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Bacterial Keratitis: Perspective on Epidemiology, Clinico-Pathogenesis, Diagnosis and Treatment

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التهاب القرنية الجرثومي : الأبعاد الوبائية، المرضية السريرية، التشخيصية والعلاجية

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الملخص: التهاب القرنية الجرثومي قد يكون حادا أو مزمنا، عابرا أو متكررا يصيب المناطق المختلفة من القرنية مثل الوسطية أو المحيطية . وقد يكون خطرها في تهديد البصر كامنا . وتنتج عن عوامل مؤهبة أكثرها انتشارا استعمال العدسات اللاصقة . المعطيات الوبائية تشير إلى انتشارها بشكل شامل . مع التقدم الحاصل في عوامل الإمراض والفحوص المخبرية مثل المناعة الكيميائية - النسيجية والمجهر المتألق والمقايسة المناعية وعلم الأحياء الجزيئي ووجود الجيل الرابع من المضادات الحيوية . كلها أثرت بشكل إيجابي على النتيجة النهائية لالتهاب القرنية الجرثومي. يجب الانتباه بشكل خاص لتلك الحالة وذلك لاحتمال تطورها بشكل سريع مما يؤدي إلى تلف القرنية بصورة كاملة خلال 24 - 48 ساعة . التشخيص المبكر وهو سريري بصورة أولية مدعوما بالمعطيات المجهرية الدقيقة والعلاج السريع مهم جدا لتقليل احتمالية فقدان البصر الدائمي والضرر البنيوي للقرنية .

مفتاح الكلمات: التهاب القرنية . السموم . عدسات لاصقة.

ABSTRACT: Bacterial keratitis is an acute or chronic, transient or recurrent infection of the cornea with varying predilection for anatomical and topographical parts of the cornea like marginal or central. It is a potentially sight-threatening corneal infection in humans that is generally found in eyes with predisposing elements, the most common of which is contact lens wear. The epidemiological data reveals the universal occurrence of this disease. With advances in the understanding of its pathogenesis, laboratory investigations like immunohistochemistry, fluorescent microscopy, enzyme immunoassays and molecular biology, and the availability of fourth generation antibiotics, the overall visual outcome in bacterial keratitis has improved with time. Particular attention should be given to this condition as it can progress very rapidly with complete corneal destruction occurring within 24-48 hours. Early diagnosis, which is primarily clinical and substantiated largely by microbiological data, and prompt treatment are needed to minimise the possibility of permanent visual loss and reduce structural damage to the cornea.

Keywords: Keratitis; Toxins; Contact lens

Bacterial keratitis is an acute or chronic, transient infection of the cornea with varying predilection for anatomical, topographical and geographic parts of the cornea. It can be of a slowly progressive or rapidly deteriorating suppurative type involving any part of the cornea. A variety of pathogens like bacteria, fungi, viruses and protozoa can infect the cornea, but bacteria top the list in causing vision threatening keratitis. As the number of contact lenses users increases globally, the incidence of corneal infection increases proportionately. In spite of advances in clinical diagnosis, molecular laboratory investigations, and the availability of potent antibiotics, visual morbidity continues to be high in underdeveloped countries. The importance of this disease can be judged by the fact that bacterial keratitis remains one of the most common global causes of irreversible blindness due to corneal diseases. The aim of this article is to review the recently available perspectives on the epidemiology, pathogenesis, clinical presentations, diagnosis and treatment modalities of bacterial keratitis.

Epidemiology

Since keratitis is not included in the five target diseases of WHO for blindness prevention, most of the data regarding keratitis is from individual publications.[1] Bacterial keratitis is one of the most important causes of corneal opacifications, which is the second common cause of legal blindness world-wide after cataracts. The pattern of microbial keratitis varies with geographic region and according to the local climate. The bacteriological profile in keratitis shows huge disparities amongst populations living

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in both western[2,3] and in developing countries.[4] The incidence varies considerably between western and developing countries due to the fact that less industrialised countries have significantly lower number of contact lens users, hence fewer contact lenses related infections. For example, USA has an incidence of 11 per 100,000 persons[5] for microbial keratitis as compared to 799 per 100,000 persons in Nepal.[6] Ormerod *et al*. described the staphylococcal species, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* as major isolates in microbial keratitis in North America.[7] In Sweden, Neuman and Sjostrand found *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most common Gram-positive bacteria in central microbial keratitis while *Pseudomonas aeruginosa* was the most common Gram-negative bacteria.[8]

