

Epidemiology of interdigital infections of toe web spaces in Shanghai, China: Etiology, risk factors, and therapeutic approaches

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Abstract

Background

Interdigital infections are frequently misdiagnosed as tinea pedis and remain intractable to treatments because of high recurrence rates and potential complications. We aimed to understand the epidemiology of interdigital infections in Shanghai, China.

Methods

We conducted a cross-sectional study at Shanghai Dermatology Hospital from January 2019 to December 2019, enrolling 57 patients with acute interdigital inflammation. Patients received antibiotic therapy and underwent long-term follow-up. Clinical features and medical histories, including blood, bacterial, and mycologic examination results, cultures and drug susceptibility test results, and follow-up data were analyzed for pathogenic agents.

Results

We found *Pseudomonas aeruginosa* (40.35%), *Staphylococcus aureus* (36.84%), and other bacteria (22.8%). Compared to other bacteria, *P. aeruginosa* interdigital infections were more inclined to co-infect with fungal agents. Further, *P. aeruginosa* interdigital infections were frequently seen in the spring and autumn and in patients aged 60–69 years. However, interdigital infections caused by *S. aureus* occurred more frequently in the summer and in patients aged 31–40 years. We found that levofloxacin had excellent therapeutic effects.

Conclusion

Our findings may inform treatment and diagnostic guidelines and, subsequently, help reduce the rate of recurrence and improve patient outcomes following interdigital infections.

Background

Interdigital infections of the toe web space may present as relatively asymptomatic, mild, or scaling conditions or as acute forms with an exudative, macerated, painful inflammatory process that is frequently accompanied by a foul odor [1]. Clinically, these conditions had previously been diagnosed as tinea pedis and were considered to be purely dermatophyte induced. However, acute interdigital infections respond poorly to pure antifungal agents. Thus, the dermatophyte population cannot be solely responsible for the clinical spectrum seen in interdigital infections.

Dermatophyte fungi, however, are not the only pathogens found in toe-web intertrigo. Various species of *Candida*, gram-negative bacteria, and non-dermatophyte molds may be discovered in pathologic toe-webs and may play a contributing role in interdigital infections. Previous studies have demonstrated that *Pseudomonas aeruginosa* is the main causative agent of these clinical forms of infection, which are characterized by an acute ingravescent trend [2]. Likewise, gram-positive bacteria, such as *Streptococci spp.* and *Staphylococcus aureus*, have also been thought to cause interdigital infections, and their prevalence rates have gradually risen in recent years [1, 3]. A relapse of symptoms has frequently been seen in patients with interdigital infections, despite active treatment [1, 4]. Thus, an epidemiologic survey of interdigital infections has significant potential for improving outcomes for these patients.

To evaluate the incidence of acute ingravescent interdigital infections and their causative agents in Shanghai, China, we performed a cross-sectional study and epidemiologic survey of 57 patients with interdigital infections. The aim was to delineate the main clinical aspects, risk factors, causative organisms, age and seasonal distribution characteristics, and recommended therapeutic regimens.

Methods

Patients samples

Participants with acute inflammation of the interdigital spaces were enrolled in the study at Shanghai Dermatology Hospital from January to December 2019. Clinical characteristics of the patients included erythema, macerations, and marked erosions resulting from varying degrees of malodorous exudate in toe web spaces. Patient data, including age, sex, signs and symptoms of disease, medical history, and promoting factors were also recorded. At both the beginning and end of the treatment regimen, hematology and blood chemistry evaluations, direct fluorescence microscopy of fungus, bacterioscopic smear examinations, mycologic and bacterial cultures, microbial identifications, and antimicrobial susceptibility testing were performed on all patients. Exclusion criteria included topical or systemic use of antibiotics in the previous 4 weeks. Written informed consent was obtained from all participants. This study was approved by the Ethics Committee of Shanghai Dermatology Hospital, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis

Data were entered and managed in Microsoft Access. The database was then transferred into SPSS version 20.0 (Armonk, IBM Corp., NY) for statistical analysis. McNemar's tests were used for comparison of positive rates of direct microscopy and cultures. All statistical tests were two-sided, and results were considered significant at a *P*-value of < 0.05.

