Antimicrobial Activity of Iodoquinol 1%–Hydrocortisone Acetate 2% Gel Against Ciclopirox and Clotrimazole

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Commercially available topical formulations consisting of iodoquinol 1%–hydrocortisone acetate 2%, ciclopirox 0.77%, and clotrimazole 1%–betamethasone dipropionate 0.5% were assessed for their antimicrobial activity against cultures of Micrococcus luteus, Propionibacterium acnes, *methicillin-resistant* Staphylococcus aureus *(MRSA),* Pseudomonas aeruginosa, Corynebacterium aquaticum, Trichophyton mentagrophytes, Malassezia furfur, Microsporum canis, Candida albicans, Trichophyton rubrum, *or* Epidermophyton floccosum. *At 1 and 5 minutes following inoculation into suspensions of each product, aliquots were removed, serially diluted, and plated onto appropriate agar to determine the log reduction in colony-forming units (CFUs) for each organism. Iodoquinol 1% produced the broadest and greatest antimicrobial activity as measured by a 3-log reduction of CFU, active against all microbes tested following incubation times of 1 or 5 minutes, except* M luteus. *By contrast, ciclopirox 0.77% and clotrimazole 1% showed activity against* P aeruginosa *and* T rubrum, *with ciclopirox also killing* M luteus, P acnes, M canis, C albicans, *and* E floccosum at 5 minutes. *Iodoquinol 1%–hydrocortisone acetate 2% also was the only product that showed effective antibacterial reduction of MRSA at 1 minute.*

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Bacteria, fungi, and yeast may co-colonize and contribute to the pathophysiology of a variety of dermatoses, including intertrigo, tinea pedis, tinea cruris, tinea corporis, tinea capitis, tinea versicolor, and onychomycosis.[1,2] In the absence of a culture, differential diagnosis of bacterial and fungal infections can be challenging and can result in unresolved infections following initial therapy. Therefore, the use of broad-spectrum topical agents may be particularly useful for treating intertrigo; other mixed infections, such as dermatophytosis complex; and dermatoses at risk for infection.

A variety of common fungi, normally innocuous on the skin, can produce serious infections, especially in immunocompromised individuals. *Trichophyton rubrum* is the most prevalent dermatophyte on the human body, accounting for approximately 80% of the incidence of tinea pedis and onychomycosis.[3-7] *Trichophyton mentagrophytes* also is a common cause of tinea pedis, tinea corporis, and sometimes superficial onychomycosis.[3,4] This dermatophyte generally is more resistant to antifungal treatments (eg, ketoconazole, bifonazole) compared with *T rubrum*.[8] Both strains also have shown resistance to griseofulvin and fluconazole.[9,10] *Microsporum canis* is primarily found in cats and dogs. In humans, M *canis* is the principle cause of tinea corporis and tinea capitis.[11] Sometimes M *canis* produces mycetomalike lesions in immunocompromised hosts. M *canis* has shown resistance to fluconazole, which has been associated with up-regulation of the ubiquitin gene, *Ub*, similar to *T mentagrophytes*.[12] *Epidermophyton floccosum* causes tinea pedis, tinea cruris, tinea corporis, and onychomycosis.[7,13] Infection occurs primarily in nonliving cornified layers of the epidermis, though a small number of invasive

infections have been observed in immunocompromised patients.[14] *Malassezia furfur* causes tinea versicolor, found most commonly on the neck, back, and chest, and less frequently on the face and scalp.[15] Immunocompromised patients are particularly susceptible to infection in tissue folds. The azoles and terbinafine showed limited effectiveness against *Malassezia* species, including *M furfur,* while amphotericin B generally demonstrated better killing effects.[16] *Candida albicans,* a common and generally noninfectious bacterium in more than 80% of the population worldwide, can cause thrush in immunocompromised patients.[17] *C albicans* exhibits resistance to fluconazole, amphotericin B, and voriconazole.[18,19] Although most azole-type compounds produce good clinical resolution and mycologic conversion of individual fungal species in skin infections, they show limited effectiveness against a wide variety of fungi. The antibacterial activity of azole compounds is limited, generally confined to gram-positive organisms.[20]