Factors which influence the aetiology and pathogenesis of bacterial keratitis vary. They include: use of contact lenses, ocular surface diseases, corneal trauma, use of immunosuppressive medications and postocular surgery especially corneal graft. Contact lens related corneal ulcers in the general population have increased from almost 0% in the 1960s to 52% in the 1990s. Erie *et al*. [5] in Minnesota, USA, gave an incidence of ulcerative keratitis as 5.3 per 100,000 people per year, revealing an increase in incidence of 435% from the 1950s to the 1980s. Erie's study revealed contact lens wear as the most important risk factor. Epidemiology, regarding contact lenses as significant risk factor for bacterial corneal infections, is very significant. The annual incidence of ulcerative keratitis in contact lens wearers is 4-21 per 10,000 daily wear and extended wear soft contact lens wearers.[9] Extended wear soft contact lens users have a higher annual incidence of ulcerative keratitis than daily wear soft contact lenses. This was confirmed by Poggio *et al*.,[9] who in a case control study of ulcerative keratitis in soft contact lens wearers, found overnight use of contact lenses as the most important risk factor for ulcerative keratitis. The study provided the interesting revelation that smokers are three times more prone to develop keratitis than non-smokers. The rate of ulcerative keratitis is 1 in 2,500 daily wear contact lens users as compared to 1 in 500 extended wear contact lens users per year.

Pathogenesis

Several factors can be attributed to the onset of bacterial keratitis. Bialasiewicz *et al*. reported that trachoma, trauma and contact lens overwear are significant risk factors for infectious keratitis in Oman.[10] In almost all situations, it is the break in the continuity of the epithelium that starts the bacteriopathological process of keratitis.

In penetrating keratoplasty, 12% of patients develop corneal infections.[11] These eyes have predisposing risk factors like corticosteroids, sutures, epithelial defects and contact lens wear for developing post-operative infections. Both Gram-positive and Gram-negative organisms are involved.[12,13]

GENERAL BACTERIOPATHOLOGY IN MICROBIAL KERATITIS

Eighty percent of bacterial corneal ulcers are caused by *Staphylococcus aureus, Streptococcus pneumoniae* and *Pseudomonas* species. *Pseudomonas aeruginosa* is the most frequent and the most pathogenic ocular pathogen which can cause corneal perforation in just 72 hours. Bacteria causing keratitis may be Gram-positive or Gram-negative. The ability of an organism to adhere to the edge or base of an epithelial defect signatures its pathogenicity. Such an organism has the ability to invade stroma despite adequate host-defenses.[14] *Staphylococcus aureus, Streptococcus pneumoniae* and *Pseudomonas aeruginosa* have such an ability.[15,16] Membrane appendages such as fibrillae in Gram-positive organisms, fimbriae and glycocalyx in Gram-negative bacteria help these organisms adhere to damaged epithelial cells[14] and stroma. Bacteria loose their glycocalyx envelope once inside the stroma. *Pseudomonas aeruginosa* and *Neisseria gonorrhea* utilise glycocalyx to adhere to each other and to diseased epithelial cells[17] and contact lenses.[18] The adhering quality of *Pseudomonas aeruginosa*[19] is due to its pili containing calcium and magnesium. *Pseudomonas aeruginosa* gets attached to both contact lenses and epithelial breaks[17] due to its biofilm, a coating around the organism.

During bacterial corneal infections, there is activation of plasminogen to plasmin which is active proteolytically. Protease, chymase and tryptase cause epithelial microlesions and healing is delayed

due to the degradation of adhesive glycoproteins by proteolytic enzymes.[19] Some bacteria improve their chances of survival and become more pathogenic by producing a chemical slime which even resists phagocytosis and the bacteria can decrease their metabolic demand.[20] Proteases and certain lytic enzymes can help organisms like *Neisseria gonorrhea, Corynebacteium diphtheriae,* and *Listeria, Shigella* and Koch-Weeks bacilli to produce keratitis even through the intact epithelium. Proteases attack peptide bonds to dissolve elastin. Certain bacterial strains like *Pneumococci* resist ocular lysozyme and phagocytosis by forming polysaccharide capsules around them.

There are certain bacterial toxins and enzymes, including enzymes produced by polymorph nuclear cells, which help in the digestion and degradation of the corneal matrix. These include exotoxins produced by actively multiplying bacteria, endotoxins produced by organisms after their death, proteases, collagenases, coagulases, lipases and fibrinolysins. Endotoxins are lipopolysaccharides within the cell wall of Gram-negative bacteria. They are responsible for corneal ring infiltrates which are polymorph nuclear cells in stroma attracted by C-pathway and properdin activated chemotoxins. Ring infiltrates are believed to be antigen-antibody precipitates and are also seen on viral, fungal and *acanthamoeba* infections. The immune response does not have an established role in suppurative keratitis.

