Decision-making in the Management of Microbial Keratitis

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Abstract: The successful management of suppurative microbial keratitis requires five steps: (1) make the clinical diagnosis, (2) perform the proper laboratory procedures, (3) initiate antimicrobial therapy, (4) modify the initial therapy, and (5) terminate therapy. The most helpful guidelines to decision-making in these steps are: (1) the clinical impression, (2) severity of keratitis, (3) results of laboratory studies, (4) disease potential of the responsible organism, and (5) effectiveness and toxicity of various antimicrobial agents. Selection of initial antibiotics ideally should be directed by interpretation of the corneal smears. The preferred initial antibiotic for keratitis caused by a Gram-positive coccus is cefazolin; for a Gram-negative rod, gentamicin; and for a filamentous fungi or yeast, natamycin. Broad, antibacterial therapy should be reserved for suspected bacterial keratitis with negative smears or for severe infections with antecedent treatment. Miconazole may be an effective, alternate agent in fungal keratitis. The safety and efficacy of corticosteroids in microbial keratitis have not been established. [Key words: bacterial keratitis, corneal ulcer, fungal keratitis, microbial keratitis.] Ophthalmology 88:814–820, 1981

The management of suppurative, microbial keratitis requires a succession of five steps: (1) make the clinical diagnosis, (2) perform the proper laboratory procedures, (3) initiate antimicrobial therapy, (4) modify the initial therapy, and (5) terminate therapy. Only one step is relatively fixed and automatic in methodology, that is the technique of laboratory investigation. The others confront the ophthalmologist with several options and require decisions based on the clinical signs, results of laboratory studies, disease potential of the responsible organism, and effectiveness and toxicity of various antimicrobial agents.

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Step one, making the clinical diagnosis, necessitates skill and experience in distinguishing microbial keratitis from other types of ulcerative and infiltrative keratitis. This decision is based on antecedent factors and the clinical features. The most decisive elements of the history are trauma, antimicrobial or immunosuppressive therapy, general health of the host, and antecedent status of the cornea. As there is no absolute, biomicroscopic sign of infection, the ophthalmologist must proceed with laboratory investigations if there is any equivocation about the possibility of microbial keratitis. Initiation of antimicrobial therapy without these studies is a grave, but all too frequent, error in management. A plan for obtaining and utilizing corneal material for smears, cultures, and special studies is outlined elsewhere.[1,2] This and subsequent guidelines are based on the recognition that the principal causes of suppurative, microbial keratitis in the United States are the aerobic bacteria, anaerobic nonspore-forming bacteria, filamentous fungi, and yeasts.[1,3]

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SELECTION OF INITIAL THERAPY

Having completed the laboratory studies, the ophthalmologist faces three options: (1) initiate antibacterial or antifungal agents based on the microorganisms detected in the Gram, Giemsa, or special stains; (2) initiate some form of broad antibacterial therapy, not guided explicitly by the results of the smears; or (3) defer antimicrobial therapy pending the ensuing clinical course and results of the cultures.

I contend that the initial decision should be based on the interpretation of the corneal smears, the assessment of the severity of the keratitis, and the clinical impression (Table 1),[1,4] Adopting this plan requires adequate sampling of the areas of corneal suppuration, confidence in the interpretation of the corneal smears, and, ideally, absence of antimicrobial therapy within the previous 24 to 48 hours. This strategy has evolved from consideration of the most likely responsible microorganisms, relative validity of the corneal smear in the detection of bacteria and fungi, and safety and efficacy of a restricted number of antibiotics. Complete, empiric antimicrobial coverage cannot be achieved in infectious keratitis. The proposal that all cases of suspected microbial keratitis should be treated with two or more, broad spectrum, antibacterial antibiotics without regard for the corneal smears seems inappropriate.

The most common causes of bacterial keratitis are the Micrococcaceae (*Staphylococcus, Micrococcus*), *Streptococcus* species, *Pseudomonas* species, and the Enterobacteriaceae (*Citrobacter, Enterobacter, Klebsiella, Proteus,* and *Serratia*). Among 188 consecutive cases of bacterial keratitis at the Baylor College of Medicine and the Cullen Eye Institute, 162 (86%) were caused by one or more of these bacteria.[1] Similar experience has been reported by others.[3] The most common cause of fungal keratitis is the hyphate group of filamentous fungi, which include *Aspergillus, Cephalosporium, Curvularia,* and *Fusarium.*[1,3] *Candida albicans* is the most frequently isolated yeast. The free-living amoeba, *Acanthamoeba,* is a newly recognized cause of suppurative keratitis, which is clinically indistinguishable from bacterial and fungal infections.[5,6]

Our experience has demonstrated that the Gram and Giemsa stains are relatively reliable for detecting the presence and type of organism in the corneal smear.