Bacteria are known to adapt and develop antibiotic resistance quickly under selective pressure in both laboratory settings and patient populations in which a high level of antibiotics is being used. *Propionibacterium acnes* is present in skin acne,[21] *Corynebacterium aquaticum* is a causative agent in meningitis and urinary tract infections,[22-24] and *Micrococcus luteus* generally is a nonpathogenic organism associated with endocarditis[22,25]; each is found in healthy individuals and all have been found to be resistant to both tetracycline and erythromycin.[21-24] *Pseudomonas aeruginosa* infections frequently cause increased morbidity and mortality in hospitalized and immunocompromised patients.[26] This organism increasingly has been associated with urinary tract infections, particularly with the use of catheters, and has been found to be intrinsically resistant to ampicillin, most cephalosporins, and macrolides because of an impermeable outer membrane and the ability to actively transport the antibiotic out of the cell.[27] *P aeruginosa* also has shown resistance to gentamicin, tobramycin, and amikacin sulfate.[28] Currently, one of the more insidious bacterial infections with potentially deadly effects is caused by *Staphylococcus aureus*. Methicillin-resistant *S aureus* (MRSA), originally found primarily in hospital or chronic care settings, more recently has occurred in community-based settings.[29] It has been shown that the most common sites of MRSA infection are skin and soft tissue, accounting for 80% to 90% of all infections.[30] Often originating from skin inoculation,[31] MRSA is 1 of the 2 most frequent causes of bacteremia and carries a high rate of morbidity and mortality.

With the possibility of coinfection and the use of gross examination as the first and possibly only diagnostic criterion of skin conditions, it is necessary to use a broad-based antifungal and antibacterial agent with a lower-potency steroid to avoid suppression of skin immunity. Iodoquinol (and related 8-hydroxyquinolines) and ciclopirox olamine are 2 agents that have shown efficacy against a wide range of bacteria and fungi in clinical studies or in vitro kill testing.[20,32,33] Despite widespread use of iodoquinol as a topical anti-infective, data demonstrating its killing activity against bacteria and fungi in vitro are limited. To compare the anti-infective potency of commonly used antifungal agents in vitro, log reduction kill tests were conducted using commercially available topical preparations of iodoquinol 1%–hydrocortisone acetate 2%, ciclopirox 0.77%, and clotrimazole 1%–betamethasone dipropionate 0.5% on a variety of pathogenic bacteria, fungi, and yeast responsible for common skin infections.

Material and Methods

Test Products and Microorganisms—The anti-infective test products were all prescription products: iodoquinol 1%–hydrocortisone acetate 2% gel (each gram contains 20 mg of hydrocortisone acetate, 10 mg of iodoquinol, and 10 mg of aloe polysaccharide in purified water, carbopol, magnesium aluminum silicate, PPG-20 methyl glucose ether, aminomethyl propanol, propylene glycol, glycerine, benzyl alcohol, SD alcohol 40-B, biopeptide, hydrochloric acid, FD&C blue 1, and FD&C yellow 10); ciclopirox 0.77% (each gram contains 7.70 mg of ciclopirox olamine in a water-miscible vanishing cream base consisting of purified water USP, cetyl alcohol NF, mineral oil USP, octyldodecanol NF, stearyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF [1%] as preservative); and clotrimazole 1%–betamethasone dipropionate 0.5% (each gram contains 10 mg of clotrimazole and 0.64 mg of betamethasone dipropionate [equivalent to 0.5 mg of betamethasone] in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic, and phosphoric acid, as well as benzyl alcohol as a preservative). All of the topical products were purchased from a retail pharmacy.

All microorganisms were purchased from American Type Culture Collection (ATCC®). The bacterial strains used were *M luteus* (ATCC No. 10240b), *P acnes* (ATCC No. 6919), *S aureus* (MRSA) (ATCC No. 700698),

P aeruginosa (ATCC No. 15691), and C *aquaticum* (ATCC No. 14665). The strains of fungi used were *T mentagrophytes* (ATCC No. 10270), M *furfur* (ATCC No. 44338), M *canis* (ATCC No. 10214), C *albicans* (ATCC No. 10231), *T rubrum* (ATCC No. 11900), and *E floccosum* (ATCC No. 52066).