CONTACT LENS ASSOCIATED PATHOGENESIS

Contact lens wearers are more prone to bacterial infection, especially with Gram-negative organisms. The contact lens induces hypoxia, increases corneal temperature and decreases tear flow over the corneal surface. The adhering [21] of microorganisms (*Staphylococci, Moraxella, Candida*) to the contact lens and epithelium [22-24] is aided by mucus and proteins. The risk of developing corneal infections is 9-15 times greater with overnight use of contact lenses compared to daytime use. Aphakic eyes are more prone to microbial keratitis with extended wear soft contact lenses. There is a higher risk of bacterial keratitis with disposable contact lenses used overnight.[24] The most common organisms associated with contact lens related bacterial keratitis are *Pseudomonas aeruginosa* and *Staphylococci*. Bandage soft contact lenses are more often associated with polymicrobial infections (*Staphylococci, Streptococci, Serratia*). Extended wear soft cosmetic lenses are more prone to *Pseudomonas* infections.[25]

While Gram-negative organisms like *Pseudomonas, Haemophilus* and *Moraxella* cause infectious keratitis in extended wear cosmetic contact lens users, therapeutic soft contact lens wearers on the other hand are prone to corneal ulcers caused by Gram-positive bacteria especially *Streptococci*.

Clinical Presentation

The overall clinical course in bacterial keratitis is acute in onset with features relating to visual and sensory functions. Lid and conjunctival oedema, reduced vision, pain, redness, photophobia and discharge form the commonly presenting signs and symptoms.

The severity of signs and symptoms depends on the virulence of the organism, the host immune status, any prior disease of the cornea, any previous therapy with corticosteroids and the duration of the infection. The conjunctival reaction may be non-specific. Gonococcal, *Haemophilus* and pneumococcal corneal infections may have associated moderate to severe conjunctivitis with chemosis and sometimes pseudomembranes. The clinical signs and symptoms in bacterial keratitis may be altered or difficult to interpret if the cornea has had previous pathology like stromal inflammation, necrosis or opacification. Slit-lamp biomicroscopy shows cells and debris in the precorneal tear film and meniscus, absent corneal epithelium over an area of infection and focal suppurative process. It is important to document the size of any epithelial and stromal defect in at least two meridians.

Several authors have given grading systems in corneal ulcers, creating some difficulty in following them on an individual basis. For the sake of convenience, the following overall guidelines, can be employed for clinical diagnosis, treatment and follow-up: 1) mild reaction: focal, superficial suppuration; 2) moderate reaction: suppuration confined to superficial two-third of the cornea; 3) severe reaction: suppuration confined to posterior one-third of the cornea and may present as a ring abscess, scleral suppuration and impending

perforation.

Overall Gram-positive cocci form localised, round or oval, gray-white lesions with clear margins, minimal surrounding epithelial oedema and stromal infiltrates. Staphylococcal ulcers are more often found in compromised corneas like bullous keratopathy, dry eyes, chronic herpetic keratitis, atopic disease and rosacea keratitis. *Staphylococcus aureus* is found in 15% of cultures from lids of normal persons. This pathogen produces more severe corneal infiltration than *Staphylococcus epidermidis*. Both these strains frequently produce indolent lesions with distinct borders, non-oedematous surrounding stroma and they tend to be localised.

Long standing staphylococcal ulcers dig deep into the stroma producing intra-stromal abscesses and sometimes perforation. Occasionally multiple satellite stromal microinfiltrates may be seen. There may be radiating folds in the Descemet's membrane due to loss of stromal substance. Coagulase-negative staphylococcal corneal infections are usually associated with surgical procedures, foreign bodies and intraocular prosthetic devices.

Streptococcal bacterial keratitis has a rapid course. *Streptococcus viridans* keratitis is characterised by a distinct, non-inflammatory, indolent crystalline keratopathy. This entity is typically seen after penetrating keratoplasty. Clinically, one may find epithelial defects and loose sutures and there may be history of contact lens use and corticosteroids, resulting in a chronic infective process of the cornea.

Bacillus cereus, a large aerobic Gram-positive rod is extremely virulent. It causes rapid and devastating bacterial keratitis, starting as a ring infiltrate in the cornea away from the site of the injury and rapidly progresses to abscess formation often with corneal perforation. Other pathogens which produce ring infiltrates and ring abscesses in cornea are *Proteus, Pseudomonas aeruginosa, Streptococcus* and *Listeria* monocytogenes. Most of the ring abscesses develop following penetrating injuries at the limbus.[26]

Mycobacterium,[27] *Nocardia*[28] and *Actinomyces* species are Gram-positive branching filamentous bacteria found in soil. The keratitis follows soil contaminated corneal injury and produces an indolent ulcer with elevated hyphate edges, often with satellite lesions, mimicking a fungal ulcer. The cornea has a typical cracked windshield appearance.