Table 1. Severity Grade of Microbial Keratitis

Feature	Severity Grade	
	Nonsevere	Severe
Rate of progression	Slow, moderate	Rapid
Suppuration: Area	< 6 mm diameter	> 6 mm diameter
Depth	Superficial 2/3	Inner 1/3
Depth of ulceration	Superficial 1/3	Inner 1/3
Perforation	Unlikely to occur	Present, imminent
Scleral suppuration	Absent	Present

Among cases of bacterial keratitis, the Gram stain correctly identified the staining property and morphology of the responsible organism in 62 of 83 (75%) single infections and 17 of 46 (37%) mixed infections (overall 61%).[1] The corneal smears directed initiation of one or more effective antibiotics in 77 of 83 (93%) single infections and 33 of 46 (72%) mixed infections (overall, 85%), based on the design for utilization of two antibacterial agents in the absence of detectable organisms. Hyphal fragments of filamentous fungi or blastospores or pseudohyphae of yeasts were detected in 32 of 41 (78%) cases of fungal keratitis.

My plan for initial therapy of nonsevere keratitis is based on the interpretation of the smears and the clinical impression (Table 2). The selection and dosage of antibiotics for each common variable of stain morphology for bacteria and fungi are listed in Table 3. The term "combined (broad) antibacterial therapy" implies the use of a cephalosporin antibiotic (cefazolin or cephaloridine) and gentamicin. Animal studies have indicated that the efficacy of antibiotic therapy is enhanced by increasing the concentration of drug in the topical preparation[7,8] and reducing the interval between application of drops.[9] Antibacterial drops should be administered every 15 minutes during the first 24 to 48 hours of therapy. Natamycin is generally applied hourly as the suspension adheres to the surface of the cornea and remains in the inferior fornix for this interval. The rationale for subconjunctival injection of antibiotics is based on animal studies that have demonstrated that subconjunctival injections produce higher drug levels in corneal tissue and aqueous humor than can be achieved by topical application of the same medication. Several studies have failed to demonstrate

Table 2. Initial Therapy of Nonsevere Keratitis

Result of smears	Selection of agent(s)
One type of bacterium	One antibacterial agent
Two or more types of bacteria	Multiple, specific antibacterial agents
Hyphal fragments, yeasts, or pseudohyphae	Natamycin
No microorganisms	Clinical impression:
	Bacterial keratitis: Combined (broad) antibacterial therapy
	Fungal keratitis: Defer therapy
	Non-infectious keratitis: Defer therapy

Table 3. Selection of Initial Antibiotics Based on Smear Morphology

Smear Morphology	Antibiotic		
	Topical	Subconjunctival	Intravenous*
Gram-positive cocci	Cephaloridine or cefazolin (50 mg/ml)	Cephaloridine or cefazolin (100 mg)	Methicillin (200 mg/kg/day)
Gram-positive rods	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Gram-positive filaments	Penicillin G (100,000 units/ml	Penicillin G (500,000 units/ml)	Penicillin G (2.0–6.0M units/4 hrs)
Gram-negative cocci	Penicillin G (10,000 units/ml)	Penicillin G (500,000 units/ml)	Penicillin G (2.0–6.0M units/4 hrs)
Gram-negative rods	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Acid-fast bacilli†	Amikacin (10 mg/ml)	Amikacin (25 mg)	Amikacin (5 mg/kg/day)
Two or more bacteria	Cephaloridine or cefazolin (50 mg/ml) and Gentamicin (14 mg/ml)	Cephaloridine or cefazolin (100 mg) and Gentamicin (20 mg)	Methicillin (200 mg/kg/day) and Gentamicin (3.0–7.0 mg/kg/day)
Hyphal fragments	Natamycin (50 mg/ml)	none‡	none§
Yeasts, pseudohyphae	Natamycin (50 mg/ml)	none‡	none¶

* Reserve for scleral suppuration or corneal perforation (impending or existing).
† Reserve for suppurative *Mycobacterium* species (atypical complex).
‡ Consider miconazole in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration (5 mg).
§ Consider intravenous miconazole in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration (1200–3600 mg/day).
¶ Consider oral flucytosine in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration (150 mg/kg/day).

a significant therapeutic effect of subconjunctival antibiotics in a rabbit model of *Staphylococcus aureus* and *Pseudomonas aeruginosa* keratitis.[10,11] Adverse reactions of subconjunctival or periocular injections include pain; conjunctival and corneal inflammation; inadvertant intraocular injection; and those associated with systemic blood levels of the agent, such as anaphylaxis. I conclude that the potential advantage of enhanced intracorneal concentration of drug outweighs these risks, and I prefer to inject the selected antibiotic every 12 to 24 hours during the initial 24 to 48 hours of therapy.