Results

Clinical features of patients with interdigital infections of toe web spaces

During a year of observation, 57 patients with acute interdigital infections were recruited (Table 1). Men were affected more, with a men/women ratio of 3:1. The mean age of patients was 49.88 years (range: 7–97 years). Among all patients, 37 (64.91%) had both feet involved, and 20 (35.09%) had only one foot affected. The search for possible promoting factors showed that 23 (40.35%) patients had a history of scratching or rubbing because of pruritus and 12 (21.05%) patients had a history of performing a hot-water foot bath. Sixteen cases (28.07%) had a history of self-medication with locally available unreasonable treatments (such as keratolytic irritation medicines, antifungals, or corticosteroid creams) for a condition they suspected to be tinea pedis. Nine (15.79%) patients experienced pruritus and developed symptoms after rainfall; four (7.02%) reported that they had attended public swimming pools and baths. Primary dermatosis, such as allergic contact dermatitis and hyperhidrosis, were observed in five (8.77%) patients.

Table 1

Clinical features of patients with interdigital infections of toe web spaces enrolled in the study.

Characteristic	n	%
No. of cases	57	
Male	42	73.68
Age, y (range)	48 (7–97) [†]	
Site		
Biped	37	64.91
Monopodia	20	35.09
Predisposing factors		
Scratching or rubbing	23	40.35
Previous unreasonable treatment; use of Local keratolytics, irritating medicines, antifungals, corticosteroids, etc.	16	28.07
Hot water scalding	12	21.05
Wading rainfall	9	15.79
Primary dermatosis: allergic contact Dermatitis, hyperhidrosis, etc.	5	8.77
Attending swimming pools, public baths, etc.	4	7.02
[†] Data are given as median (range), or frequencies.		

Clinical symptoms were similar in most patients and mainly manifested as erythema, vesicopustules, erosions, and marked maceration resulting from varying degrees of malodorous exudates. The color of the macerated lesions was yellowish-green (Figs. 1a-c) in 23 patients, and yellowish-white (Figs. 1g-i) in the other 34. The lesions affected the interdigital spaces of one or both feet, whereas the inflammatory process extended toward the digito-plantar sulcus, the sole, and even the back of the foot. The affected patients complained of itching, pain, burning, and restricted mobility.

Pathogens isolated in interdigital infections

Bacteriological studies were performed for all patients (Fig. 2). The most common pathogens isolated from the interdigital infections were *P. aeruginosa* (23/57, 40.35%) and *S. aureus* (21/57, 36.84%). Other gram-negative bacteria included *Escherichia coli* (2/57, 3.51%), *Serratia marcescens* (2/57, 3.51%), *Proteus mirabilis* (1/57, 1.75%), *Citrobacter koseri* (1/57, 1.75%), and *Enterobacter cloacae complex* (1/57, 1.75%). In addition to *S. aureus*, isolated gram-positive bacteria also included *Enterococcus faecalis* (3/57, 5.26%), *Streptococcus pyogenes* (1/57, 1.75%), *Staphylococcus epidermidis* (1/57, 1.75%), and *Staphylococcus haemolyticus* (1/57, 1.75%).

Meanwhile, mycological tests were performed on all patients with different pathogenic bacteria (Table 2). The positive rate of microscopic examination of fungi was 43.86% (25/57) at the initial visit. More rarely, fungi were isolated contemporaneously at a rate of 36% (9/25). For those patients who had a previous negative fungal microscopy result, repetition of mycological tests at the end of the antibiotic treatment showed a 46.88% (15/32) positive rate. The positive rate of fungal culture after bacterial infection recovery was 86.67% (13/15), significantly higher than that from the first visit (86.67% vs. 36%, $P=0.001$; Supplementary Table 1). We further analyzed the correlations between fungal and bacterial infections. The positive rate of microscopic examination of fungi was 95.65% in interdigital infections caused by *P. aeruginosa*, compared to 52.38% and 53.85% in interdigital infections caused by *S. aureus* and other bacteria ($P=0.002$ and $P=0.003$, respectively; Supplementary Table 2).