Gram-negative corneal bacterial infections, on the other hand, are mostly rapid in onset and progress fast due to lytic enzymes like protease, lipase and elastase. These infections can lead to corneal perforation and the loss of an eye. The most common and virulent Gram-negative ocular pathogens belong to *Pseudomonas* species. *Pseudomonas* can contaminate ophthalmic solutions like fluorescein, ocular cosmetics like mascara and any substance containing traces of organic carbon.

Transmission electron microscopy[29] has shown that *Pseudomonas* can infect stroma within one hour of adhering to an injured corneal epithelium. Within 6-8 hours, it produces grayish superficial epithelial and stromal microinfiltration with oedema at the edge of the injury. During the next 18-24 hours, the stromal infiltration extends horizontally and vertically. There is a severe anterior chamber reaction with hypopyon. The symmetric and concentric extension involves the whole width and depth of the cornea. There is a characteristic diffuse grayish, epithelial inflammation and infiltration away from the main corneal lesion. During the next 48-96 hours, if untreated, a ring infiltration develops with scleral and corneal melting associated with greenish yellow mucopurulent discharge adhering to the ulcer. Within 2-5 days, an untreated corneal ulcer may lead to descemetocele formation and perforation of the cornea.[30]

Moraxella species,[30] a Gram-negative diplobacillus, causes infective keratitis in debilitated patients with a history of alcoholism, diabetes mellitus and chronic malnutrition. Trauma is an important predisposing factor. Typically, the location is paralimbal or paracentral, involving the inferior cornea. The lesion is oval, grayish white, shallow, irregular and indolent with mild to moderate anterior chamber reaction. The inflammation often remains localised, but if untreated, can spread to deep stroma[31] leading to endothelial decompensation and severe stromal and anterior chamber reactions.

Klebsiella, *Escherichia coli* and *Proteus keratitis* are common in compromised corneas with chronic epithelial disease, often without any history of trauma. A typical lesion has an indolent course with mild anterior chamber reaction.

The non-spore forming anaerobes like *Peptococci, Peptostreptococci* and *Propionibacterium* form a broad group of Gram-positive and Gram-

negative rods, found in mixed infections of the cornea. They are active and invasive under compromised conditions like trauma, surgery, corticosteroids and antibiotics.

Diagnosis

COLLECTION AND PROCESSING OF CLINICAL SAMPLES

Undoubtedly, microbiology remains the critical tool in the diagnosis of bacterial keratitis. Clinical acumen, though valuable, may falter in cases where keratitis has atypical manifestations due to prior therapy or certain ulcers. The rule however remains that wherever and whenever possible, a meticulous microbiological workup of bacterial keratitis should be done before therapy is initiated. Smears, culture and sensitivity to antimicrobials form the three fundamental tools of diagnosis. Cultures should always be preferred to smears as they are more specific and information yielding. The culture positive rate in bacterial keratitis and ulcers is 40-73%[31,32] as compared to 0-57% in Gram's staining.[31,33-34] Thirty-two percent of patients with bacterial keratitis have two or more bacteria. In polymicrobial keratitis,[34-36] Gram's staining is not of much value in identifying the causative pathogen. An infection that is deteriorating despite antibiotic therapy yields a poor bacterial count for examination and diagnosis. It is important to know that, while positive cultures and smears are very useful for diagnosis, negative results may not rule out corneal infection, especially where antibiotics have already been given. In this situation, a corneal biopsy may be mandatory to establish diagnosis or the suspension of the antibiotic therapy for 72 hours to enable a repeat culture. It is wise to obtain cultures from lids and conjunctiva of both eyes, even if there is unilateral bacterial keratitis, and use blood and chocolate agar plates. In spite of clinical evidence of bacterial keratitis, a methodology for diagnosis should be used. This should include aerobic bacteria, anaerobe non-spore forming bacteria, filamentous fungi and yeasts. There are occasions when preliminary fungal ulcers are infected secondarily by bacterial pathogens. *Mycobacteria* (acid fast), *Actinomyces* (non-acid fast) and *Nocardia* (variable) can be identified by Carbol-Fuchsin or Ziehl-Nelson stains. *Mycobacteria* can also be identified by fluorochrome stain and fluorescence microscopy. Immunological techniques available for the detection of bacterial antigens include direct immunofluorescence, immunoelectrophoresis, immunohistochemistry, fluorescent microscopy, enzyme immunoassays, agglutination, radioimmunoassay and molecular techniques.