For the selection of initial antibiotics (Table 4), designation of keratitis as "severe" generally requires the presence of at least three of the features listed in Table 1. The determinants within this algorithm are the interpretation of the smears and the use of antimicrobial agents within the preceding 24 to 48 hours. Antibacterial drops should be administered at 15-minute intervals. I repeat subconjunctival antibiotics every 12 hours during the initial 24 to 48 hours of therapy. Systemic therapy should be reserved for scleral suppuration or impending or existing corneal perforation. The rationale for systemic antibiotics is based on pharmacokinetic studies and animal models of keratitis, which suggest that this route may increase drug concentration in the cornea and aqueous humor and thereby enhance topical and periocular therapy. Efficacy in human keratitis has not been established. As for other infections, the decision for utilization of intravenous antibiotics must be based on consideration of the potentially serious, adverse effects. Ideally, administration should be monitored by an internist or infectious disease clinician.

The basis for selection of each initial antibiotic in the schema has been previously reviewed.[1] The cephalo-

Table 4. Initial Therapy of Severe Keratitis

Results of Smears	Selection of Agent(s)
One type of bacterium	Antecedent therapy None: One antibacterial agent Received: Combined (broad) antibacterial agent
Two or more bacteria	Combined (broad) antibacterial therapy
Hyphal fragments, yeasts, or pseudohyphae	Natamycin and/or micronazole
No microorganisms	Combined (broad) antibacterial therapy

sporin antibiotics are generally more active in vitro against penicillinase-producing staphylococci and the streptococci than bacitracin, erythromycin, and lincomycin.[12–14] Cefazolin (50 mg/ml) is less toxic than bacitracin (10,000 units/ml) to the conjunctiva and cornea following topical application and less irritating than methicillin or other semisynthetic penicillins following subconjunctival injection of equal doses (100 mg). There is insufficient pharmacokinetic, experimental, and clinical data to select the most effective and least toxic cephalosporin antibiotic for staphylococcal and streptococcal keratitis. Cefazolin has a low degree of serum binding and produces less pain following injection than other cephalosporin derivatives. The potential role of the newer cephalosporin antibiotics in the management of bacterial keratitis has not been defined. One second generation drug, cefoxitin, is more effective against certain genera of Enterobacteriaceae (*Citrobacter, Serratia*) than the older agents and is more active against a variety of anaerobic, Gram-negative rods than clindamycin or erythromycin. A variety of third generation cephalosporin antibiotics are currently being investigated. These compounds retain the activity of the original cephalosporins against *Staphylococcus* and *Streptococcus* but are equally effective as the aminoglycoside antibiotics against pseudomonas and other Gram-negative rods.

Gentamicin remains the initial antibiotic of choice in suspected Gram-negative rod keratitis on the basis of stability, corneal and intraocular penetraiton, and bactericidal activity against *Pseudomonas, Enterobacter, Klebsiella,* and other aerobic gram-negative organisms. Tobramycin is two- to four-fold more active by weight than gentamicin against *Klebsiella, Enterobacter, Serratia,* and *Proteus*. The clinical significance of these differences in the therapy of keratitis has not been defined. Strains of *Pseudomonas* resistant to gentamicin are usually also resistant to tobramycin. Since amikacin is less susceptible to inactivation by bacterial enzymes than either gentamicin or tobramycin, strains of Gram-negative bacteria resistant to gentamicin and tobramycin may be sensitive to amikacin. With regard to the consideration of parenteral therapy of severe bacterial keratitis or other ocular infection, a recent study suggested that tobramycin may be less nephrotoxic than gentamicin.[15]

The initial drug of choice for nonsevere keratitis caused by either filamentous fungi or yeasts is natamycin (pimaricin) 5% suspension (Natacyn™). Natamycin is a tetraene polyene antibiotic that achieves fungicidal activity by binding to the sterol membrane to produce lethal imbalances of intracellular constituents. The majority of isolates of *Aspergillus, Cephalosporium, Curvularia, Fusarium,* and *Candida* are susceptible in vitro and do not acquire resistance. Unlike other polyenes, natamycin suspension is stable at room temperature and is relatively nonirritating to the conjuctiva and cornea following topical application. We have recently noted, however, two patients with moderately severe conjunctival hyperemia, follicle formation, and persistent epithelial ulceration following topical use of natamycin for four and six weeks. Natamycin is not absorbed from tissue and produces necrosis and granulomata following injection.