Table 2
Fungal isolation in interdigital infections before and after antibiotic treatment.

	Fungal infections together with bacteria		Fungal infections after bacteria recovery		Total (Direct microscopy%)
	Direct microscopy	Culture	Direct microscopy	Culture	
<i>Pseudomonas aeruginosa</i> (n = 23)	13	3	9	8	22(95.65%)
<i>Staphylococcus aureus</i> (n = 21)	8	5	3	3	11(52.38%)
Other (n = 13)	4	1	3	2	7(53.85%)
Total	25 (43.86%) [†]	9 (36%) [‡]	15 (46.88%) [§]	13 (87.67%) [¶]	
Note: Other, including <i>Escherichia coli</i> , <i>Proteus mirabilis</i> , <i>Serratia marcescens</i> , <i>Enterococcus faecalis</i> , <i>Streptococcus pyogenes</i> and <i>Staphylococcus epidermidis</i> .					
[†] The positive rate of direct microscopy was 43.86% (25/57) before antibiotic treatment.					
[‡] The positive rate of fungal culture was 36% (9/25) before antibiotic treatment.					
[§] The positive rate of direct microscopy in those patients who had a previous negative mycological test result was 46.88% (15/32) after antibiotic treatment.					
[¶] The positive rate of fungal culture in those patients who had a previous negative mycological test result was 87.67% (13/15) after antibiotic treatment.					

Seasonal and age distribution curves of patients with interdigital infections

The onset of interdigital infections revealed a seasonal distribution, but they mainly occurred between March and November (Fig. 3a), and the incidence peak occurred in July. With gram-negative bacterial infections, represented by *P. aeruginosa*, the main incidence peak occurred in spring, and the sub-incidence peak occurred in autumn. As the most common gram-positive bacteria, the main morbidity season of *S. aureus* infection was summer.

Patients were categorized into eight groups according to age (< 20 years, 21–30 years, 31–40 years, 41–50 years, 51–60 years, 61–70 years, 71–80 years, and > 80 years) (Fig. 3b). The results showed that the age group most affected was 61–70 years for interdigital infections caused by *P. aeruginosa*, followed by

51–60 years and 71–80 years. Furthermore, *S. aureus* infection primarily affected individuals aged between 21 and 50 years, peaking in the 31–40 years age group.

Antibiotic sensitivity patterns of bacterial isolates from interdigital infections

The majority of gram-negative bacteria showed sensitivity to cefepime (83.33%), imipenem (80%), amikacin (93.33%), cefoperazone-sulbactam (96.67%), and levofloxacin (100%), but low sensitivity to amoxicillin/clavulanic acid (53.33%) and ceftazidime (76.67%) (Table 3). Gram-positive bacteria isolates were highly resistant to penicillin (70.37%), erythromycin (59.26%), and clindamycin (62.96%) but sensitive to levofloxacin (92.59%), linezolid (100%), vancomycin (100%), and tigecycline (100%). The overall sensitivity rate of bacteria (including gram-negative and gram-positive bacteria) to levofloxacin was 96.49%.

Table 3
Antibiotic sensitivity pattern of bacterial isolates from interdigital infections.

	Gram-negative (n = 30)	Gram-positive (n = 27)	Total (n = 57)
Amoxicillin/clavulanic acid	16 (53.33%)	ND	
Ceftazidime	23 (76.67%)	ND	
Cefepime	25 (83.33%)	ND	
Imipenem	24 (80%)	ND	
Amikacin	28 (93.33%)	ND	
Cefoperazone-Sulbactam	29 (96.67%)	ND	
Levofloxacin	30 (100%)	25 (92.59%)	55 (96.49%)
Penicillin	ND	8 (29.63%)	
Erythromycin	ND	11 (40.74%)	
Clindamycin	ND	10 (37.04%)	
Linezolid	ND	27 (100%)	
Vancomycin	ND	27 (100%)	
Tigecycline	ND	27 (100%)	

ND, not detected.