It is important to remember that the topographical importance of the site of lesion chosen for smear taking is important for an effective yield of the bacteria, e.g. *Streptococcus pneumoniae* are more active near edge of the ulcer while the crater gives better yield for *Moraxella.*

In the presence of deep ulcers and abscesses without surface suppuration, it may be necessary to obtain corneal fragments with a blade, microsurgical scissors or a trephine. These fragments can be crushed on a glass slide for staining and also inoculated in thioglycolate and brain heart infusion (BHI). All corneal lesions due to contact lenses should be presumed to be infectious in origin, unless proved otherwise. It is mandatory to send the contact lenses, contact lens solutions and the carrying cases for laboratory cultures.

Preservatives in topical anesthetics may be bacteriostatic or bactericidal and may interfere with the results, besides which the drops may also be contaminated. Proparacaine is the least bactericidal and is recommended. Usually corneal specimens contain small numbers of organisms, especially with prior antibiotic therapy. Under such circumstances, it is mandatory to inoculate the specimen material directly into the culture media and avoid carrier and transport media. Debris from the corneal ulcer can be inoculated on the same blood agar plates which have the lid and conjunctival inoculates.

The scraping from the advancing edge and center of the infected ulcer can be done using a modified Kimura platinum spatula. A large gauge disposable needle is a possible alternative. The use of a slit-lamp makes the procedure more scientific. The material thus obtained is to be streaked on blood agar in a C shape. Growth along the C streak is microbiologically significant while any growth away from the C streak is probably a contamination. Additional specimens should be reserved for chocolate agar and Sabouraud agar without cycloheximide. Chocolate agar provides hemin (X-factor) and V-factor, essential for growth of *Haemophilus* and is ideal for isolation of *Neisseria*

and *Moraxella*. For anaerobic pathogens, it is ideal to use chopped meat glucose broth or thioglycolate medium with vitamin K. Thioglycolate broth also provides basic nutrients for aerobic organisms. Its sulfhydryl (SH) compound acts as an oxygen reducing agent which is suitable for anaerobic bacteria. BHI is valuable if a poor yield of organisms is expected as in patients on prior antibiotics. In patients with any signs or symptoms of dacryocystitis, fluid expressed from the lacrimal sac should be cultured.

Overall, Gram's stain is appropriate for bacteria and can also show dimorphic fungi in the yeast phase; however, cellular details appear better with a Giemsa stain. Gram-positive bacteria appear blue-purple and retain gentian violet while Gram-negative bacteria lose gentian violet and appear pink with safranin. If done meticulously, Gram's stain can identify the pathogen (single organism) in 75% of cases and in 37% of cases having mixed bacterial infections.[37] Giemsa can distinguish non-infectious keratitis by the type of inflammatory cells. In indolent corneal infections, it may be necessary to use acid fast stains for *Mycobacterium, Nocardia* and *Actinomyces* species. In order to get the maximum information, the sample should cover an area approximately 1cm in diameter on the glass slide. Excessive decolorisation should be avoided and immersion of the slide in 95% methanol or cold acetone for 5-10 minutes is preferable to heat fixation in maintaining the morphology and staining characteristics of the pathogens.

In addition to Gram's and Giemsa stains, an extra slide and some specimen material should be reserved for special stains like periodic acid Schiff, calcofluor, Gomori, acid fast bacilli and methenamine silver. All refrigerated media should be warmed to room temperature before inoculation to prevent fatal cold shock to the organisms.

INTERPRETATION OF CULTURE MEDIA

Though pathogens can be identified within 12-15 hours of inoculation, most aerobic bacteria in microbial keratitis appear only within 48 hours on standard culture media. The plates should be examined on daily basis and liquid media observed for turbidity. Blood agar is best for isolation of aerobic bacteria. Anaerobes are slow growing; therefore, cultures should be incubated for at least 10 days. The most common combination found in polymicrobial keratitis is aerobic Gram-positive coccus plus Gram-negative rod,[35] followed by fungus plus bacteria.[36] There are no established criteria for true diagnosis of corneal infections. One of the authentic criteria was put forward by Jones[35] which includes clinical signs of infection and isolation of ten or more colonies of bacteria on one solid medium and one additional medium in presence of a positive smear.

It is unusual to find Gram-positive rods or Gram-negative cocci or when two or more organisms are found in smears or cultures, so one should be cautious when such a result is obtained. Such observations are not correct in 75% cases.

The reasons for poor or negative results could be prior antibiotic therapy; an insufficient sample; excessive heat fixation; mechanical damage to cell wall architecture and a reluctance to examine the whole slide.