Miconazole is an inert, stable imidazole antifungal antibiotic, similar in structure and mechanism of action to thiobendazole, clotrimazole, and econazole. Our experience and that of others[16,17] suggest that topical application (10 mg/ml) and subconjunctival injection (5–10 mg) of the undiluted, parenteral preparation of miconazole (Monistat®) is effective in superficial and deep keratitis caused by *Candida albicans, Aspergillus* species, and other susceptible fungi. The drug is relatively nonirritating in these dosages and routes of administration. Intravenous administration (30 mg/kg/day) produces inhibitory concentrations of drug in aqueous of inflamed eyes and may aid in therapy of fungal endophthalmitis sequential to deep keratitis.[18,19] Adverse reactions to intravenous miconazole include chills, fever, nausea, anorexia, altered sensorium, cardiac arrest, anaphylaxis, and anemia.[20]

The use of corticosteroids in the initial and subsequent management of microbial keratitis remains controversial. Corticosteroids are the most effective agents for suppression of the harmful effects of the inflammatory response, and there is ample evidence that topically applied corticosteroids suppress corneal inflammation.[21–23] Animal studies of *S aureus*[24] and *P aeruginosa*[7,25] keratitis have implied that topical corticosteroids do not interfere with the bactericidal activity of antibiotics to which the organisms are sensitive. Other experimental studies[25] have suggested that corticosteroids prolong replication of the responsible organisms and delay wound healing despite concurrent antibacterial therapy. The safety and efficacy of corticosteroids in human microbial keratitis have not been established by controlled clinical trials. The role of nonsteroidal, anti-inflammatory agents and various anti-collagenase compounds has not been defined.

MODIFICATION OF THERAPY

The number and type of options during the first days of therapy vary with the initial decisions and the results of the corneal cultures. Among other factors, the decision to modify therapy is based on the clinical response, potential severity of keratitis caused by the responsible organism(s), tolerance of the antimicrobial agents and in vitro susceptibility of the isolate(s) to various antibiotics. Regardless of the laboratory studies, it may be desirable to continue the initial agent for 48 hours if there is clinical improvement. Criteria for a positive culture must consider the adequacy of sampling of corneal material, potential of contamination of media by microflora of the precorneal tear film, capacity of the organism(s) to grow in the various media selected for primary isolation, differential rate

Table 5. Modified Antibiotic Therapy Based on Preliminary Identification of Selected Organisms

Organism	Antibiotic		
	Topical	Subconjunctival	Intravenous*
Micrococcaceae, sensitivities unknown	Cephaloridine or cefazol in (50 mg/ml)	Cephaloridine or cefazolin (100 mg)	Methicillin (200 mg/kg/day)
Micrococcus, Staphylococcus: penicillin-resistant	Cephaloridine or cefazolin (50 mg/ml)	Cephaloridine or cefazolin (100 mg)	Methicillin (200 mg/kg/day)
Micrococcus, Staphylococcus; penicillin-sensitive	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	Penicillin G (2.0–6.0M units/4 hrs)
Streptococcus,† Pneumococcus	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	Penicillin G (2.0–6.0M units/4 hrs)
Anaerobic gram-positive coccus	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	Penicillin G (2.0–6.0M units/4 hrs)
Corynebacterium species	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	Penicillin G (2.0–6.0M units/4 hrs)
Azotobacter species	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Mycobacterium species	Amikacin (10 mg/ml)	Amikacin (20 mg)	Amikacin (5 mg/kg/day)
Neisseria gonorrhoeae *N. meningitidis*	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	(2.0–6.0M units/4 hrs)
Enterobacteriaceae	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Pseudomonas species	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Other aerobic, Gram-negative rod	Gentamicin (14 mg/ml)	Gentamicin (20 mg)	Gentamicin (3.0–7.0 mg/kg/day)
Anaerobic Gram-negative rod	Penicillin G (100,000 units/ml)	Penicillin G (500,000 units)	Penicillin G (2.0–6.0M units/4 hrs)
Fusarium species	Natamycin (50 mg/ml)	None	None
Other filamentous fungi	Natamycin (50 mg/ml)	None§	None**
Candida species	Natamycin (50 mg/ml)	None§	None¶