Culture Conditions—All bacterial organisms were prepared by inoculating the surface of trypticase soy agar (TSA) slants (containing pancreatic digest of casein, enzymatic digest of soybean meal, sodium chloride, and agar), and fungi were prepared by inoculating the surface of TSA plates (containing enzymatic digest of casein, enzymatic digest of animal tissue, agar, and dextrose). Each bacterial culture then was incubated at 30° to 35°C for 18 to 24 hours, whereas fungi were incubated at 23° to 28°C for 48 hours for yeasts and a minimum of 5 days for mold. *T mentagrophytes* and M *furfur* required a humid environment (growth conditions maintained at 75% relative humidity) to obtain sufficient numbers of organisms for testing. Following the incubation period, microorganisms were harvested by washing the slants and plates with sterile phosphate-buffered saline (PBS). Using a spectrophotometer, each microbial suspension was adjusted to approximately 10^8 colony-forming units (CFUs) per milliliter to create a stock suspension. The stock solution was diluted further in a 1:10 ratio with PBS for a final concentration of 10^7 CFU/mL.

Log Reduction Test Protocol—Log reduction kill testing was used to determine the effectiveness of each product at reducing specific microorganism populations. For each microorganism tested, 20 mL of test product or 20 mL of PBS as a control was inoculated with 0.2 mL of microorganism in sterile centrifuge tubes to yield a final inoculum of 10^5 CFU/mL. The test product and control PBS tubes were shaken for 1- and 5-minute intervals. At 1 and 5 minutes, 1 mL of inoculum from the test product and control PBS tubes was removed and diluted with neutralizing broth in a 1:10 ratio. Additional dilutions were performed to give 1:100 and 1:1000 dilutions.

To determine reduction of CFU following incubation with anti-infective test products, 1 mL from each dilution was plated in sterile Petri dishes using melted TSA agar for bacteria and Sabouraud dextrose agar for fungi as growth media. Bacterial plates were incubated at 30° to 35°C for 48 hours and fungal organisms at 22° to 28°C for 5 to 7 days. Control samples treated with PBS were given the same treatment. After incubation, plates were counted to determine the number of CFUs remaining after treatment. All tests were performed in triplicate.

Data Analysis and Antimicrobial Threshold—The standard 99.9% (3 log) decrease in the initial inoculum was used as a threshold for anti-infective compounds to be considered bactericidal and fungicidal against specific microorganisms.[34]

Results

The log reduction results for each microorganism are shown in Figures 1 and 2. Control conditions are not displayed because PBS did not produce any significant killing of the bacterial or fungal isolates, supporting the specificity of the test products. Because this study was meant to determine the killing spectrum of iodoquinol versus ciclopirox and clotrimazole, iodoquinol 1%–hydrocortisone acetate 2% is referred to throughout by its anti-infective ingredient, iodoquinol.

Of the 11 bacteria and fungi tested, iodoquinol 1% displayed the broadest killing activity against microorganisms. M *luteus* was the only bacterium not killed to the 3-log threshold in 1 minute (Figure 1). At 5 minutes, M *luteus* was reduced by 2.9 logs, just below the specified threshold. *T mentagrophytes* and M *furfur* were not killed to the 3-log threshold among fungi in 1 minute (Figure 2). At 5 minutes, however, all fungi were reduced by greater than 3 logs by iodoquinol.

Ciclopirox 0.77% also demonstrated both bactericidal and fungicidal activity but failed to meet the killing threshold of 3-log reduction in CFU for MRSA and C *aquaticum*, even at 5 minutes (Figure 1), whereas it showed a 3-log reduction against all fungi except *T mentagrophytes* and M *furfur* at 1 minute (Figure 2). Even by 5 minutes of incubation, ciclopirox did not reduce *T mentagrophytes* and M *furfur* to the 3-log threshold.

By contrast, clotrimazole 1%–betamethasone dipropionate 0.5% only was active against *P aeruginosa* bacteria in 1 minute (Figure 1). Clotrimazole failed to reduce any other bacterial species to the 3-log threshold, even by 5 minutes. Unlike iodoquinol and ciclopirox, clotrimazole displayed no killing of M *canis* and C *albicans* (Figure 2). Clotrimazole only reached the 3-log reduction threshold against *T rubrum* and *E floccosum* at 5 minutes, though reduction of *T mentagrophytes* was just below this threshold at the same time (2.8 logs).

The Table summarizes the number of microorganisms for which the CFU was reduced by at least 3 logs. Iodoquinol displayed the most rapid and extensive antimicrobial effect, killing 8 of 11 microorganisms in 1 minute and 10 of 11 in 5 minutes. Ciclopirox killed only 5 of 11 microorganisms in 1 minute and 7 of 11 in 5 minutes. Clotrimazole killed only 1 of 11 microorganisms in 1 minute and 3 of 11 in 5 minutes.