Treatment

All patients received mycological and bacteriological tests simultaneously. The patients received corresponding antifungal and/or antibiotic therapy according to the results of the direct examination for fungus and bacteria. Systemic levofloxacin treatment was used in 57 episodes; among them, two cases were changed to erythromycin based on drug sensitivity tests. In cases in which yeasts or dermatophytes were observed, therapy was supplemented with systemic antifungal drugs. In addition to the systemic antimicrobial therapy, symptomatic treatment included oral antihistamines and topical therapy, such as compound philodendron liquid and boric acid lotion, oil, or paste. The patients who had a negative mycological test at the initial visit underwent repeat mycological testing after antibiotic therapy. When

applicable, antifungal therapy was started. Finally, all patients were given health education instruction, including information on frequent footwear changing, keeping the feet dry, avoiding scratching and scalding, and active treatment of local primary skin diseases.

After 2 weeks of systemic and local treatments, all patients experienced a significant reduction in pruritus and pain. Infections in all patients improved markedly, with rapid resolution of maceration (Figs. 1d-f, j-l). Even with strict monitoring of the microbial flora, four patients (7.02%) experienced relapse by the 6-month follow-up.

Discussion

Interdigital infection is a spectrum of relatively common, troubling, and neglected disorders [3], especially in the humid and rainy climates of southern China. It was first described as a specific dermatologic entity by Amonette and Rosenberg in 1973 [5]. A variety of terms have been used to describe this disorder, including gram-negative bacterial toe web infection, which is characterized as an acute bacterial infection of the toe web spaces due to *Pseudomonas spp.* alone, or with other gram-negative bacteria. However, gram-positive bacteria, such as *E. faecalis* and *S. aureus*, have also been isolated as pathogenic germs from interdigital infections [4, 6]. Meanwhile, the prevalence of this disease caused by gram-positive bacteria has been rising in recent years [2, 7]. In the present study, we examined 57 cases of pathological toe webs and found *P. aeruginosa* to be the causative agent in 40.35% of cases and *S. aureus* in 36.84% of cases. We suggest that gram-positive bacteria are present in a considerable number of cases of interdigital infection; thus, as a possible pathogen, they are worthy of attention. Consequently, the original term “gram-negative bacterial toe web infection” might not cover all causative infectious agents; perhaps interdigital infection is the most suitable term for this disease.

The interdigital space is typically colonized by polymicrobial flora [8, 9]. We found 40 patients with positive microscopic fungi before and after antibiotic treatment. Previous studies have suggested that a strong correlation exists between dermatophytes and bacteria [8]. The former organism seems to act as a triggering factor, while the latter organism may play a role in the symptoms associated with interdigital infections. Dermatophytes initiate damage to the stratum corneum, thus, facilitating bacterial invasion; consequently, penicillin- and streptomycin-like antibacterial substances are produced, favoring specific colonization and overgrowth of the physiological skin flora by gram-negative bacteria and antibiotic-resistant gram-positive bacteria [10, 11]. Moreover, we observed that the positive rate of fungal cultures was significantly lower in acute interdigital infections that were not treated with antibiotics. Fifteen patients were found to be positive for microscopic fungi even with effective antibiotic therapy. It is postulated that the cases of unsuccessful fungal tests may be due to factors caused by bacterial overgrowth and the inflammatory response [11–13]. As fungal infections might be a triggering factor for interdigital infections and may cause false-negative results during the acute phase, it is recommended to repeat testing for fungi at the end of the antibiotic treatment.