* Reserve for scleral suppuration or corneal perforation (impending or existing).
† Excludes *S. faecalis;* requires combined therapy (eg, penicillin G or gentamicin).
‡ Atypical *Mycobacterium* complex.
§ Consider miconazole (5 mg) in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration.
¶ Consider oral flucytosine (150 mg/kg/day) in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration.
** Consider intravenous miconazole (1200–3600 mg/day) in the presence of scleral suppuration, corneal perforation, or intraocular extension of suppuration caused by susceptible strains.

of growth of organisms on various media, and possibility of polymicrobial keratitis. In our series of microbial keratitis, 74 of 232 cases (32%) were caused by two or more bacteria or fungi as interpreted by standard criteria.[1] Antecedent therapy may also invalidate the corneal cultures.

If the corneal cultures yield an organism generally considered to be substantially more susceptible to an antibiotic other than that initially selected, I substitute that drug according to the guidelines in Table 2. If initial therapy was broad coverage with cefazolin and gentamicin and one organism is isolated, I terminate the less effective drug or select a preferred agent (Table 2). The theoretical advantages of single antibiotic include reduction in the likelihood of adverse drug reactions, dilutional effect, drug antagonism, and superinfection. If the cultures remain negative, consideration must be given to the likelihood of noninfectious keratitis and antibiotics may be discontinued in consideration of corticosteroid or other therapy. The majority of aerobic bacteria responsible for keratitis appear in standard media within 48 to 72 hours. In our series, 77% of filamentous fungi and yeasts grew in one or more media within three days of inoculation.[1]

Ophthalmologists must recognize that standard, disc diffusion, antibiotic susceptibility tests are based on concentrations of antibiotics achievable in serum and do not relate to the potential effectiveness of a drug in the preocular tear film or cornea following topical and subconjunctival administration. Modification of antibacterial therapy is best guided by determination of the minimal inhibitory and bactericidal concentrations of appropriate agents against the isolate. Additional studies are required to define the pharmacokinetics of these agents in tear film and tissue following the standard routes of administration. The significance of in vitro susceptibility testing of antifungal agents has not been determined.

TERMINATION OF THERAPY

Strict guidelines cannot be provided for the decision to reduce or terminate antibiotics in keratitis improving on therapy. The duration of viable organisms in the cornea must vary by the responsible bacterium or fungus, duration of infection, severity of the suppuration, and multiple other factors. Such data on human keratitis is not available. Repeat corneal cultures during therapy are not reliable. Tissue destruction may occur by mechanisms other than replication of microorganisms.[26] The objectives of this stage of management are to halt additional structural alteration, promote stromal healing and re-epithelialization, and prevent drug toxicity.

Decision should be based on daily slit-lamp examinations and corneal drawings, with notation of the area of epithelial and stromal ulceration; density and location of the stromal suppuration; appearance of the perimeter of the stromal suppuration; degree and area of cellular infiltration in the adjacent stroma; and severity of the anterior chamber reaction. The dimensions of the areas of ulceration and suppuration should be estimated by means of an eyepiece reticule or a continuously variable height of the slit beam. The most helpful signs of improvement are blunting of the perimeter of the stromal suppuration, reduction in the cellular infiltrate and edema in the transition zone in the adjacent stroma, and progressive reepithelialization. Fibrin exudate on the endothelium and hypopyon may resolve slowly and do not necessarily reflect the degree of improvement of the corneal process. In keratitis responding to therapy, I generally terminate subconjunctival antibiotics and reduce the frequency of instillation of drops after 48 or 72 hours. Topical therapy is further reduced by doubling the interval between application of drops every three to four days. The number of days between dose reduction should be prolonged in therapy of organisms known capable of persisting in the cornea for extended periods such as *P. aeruginosa, F. solani,* other filamentous fungi, and *C. albicans.* Following discharge from the hospital, the patient should be alert to the danger signs of resurgent keratitis and promptly report increased pain, decreased vision, or purulent discharge. The end point of therapy must not be complete re-epithelialization as any of these antibiotics may deter epithelial healing and produce other toxic and allergic reactions. The role of corticosteroids in the late stages of management has not been defined.

The successful therapy of suppurative microbial keratitis requires negotiation of a series of decisive steps. The complexity of decisions in this sequence can be minimized by proper utilization of the microbiology laboratory, rational selection of antibiotics, and a plan for reduction and termination of therapy.

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