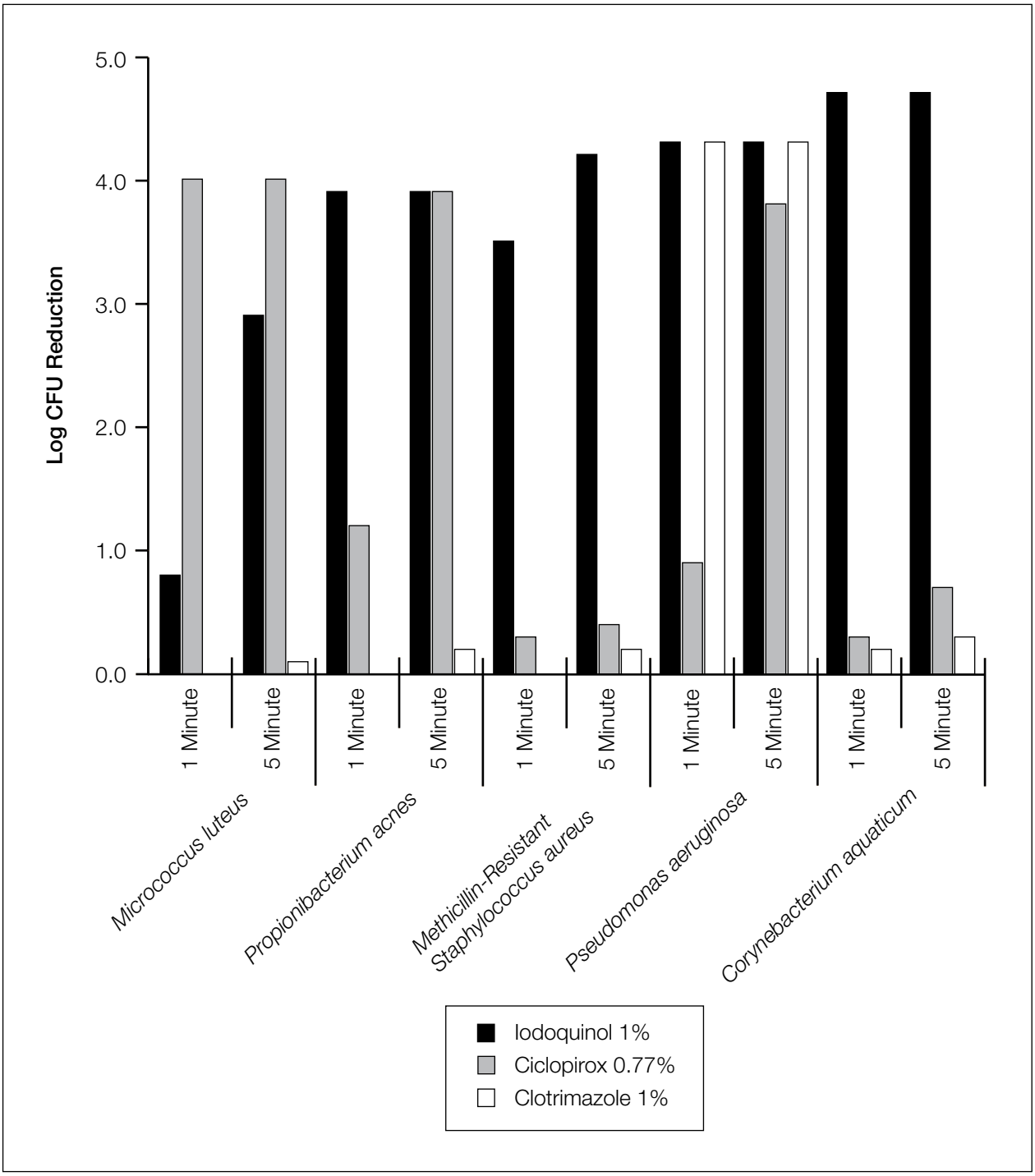

Figure 1. Bactericidal activity of topical products (iodoquinol 1%–hydrocortisone acetate 2% in a gel formulation; ciclopirox 0.77% in a cream formulation; and clotrimazole 1%–betamethasone dipropionate 0.5% in a cream formulation). CFU indicates colony-forming unit.