Management

GENERAL CONSIDERATIONS

Bacterial keratitis is a rapidly destructive form of microbial keratitis. Any doubtful microbial keratitis should be treated as bacterial keratitis unless proven otherwise. Some preventive approaches would go a long way towards minimising bacterial keratitis and its sequelae. Though the expanded range of antibiotics has made the treatment of bacterial keratitis easy, at times it may be devastating to loose an eye despite having dozens of anti-microbial drugs at our disposal. Eighty seven percent of bacterial corneal ulcers are caused by four groups of organisms, but no single antibiotic is effective against all organisms.

Baum and Barza have provided a historical review of current therapy of bacterial keratitis.[37] In the USA, patients of bacterial keratitis are treated on an outpatient basis, while in the UK such patients are usually admitted.

Gram's stain is a quick and helpful means of starting antibiotic therapy, however, there is a poor correlation between Gram's stain and culture results[38] and hence one should not rely too heavily on Gram's results. Gram's and Giemsa stain results may be non-diagnostic or inaccurate 30% of the time. It is ethical to start with wide spectrum antibiotics in corneal infections until culture reports and sensitivities are available, keeping in view the seriousness of the

disease and the few side effects of the drugs. An ideal antibiotic should be bactericidal, least allergic, and least toxic with good ocular penetration. The main aims of treatment of bacterial keratitis should be bacterial inhibition, healthy epithelialisation and prevention of complications.

One of the impressive antibiotics in the treatment of corneal infections has been ciprofloxacin (0.3%). It covers virtually all common corneal pathogens and has an edge over a combination therapy of aminoglycosides and cephalosporins in that ciprofloxacin is effective against many strains of aminiglycoside resistant *Pseudomonas*[39] and methicillin-resistant *Staphylococcus aureus* (MRSA).[40] The drug is also very effective against *Neisseria* species. Ciprofloxacin eye drops are very well tolerated; however, precipitate formation in the area of an epithelial defect occurs in 16% of cases, which usually resolves in spite of continued treatment.[41] Ofloxacin (0.3%) can be substituted for ciprofloxacin as a monotherapy in situations of unknown organisms or a new case or where there is no growth on first culture. Increasing resistance to the fourth generation fluoroquinolones has been reported amongst *Staphylococcus* species in the USA, and *Pseudomonas* species in India.[42] New generation fluoroquinolones like moxifloxacin and gatifloxacin have been introduced to treat such cases.[43-46]

One of the best combinations in the treatment of bacterial keratitis has been that of cefazolin 5% and tobramycin or gentamicin 2% fortified. Cefazolin (cephalosporin) covers Gram-positive cocci and some Gram-negative rods while tobramycin (aminoglycoside) covers most Gram-negative rods including *Pseudomonas* and some Gram-positive pathogens. Tobramycin is three times more potent than gentamycin against *Pseudomonas aeruginosa*, has good corneal penetration and less epithelial and conjunctival toxic than gentamycin.

In vitro resistance to antibiotics may not hold true under clinical conditions where a very high concentration of drugs is used in the form of topical drops. Acquired antibiotic resistance in bacterial keratitis is a problem with nosocomial infections in intensive care units and burn units.

The availability of single, broad spectrum antibiotics has made it possible to treat even moderate to severe infections of the cornea on an outpatient basis due to better drug compliance. Daily follow-up and frequent (up to 55 drops per day) drug instillation can take care of the patient satisfactorily. Clinical trials have shown that monotherapy with fluoroquinolones is as effective as combination therapy, with less toxicity.[47] Alexandrakis *et al*. have reported that fortified antibiotic preparations may be helpful in situations like advanced bacterial keratitis and resistance to fluoroquinolones.[48]

New generation broad spectrum penicillin drugs such as ticarcillin and piperacillin are undoubtedly potent weapons against certain corneal pathogens. Ticarcillin is 2-4 times more active against *Pseudomonas aeruginosa* than carbenicillin. Piperacillin has very high activity against *Klebsiella* and *Pseudomonas,* but should be combined with aminoglycosides to avoid the development of resistance. The incidence of allergic reaction to ticarcillin and piperacillin is 3.5% in the general population and 10% in penicillin treated patients. Ten percent mortality during anaphylaxis has been reported.[49]

BACTERIAL KERATITIS UNDER SPECIAL CIRCUMSTANCES

There are moments when there is no response to first line of treatment, neither can any organisms be identified. Here a second line of broad spectrum antibiotics should be started including vancomycin 5% (50 mg/ml), amikacin 5% (50 mg/ml) and trimethoprim 0.1% (16mg/ml). This combination kills resistant *Streptococci, Nocardia* and *Mycobacterium* as well. Erythromycin (0.5%) or rifampicin (2.5%) ointment may be used at night. *Mycobacterium chelonae* used to be the cause of severe and chronic keratitis after radial keratotomy. The pathogen is sensitive to topical amikacin 5%. *Nocardia* can be responsible for refractory keratitis. It may respond to topical amikacin 5% and erythromycin 0.5% with or without vancomycin 5% and trimethoprim 0.1%. Surgical debridement of the lesion helps in early recovery. The role of enzyme inhibitors like disodium edentate (0.05 M), acetylcysteine (20%), heparin (2%) has not been proven clinically in bacterial keratitis.