Interestingly, we noted that the incidence of interdigital infections caused by different types of bacteria had obvious seasonal and age distribution characteristics. We speculated that the seasonal peaks of interdigital infections may be mainly related to air temperature, humidity, proliferation of fungi, and personal habits required for bacterial production. *P. aeruginosa* interdigital infections were frequently seen to increase during spring and autumn. The rate of fungal infections accompanying *P. aeruginosa* interdigital infections was found to be up to 96.65%. We speculated that the morbidity of interdigital infections caused by *P. aeruginosa* might be related to the proliferation of fungi. The optimal culture temperature of dermatophytes ranges from 22°C to 28°C, and these temperatures usually appear in spring and autumn in Shanghai; furthermore, gram-negative bacteria, particularly *P. aeruginosa*, thrive in a warm, moist, and occluded environment [14–16]. As people prefer to wear porous sandals in the summer, leading to the feet being in less moist occlusive conditions, *P. aeruginosa* interdigital infections become uncommon. In addition, the most common age group affected by *P. aeruginosa* interdigital infections was the 60–69 years group. This corresponds with the age of onset of tinea pedis [17]. Furthermore, other predisposing factors, such as scratching or rubbing, unreasonable treatment, and hot-water scalding are more common in this age group (data not shown). Interdigital infection caused by *S. aureus* was more liable to occur in summer and might be associated with more frequent attendance at swimming pools and public baths and prolonged exposure to rain. These conditions increase the risk of foot exposure to *S. aureus*. Moreover, the prevalence of occupations by interdigital infections caused by *S. aureus* may be explained by professional and non-professional reasons or the practice of strenuous exercise, all of which are prone to skin damage and increase the risk of *S. aureus* infection.

With high recurrence rates and possible complications, such as immobility, cellulitis, wound healing disorders, and autosensitization dermatitis, interdigital infections present a frequent therapeutic challenge in clinical practice [4, 5, 18]. However, data supporting a standardized regimen remain insufficient [19]. Therefore, we theorized a therapeutic algorithm for interdigital infections through a year-long cross-sectional study (Fig. 4). In order to prevent relapse and reduce complications, we suggest the following: first, levofloxacin may be a preferred first-line therapy administered before drug sensitivity testing because it was much more effective and provided excellent results against both gram-negative and gram-positive bacterial interdigital infections [1]. Subsequently, the therapeutic regimen could be adjusted based on drug sensitivity tests. Second, effective monitoring of local primary skin diseases, such as tinea pedis, onychomycosis, and allergic dermatitis, might be a critical factor in reducing relapse of interdigital infections. Third, health education for patients, such as lifestyle changes, has generally been ignored and may prove to be a simple method for prevention. Finally, recent literature has confirmed that immersing feet in 1% acetic acid is a relatively effective adjuvant treatment to significantly reduce relapse of interdigital infections caused by *P. aeruginosa* [20–22].

The present study has some limitations. First, only acute symptomatic cases were included in this study. It was difficult to research asymptomatic, mild cases since these cases usually fail to attract attention from patients. However, we believe that the prognosis of interdigital infections is favorable if there is an early, accurate diagnosis and appropriate treatment. Topical antibiotics alone or in combination with topical antifungal agents, produce good curative effects for mild cases. Second, because of the small

sample size and limited study period, future research should include larger sample sizes with longer study periods to better elucidate the epidemiological characteristics of interdigital infections.

Conclusions

This epidemiologic study of the characteristics of interdigital infections in Shanghai, China, may provide a basis for diagnosing causative pathogens and suggest an effective management which, subsequently, may help reduce recurrence and improve outcomes.

Abbreviations

P. aeruginosa /PAE, *Pseudomonas aeruginosa*; *S. aureus* /SAU, *Staphylococcus aureus*

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants, and also from the parents of the participants under 16 years old. This study was approved by the Ethics Committee of Shanghai Dermatology Hospital, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author in reasonable request.

Competing interests

The authors have no conflict of interest to declare.

