important information to note when taking a corneal scrape:

OUT OF HOURS:

1. The plates are always in the out of hours fridge outside pathology reception and are replaced regularly. You can collect these anytime.

2. Between 9am and 8pm, gram stains will be done by BMS (biomedical science) staff and they will incubate the plates in the lab – ring them to arrange

3. Between 8pm and 9am, leave the scrape and the plates in the out of hours incubator outside pathology reception. BMS will gram stain at 9am and transfer plates to incubators inside lab. (Any contact lenses/ cases should be placed in the fridge). To make sure the BMS staff know they are there, please phone just after 9am to check they have been found.

4. If stain is really needed urgently between 8pm and 9am, ring Consultant Microbiologist to discuss why the result may affect immediate management.

Availability of results

Gram stains and microscopy of contact lens cases ready in few hours, initial culture ready 48hours, culture for fungi and amoebae continued for minimum 14 days.

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Indolent or progressive ulcers may require repeat scraping or corneal biopsy. Consider seeking advice from the microbiology team and an ophthalmology consultant or senior, if multiple scrapes are required.

Treatment

Empirical antimicrobial therapy [10-11]

- Initial empirical therapy for small ulcers (<1mm) contact lens related keratitis is Levofloxacin 0.5% eye drops hourly day and night for 24 hours and then hourly by day only. Review at 48 hours
- Initial empirical therapy for large ulcers (>1mm) or in patients with ocular surface disease is: Levofloxacin 0.5% eye drops and Cefuroxime 5% eye drops hourly both day and night for 24 hours and then hourly by day only. Review at 48 hours.
- If the patient gives a clear history of anaphylaxis to penicillin or a clear history of allergy to cephalosporin then empirical regimen is Levofloxacin 0.5% eye drops hourly plus Gentamycin 1.5% eye drops (instead of Cefuroxime). Both drops should be instilled hourly day and night for 24 hours then hourly for one day and review at 48 hours.
- Topical Gentamycin 1.5% eye drops should be reserved for second line therapy and used in place of Cefuroxime when clinical response is suboptimal at 48 hours and cultures remain negative (or for cephalosporin allergic patients).
- Following intensive topical therapy with, they can be reduced slowly over several days to four times a day if the patient is continuing to improve clinically.
- Routine addition of antifungal treatment is NOT required prior to microbiology results unless there is a history of long term topical steroid use OR immunocompromised OR ocular contamination with vegetative matter AND multifocal corneal infiltrates are seen and considered likely to be fungal keratitis

- Empirical therapy for suspected **fungal keratitis**: amphotericin 0.15% eye drops applied hourly. Add oral antifungals (voriconazole) if evidence of deep corneal invasion /or intraocular spread or spread to limbus. You need to monitor the LFTs at baseline then weekly (at least at start).

- Preservative free products especially benzalkonium chloride free products should be used if there is a history of toxicity or evidence of toxicity develops on therapy.

In cases of suspected acanthamoeba keratitis, start intensive treatment with a polyhexamethylene biguanide (PHMB) 0.02% OR chlorhexidine 0.02%) AND propamidine 0.1% (Brolene). These are administered hourly day and night for 48 hours, reduced to one hourly daytime only for the following 72 hours, then two hourly for three to four weeks. Dual therapy is useful since many strains of Acanthamoeba may be resistant to one agent alone. Voriconazole 1% eyedrops may also have an anti-acanthamoebal effect, but may be less effective than the PHMB/chlorhexidine or Brolene [12].
Up to 40% of acanthamoeba keratitis has concurrent bacterial keratitis. Therefore always treat with antimicrobial too (levofloxacin fine). Needs to be continued until improving / negative bacterial scrape / epithelial defect healed.

Non-antimicrobial management

- Stop contact lens wear until treatment is complete
- All patients with keratitis should be started on a mydriatic with cycloplegic action.
- For severe cases of microbial keratitis (as judged clinically) atropine 1% eye drops once a day should used.
- For milder cases of microbial keratitis (as judged clinically) cyclopentolate 1% twice daily eye drops may be used as an alternative. Once the anterior chamber reaction has settled, topical cycloplegia can be discontinued.
- Topical debridement of the cornea (in conjunction with corneal scrape sampling) can be a useful adjunct to therapy as it removes necrotic tissue and enhances antibiotic penetration.
- Good lid hygiene is important in cases of blepharitis.
- Initially all topical ocular corticosteroids should be stopped or significantly reduced.
- For patient comfort a preservative free lubricant e.g. Carmellose 1% eye drops should be used especially if there are any epithelial defects.
- The use of topical corticosteroids is controversial as there is no trial data to guide decisions. Some clinicians recommend adding in topical steroids **after**

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2-3 days of anti-infective medication providing the patients is responding. If steroids are used they should be at the minimum strength and frequency to control symptoms and the patients should be reviewed at least daily. The intra ocular pressure should be monitored carefully.

Follow up

- Once treatment has been commenced, patients should be reviewed after 48-72 hours depending on severity
- Daily review is usually unnecessary and can cause increased anxiety for the patient
- Seek a Consultant or senior review for advice regarding severe infected corneal ulcers or if there is no response to treatment.

With special thanks to the corneal team at Leeds Teaching Hospital NHS trust for kindly allowing us to adapt their microbial keratitis guidelines

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