CORTICOSTEROIDS IN BACTERIAL KERATITIS

At cellular level, corticosteroids can be accepted as damage reducing agents in bacterial keratitis. Corticosteroids have two important actions:

first to decrease polymorphonuclear leukocyte activity at the level of ingestion and degranulation and, second, to reduce inflammation initiated by dividing bacteria and their toxins, host enzymes and hydrolytic enzymes from polymorphonuclear leucocytes.

Overall, steroids have a conflicting role in bacterial keratitis.[50] Davis *et al*.[51] have reported no adverse effect on bacterial status in keratitis due to *Pseudomonas* and *Staphylococcus aureus* when corticosteroids were given under cover of fortified bactericidal antibiotics. Smolin *et al*.[52] reported delayed eradication of corneal infection with combined treatment of corticosteroids and antibiotics, while Harbin[53] reported relapse of *Pseudomonas* keratitis in a corticosteroid treated patients.

It can be said that since there is no conclusive evidence about the efficacy of corticosteroids in bacterial keratitis, they should not be used at the commencement of therapy and may be used with caution under cover of antibiotics. One justifiable indication for steroids could be stromal necrosis due to Gram-negative bacilli to reduce the destructive components of inflammation.

ADJACENT THERAPY IN BACTERIAL KERATITIS

Adjacent therapy includes treatment of those extra-corneal factors which directly or indirectly initiate or enhance keratitis. Entropion, trichiasis, lagophthalmos and dry eyes should be treated meticulously. All of the following contribute significantly to effective treatment of bacterial keratitis: analgesics; control PF glaucoma; cycloplegics; patching for epithelial defects (only after elimination of bacterial infection); bandage soft contact lenses for indolent epithelial defects; extensive stromal ulcerations and microperforations. [54]

SURGICAL MANAGEMENT OF BACTERIAL KERATITIS AND ITS COMPLICATIONS

Small corneal perforations and descemetoceles can be treated with cyanoacrylate tissue glue adhesive. It helps to restore anterior segment integrity, but it is not a permanent solution. The glue just supports the eye to a later safe stage when surgery may help. The stromal ulcer bed should be debrided before applying glue and a contact lens should be used over it. Cyanoacrylate is toxic to endothelium and the lens.[49] A patch graft can be an alternative to cyanoacrylate glue, but it may be destroyed by bacteria, hence it should only be used after effective antimicrobial therapy. A conjunctival flap should never be used over active infected necrotic tissue or the flap will become necrosed. The flap can be used to promote healing over a debrided corneal ulcer bed, especially for peripheral ulcers.

Penetrating keratoplasty (PK) is indicated in about 10% of cases of bacterial keratitis. The pathogens frequently involved in such an indication include; *Streptococcus pneumoniae, Staphylococcal* species, *Pseudomonas aeruginosa, Moraxella,* beta-hemolytic *Streptococci*[55] and *Pseudomonas* species. The main indications for PK in bacterial keratitis[49] are large corneal perforations; small corneal perforations with consistent bacterial growth and progressive suppuration including scleral involvement despite antibiotic therapy. The main objectives of PK in bacterial keratitis are to eliminate the infection load, restore corneal integrity and preserve vision.[49] The outcome of PK in bacterial keratitis depends upon any previous *Herpes simplex* virus keratitis, the severity of the stromal inflammation, the size and location of the graft and any prior therapeutic measures like contact lenses or glues. The best chance of success for PK is when the procedure is done after a total bacterial kill has been achieved and before corneal vascularisation appears.

Oral corticosteroids are given 24 hours before and seven days after a PK to curtail inflammation. To prevent suture erosion, a relapse of keratitis and wound dehiscence after PK, it is important to prepare a healthy recipient edge by debriding all necrotic corneal tissue. Bites should be taken through healthy recipient corneal tissue and excised infected cornea sent for a laboratory workup to guide post PK antimicrobial therapy.