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Authors' contributions

The first draft of the manuscript was written by QY and WL. Material preparation and data collection were implemented by SK and XL. Laboratory testing and data analysis was performed by HY, ZG, and JC. LY contributed to the study design, revised, and finalized the manuscript. All authors read and approved the final version of the manuscript.

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Figures



Figure 1

Clinical manifestation of patients with interdigital infections. (a, b, c) Skin lesions of patients with interdigital infection caused by *P. aeruginosa* presented with yellowish-green maceration. (d, e, f) Skin lesions of patients with interdigital infection caused by *P. aeruginosa* improved markedly after levofloxacin treatment. (g, h, i) Skin lesions of patients with interdigital infection caused by *S. aureus*

presented with yellowish-white maceration. (j, k, l) Skin lesions of patients with interdigital infection caused by *S. aureus* subsided significantly after levofloxacin treatment.

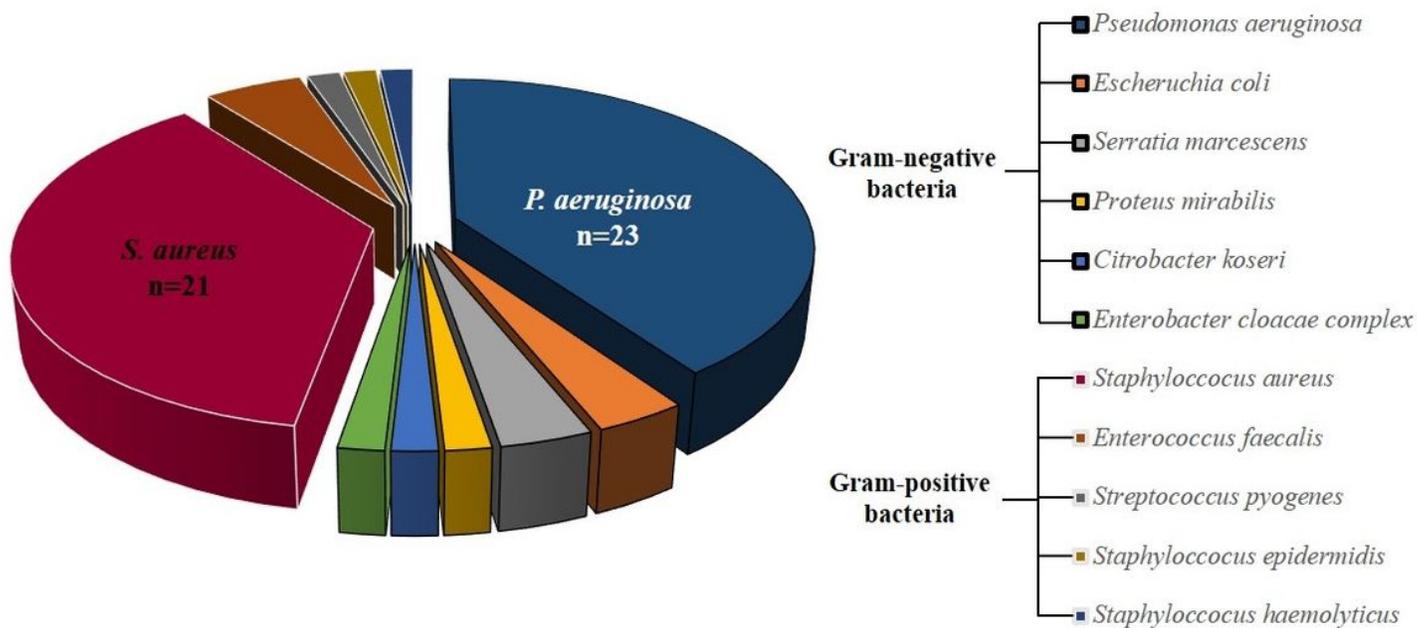


Figure 2

Main bacteria isolated in interdigital infections

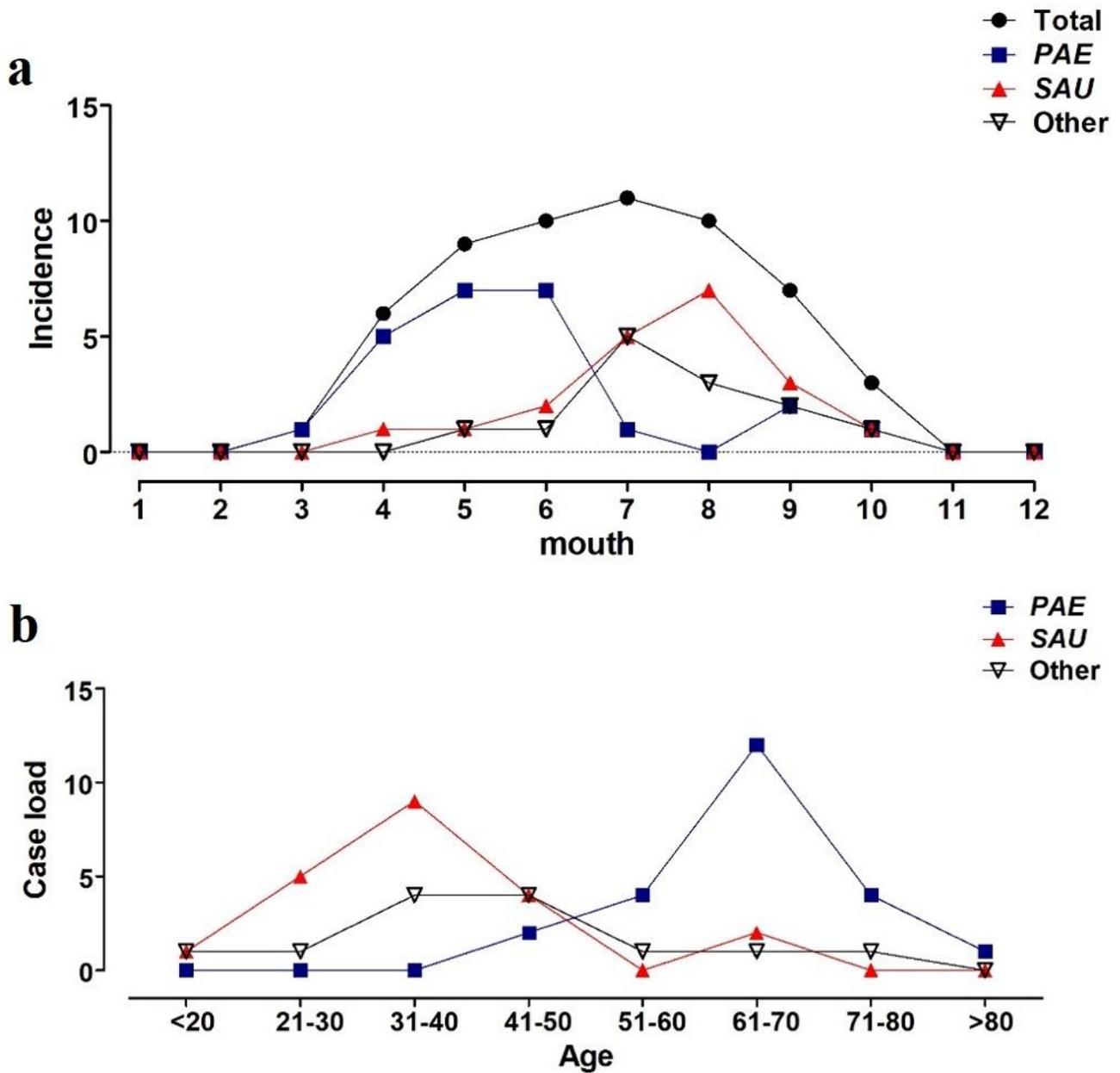


Figure 3

The seasonal and age distribution curve of patients with interdigital infections. (a) The seasonal distribution of patients with interdigital infections. (b) The age distribution of patients with interdigital infections.