Comment

Azole-based therapies and antibiotics have been widely used throughout the past 50 years in an attempt to control and treat bacterial and fungal infections. However, both bacteria and fungi have developed mechanisms to deal with this biochemical assault, especially in immunocompromised patients.[35-37] Resistance has become a major issue, requiring the use of newly developed therapies or other drugs that do not develop similar patterns of resistance. Iodoquinol, an amoebicidal drug, has shown limited development of resistance in treating protozoal

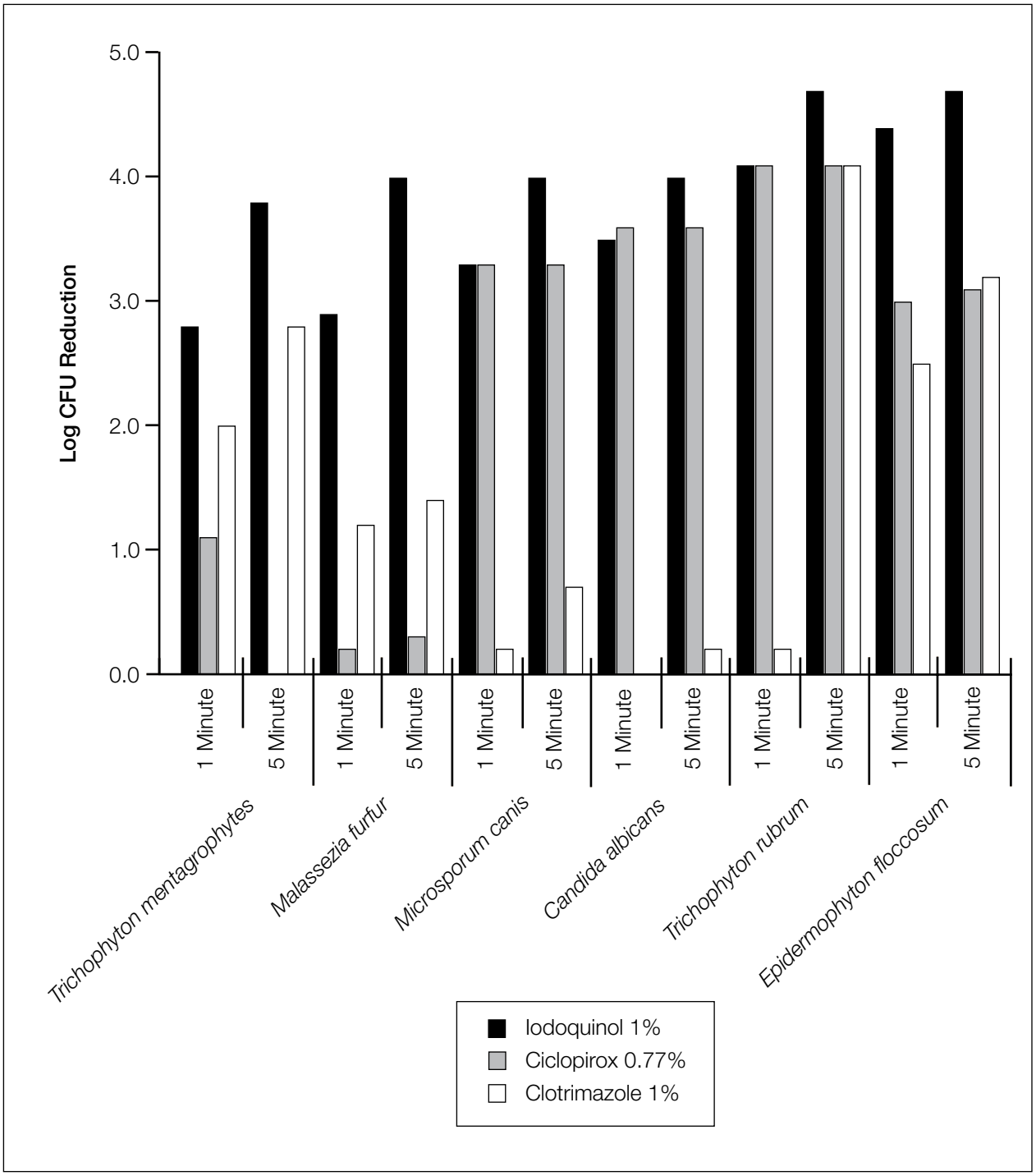

Figure 2. Fungicidal activity of topical products (iodoquinol 1%–hydrocortisone acetate 2% in a gel formulation; ciclopirox 0.77% in a cream formulation; and clotrimazole 1%–betamethasone dipropionate 0.5% in a cream formulation). CFU indicates colony-forming unit.