Gudmundsson *et al*.[56] have reported that less than 50% patients treated by PK for bacterial keratitis achieve a visual acuity better than pre-graft vision. The University Eye Hospital Erlangen-Nuremberg evolved a triple therapeutic approach for the treatment of keratitis in 223 eyes: 1) topical and systemic antibiotics; 2) antibiotics and corticosteroids; 3) antibiotics, corticosteroids and early tectonic penetrating keratoplasty. Patients with keratoplasty had the shortest hospital stay while

visual rehabilitation was better in the corticosteroid group and best in the keratoplasty group.[57]

Clinical Course and Prognosis

Even with an armamentarium of highly selective and broad spectrum antimicrobials in the therapy of bacterial keratitis, 24% of patients develop vision threatening complications like descemetoceles, perforations, endophthalmitis, atrophy and disorganisation of the affected eye. An eye with bacterial keratitis may heal with minimal or no opacification, vascularisation or visual deficit; however, inadequately, ignorantly or late treated bacterial keratitis can have an extremely dangerous clinical course because of corneal opacification, secondary glaucoma, scleral extension of infection and anterior segment disorganisation. There may be scarring of the cornea with hyalinisation, calcium and lipid deposits.

Prognosis is poor in corneal infections due to *Streptococcus pneumoniae* unless treatment begins rapidly. With increasing age and debility, the prognosis is not good. Destruction of the corneal lamella leads to corneal thinning and ectasia. Corneal fistulae, anterior synechiae due to a fibrinous anterior chamber reaction, seclusion pupillae, cataract, secondary glaucoma, panophthalmitis and pthisis bulbi can be the sequale of bacterial keratitis.

Amongst Gram-negative infections of the cornea, *Moraxella* keratitis has a good visual prognosis. Healing may be with scar formation, usually away from the visual axis. In mixed or polymicrobial infections, perforation and pthisis may develop. *Pseudomonas* infections invariably lead to corneal perforation and loss of the eye if untreated, especially in immunocompromised patients with a history of contaminated traumatic bacterial keratitis. Shah *et al*. have suggested vision improvement following prompt and standard treatment of contact lens induced severe keratitis.[58]

Conclusion

Despite all the advances in the diagnosis and treatment of bacterial keratitis, it remains the most aggressive and destructive pathogen invading the cornea and is responsible for sight threatening corneal scarring and vascularisation. On the one hand, the expansion of contact lenses wear has increased the worldwide incidence of bacterial keratitis, while, on the other hand, newer methods of diagnosis, aided by more specific laboratory investigations and newer antibiotics have revolutionised the visual outcome in these patients. Modern surgery has also contributed significantly towards minimising ocular morbidity. An early diagnosis, repetitive cultures and smears, and professional management go a long way towards preventing the complications of bacterial keratitis.

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CME Quiz Questions

1. Which type of contact lens is responsible for the highest incidence of ulcerative keratitis?
   A. Hard contact lenses
   B. Disposable contact lenses used overnight
   C. Day wear soft contact lenses
   D. Polymethyl metha-acrylate lenses
2. The most pathogenic ocular pathogen which can cause corneal perforation in just 72 hours is:
   A. *Staph.aureus*
   B. *Strep. pneumoniae*
   C. *Pseudomonas*
   D. *Neis. gonorrhea*
3. The Ring infiltrates seen in the corneal ulcer are:
   A. Damaged epithelial cells
   B. Polymorph nuclear cells in stroma
   C. Multiplying bacteria
   D. Nothing but collection of the mucus
4. If the eye with keratitis has greenish discharge the most likely causing organism is:
   A. *Moraxella species*
   B. *Klebsiella*
   C. *E. coli*
   D. *Pseudomonas*
5. The culture positive rate of the bacterial keratitis and ulcers is:
   A. 40-73%
   B. 50 -77%
   C. 20-30%
   D. >80%
6. The most common combination of organisms found on culture in polymicrobial keratitis is:
   A. Aerobic Gram-positive coccus plus Gram-negative rod
   B. Fungus plus bacteria
   C. Acanthoemeba
   D. None of the above
7. The staining used for identification of Gram-positive and Gram-negative bacteria is:
   A. Gram stain
   B. Hematoxylin
   C. Eosin
   D. NaOH (sodium hydroxide)
8. Corneal infections associated with surgical procedures, foreign bodies and intra-ocular prosthetic devices are usually caused by:
   A. Coagulase-negative Staphylococcus
   B. Strep. pneumoniae
   C. Pseudomonas
   D. Neis. gonorrhea
9. The most potent antibiotic against pseudomonas is:
   A. Ofloxacin
   B. Gentamicin
   C. Piperacillin
   D. Cefazoline
10. The incidence of developing vision threatening complications like descematoceles, perforations, endophthalmitis, as a sequel of keratitis is:
    A. 24%
    B. 10%
    C. 30-40 %
    D. <15%

Answers: 1 - b; 2 - c; 3 - b; 4 - d; 5 - a; 6 - a; 7 - a; 8 - a; 9 - c; 10 - a