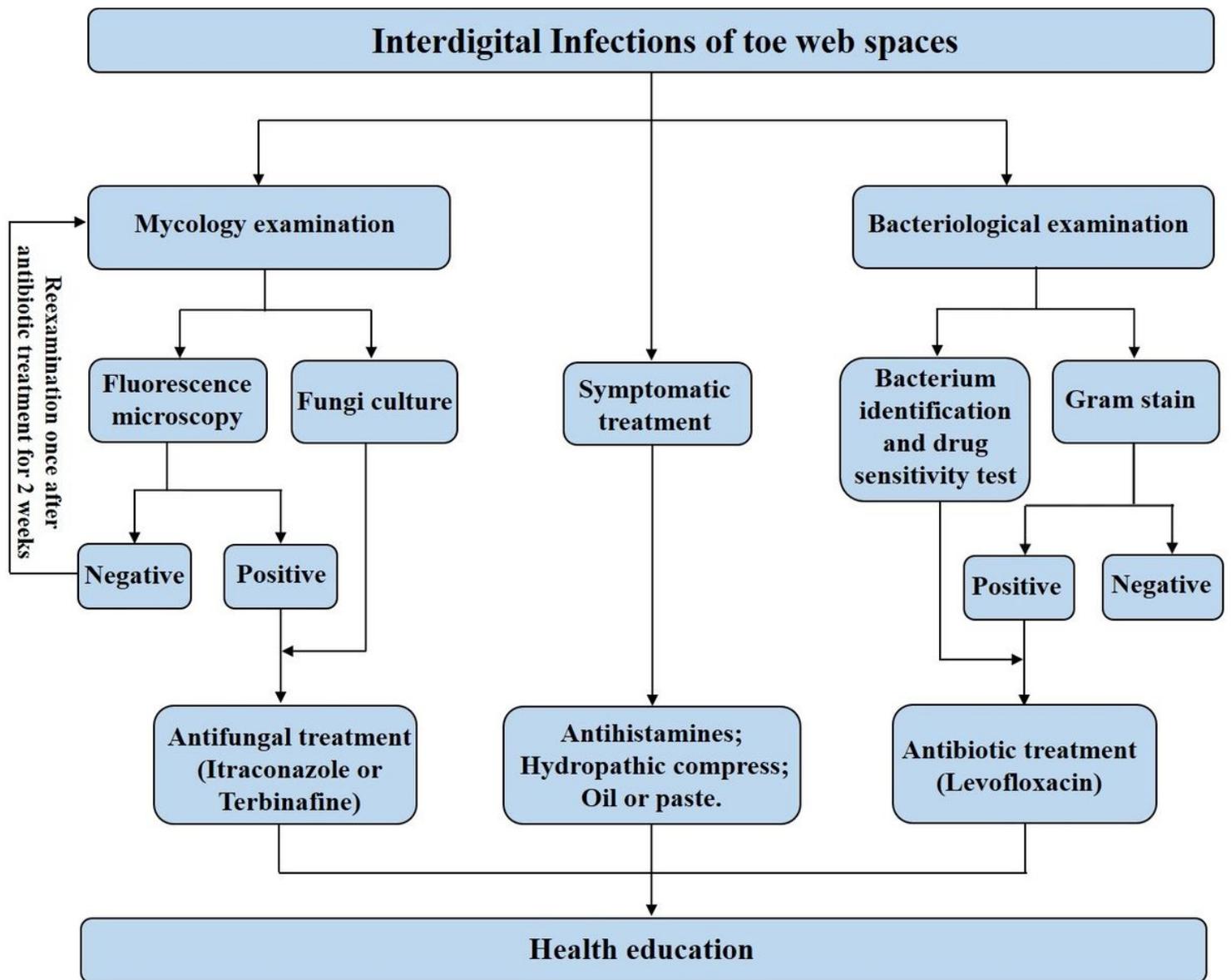


Figure 4

Therapeutic algorithm for interdigital infections.

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