parasite *Entamoeba histolytica* infections, usually through plasma pump mechanisms, which actively remove hydrophobic drugs from the protozoa.[38] Although iodoquinol has been used for years in topical preparations, only limited knowledge exists regarding the spectrum of effectiveness against a variety of common drug-resistant bacteria and fungi. Even today, identification of bacterial and fungal infections primarily is based on gross examination rather than biochemical or microscopic identification of organisms. Furthermore, because the incidence of coinfection of skin with bacteria and fungi is common,[1,2] it is

Number of Microorganisms Killed by Exposure to Topical Products (3-Log Reduction in Colony-Forming Units)[a]

	Iodoquinol 1%	Ciclopirox 0.77%	Clotrimazole 1%
Organisms killed in 5 minutes			
Bacteria (n=5)	4	3	1
Fungi (n=6)	6	4	2
Total (N=11)	10	7	3
Organisms killed in 1 minute	8	5	1

[a]Test products included iodoquinol 1%–hydrocortisone acetate 2% in a gel formulation; ciclopirox 0.77% in a cream formulation; and clotrimazole 1%–betamethasone dipropionate 0.5% in a cream formulation.

necessary to treat these complex infections with an antifungal and antibacterial agent that has the broadest spectrum possible against these common microbes.

This study demonstrated that a topical prescription product containing iodoquinol 1% killed a greater number of common pathogenic strains of bacteria and fungi than either ciclopirox 0.77% or clotrimazole 1%, as demonstrated by in vitro log reduction kill testing. As anticipated, both the iodoquinol- and ciclopirox-containing products demonstrated bactericidal activity against gram-positive and gram-negative organisms as well as common dermatophytes and yeast. Of note, ciclopirox failed to display killing activity against MRSA and *C aquaticum*. Both bacteria had previously shown susceptibility to ciclopirox.[20] This discrepancy is likely due to the longer incubation times used by Kokjohn and colleagues[20] and supports the data presented here suggesting that iodoquinol generally may produce more rapid killing of microbes than ciclopirox. This difference in onset of action may relate to a variety of factors, including the different vehicles used in the formulation of commercially available products and possible differences in the mechanism of action of the 2 agents. This latter possibility is difficult to evaluate in light of current evidence indicating that both iodoquinol and ciclopirox likely exert their antimicrobial effects, at least in part, through chelation of metals.[20,39,40]

Unlike iodoquinol and, to a lesser extent, ciclopirox, clotrimazole primarily reduced CFU numbers of fungi but not bacteria. This pattern of results was expected because imidazoles primarily are antifungal agents, with limited antibacterial activity. Not surprisingly, because of its fungistatic (rather than fungicidal) mechanism of action,[41] clotrimazole failed to reduce CFU numbers of organisms, including *M canis* and *C albicans*, that previously had shown susceptibility over longer incubation times.[42,43] It also is interesting to note that clotrimazole was active against a strain of the gram-negative bacterium, *P aeruginosa*, because the antibacterial activity of imidazoles generally are believed to be limited to gram-positive organisms.[20] To our knowledge, this is a novel finding and requires replication in other *P aeruginosa* isolates.

There are several potential clinical implications of this study. Given the widespread co-colonization of bacteria, fungi, and yeast in conditions like intertrigo and tinea pedis, iodoquinol 1%–hydrocortisone acetate 2% gel appears to be an appropriate first-line treatment of infectious dermatoses because of its broad-spectrum efficacy. Moreover, these are the first published data demonstrating the activity of iodoquinol against a MRSA isolate. This intriguing finding suggests that iodoquinol may be a useful component of prophylaxis or management of increasingly common antibiotic-resistant *S aureus* skin and soft tissue infections, including those infections acquired via community and postsurgical wound exposures.

The mechanism of action of halogenated 8-hydroxyquinolines likely is due to their ability to chelate metals from local environments, which may deprive microorganisms of essential metallic nutrients.[44] However, the exact mechanism by which iodoquinol exerts its antimicrobial action is mostly unknown.[45] Other halogenated 8-hydroxyquinolines are known to inhibit the RNA-dependent DNA polymerase involved in reverse DNA strand synthesis as well as RNA synthesis by chelation of necessary metal cofactors such as copper, manganese,

magnesium, and zinc.[46,47] It is likely that this mechanism of action will not result in development of resistance by bacteria or fungi compared with antibiotic use. Additional testing is warranted against a broader range of clinical isolates and to determine minimum inhibitory concentrations of these agents against susceptible microorganisms.

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