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ORIGINAL ARTICLE

Methicillin-resistant *Staphylococcus aureus* in skin and soft tissue infections and minocyclin treatment experience in the dermatological setting of eastern Taiwan

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ABSTRACT

Background: Staphylococcus aureus (*S aureus*) is the major cause of skin and soft tissue infections (SSTIs). Increased methicillin-resistant strains have attracted a global concern. The aim of this study is to evaluate the prevalence of methicillin-resistant *S aureus* (MRSA) SSTIs in dermatologic settings and evaluate their susceptibility results.

Methods: A retrospective chart analysis of patients diagnosed with SSTIs in the Department of Dermatology, Buddhist Tzu Chi General Hospital in Hualien, Taiwan from November 2003 to July 2007 was conducted. Wound or pus bacterial culture results from a wound site were collected. The epidemiology, microbiology, and antibiotic susceptibility were assessed. Minocycline treatment experience in 15 MRSA SSTIs inpatients was presented.

Results: Of the 443 SSTI episodes included, 59.6% were males and 40.4% were females. *S aureus* was the leading cause (53.3%), and among them 53.0% were MRSA. Minocycline (94.4%), trimethoprim/sulfamethoxazole (95.2%), levofloxacin (95.7%), and fusidic acid (98.9%) were the major susceptible antimicrobial agents to MRSA. Only 14.4% was susceptible to clindamycin. In the MRSA infected inpatients, 75.6% were community-associated. In our clinical experience, 15 inpatients with poor clinical response to beta-lactam empirical antimicrobial therapy received minocycline as combination therapy based on the susceptibility results, all of which obtained satisfied clinical remission.

Conclusions: S aureus is still the leading causative bacterial organism for SSTIs in the dermatologic settings in eastern Taiwan. Methicillin-resistant strains are increasing and among which most are community-associated in eastern Taiwan. MRSA strains are still susceptible to other non-beta lactam antibiotics, such as minocycline, trimethoprim/sulfamethoxazole, levofloxacin, and fusidic acid in dermatological settings, of which minocycline is an alternative choice in our clinical experience.

Introduction

Primary care physicians and dermatologists frequently see skin and soft tissue infections (SSTIs), especially in outpatient clinics. Impetigo, erysipelas, furuncles, carbuncles, abscesses, cellulitis, and even the more severe and life-threatening necrotizing fasciitis are all included in this spectrum. The most common bacterial causative organism is *Staphylococcus aureus* (*S aureus*), followed by group A streptococci.[1,2] However, methicillin-resistant strains now make up 22.5–59% of *S aureus* SSTIs.[1–5] This increasing number of methicillin-resistant *S aureus* (MRSA) infection is notable worldwide and has become a health concern.

Traditionally, MRSA is considered a health care-associated pathogen. However, more community-associated strains originating from the community have rapidly emerged worldwide as a cause of SSTIs and are not associated to health care settings.[6–8] MRSA infections in patients from healthy communities without the defined epidemiologic criteria for health care-associated MRSA

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(HA-MRSA, Table 1) are considered community-associated MRSA (CA-MRSA) infections.[9] Family and personal histories are the only identified risk factors for CA-MRSA SSTIs.[10] CA-MRSA and HA-MRSA isolates are distinct demographically, clinically, and in microbiologic features.[11]

In Taiwan, the resistance rate to tetracycline and clindamycin by MRSA isolates from community colonizers is reportedly increasing (up to 95.3% and 90.6%, respectively).[12] Second-generation tetracyclines, also called expanded-spectrum tetracyclines, such as minocycline and doxycycline, are becoming more widely used for their greater potency.[13]

The epidemiology, microbiology, and antibiotic susceptibility for MRSA SSTIs in eastern Taiwan, whose population accounts for only 2.5% of the total population in Taiwan (2009 census), have not been studied. The aboriginal population accounts for 29.8% of the total population in this region, more than other areas in Taiwan. The purpose of this study is to describe the profile of SSTIs pathogens and the prevalence of MRSA infections in a dermatological setting in eastern Taiwan. MRSA organism susceptibility profiles and our experience of minocycline application in 15 MRSA SSTIs inpatients are discussed.

Methods

Patients

A retrospective chart analysis of all patients, including inpatients and outpatients, at the Department of Dermatology in Buddhist Tzu-Chi General Hospital, Hualien, Taiwan, covering November 2003 to July 2007 was conducted. Patients with impression of SSTIs category, including impetigo, erysipelas, furuncles, carbuncles, cutaneous abscesses, cellulitis, and even necrotizing fasciitis were included.

Wound or pus bacterial culture results from a wound site were collected if available and patients without available bacterial culture were excluded. Comparisons of medical records and epidemiologic analysis with age and gender were performed.

Laboratory bacterial culture methods, identification, and susceptibility result of MRSA isolates

An inoculated applicator tip was transferred to a laboratory room (Bacterial Laboratory Room of Tzu-Chi General Hospital, Hualien, Taiwan). The specimens were plated onto blood agar plate/eosin methylene blue agar, chocolate agar, and thioglycolate broth according to the guideline of the National Committee for Clinical Laboratory Standards. The plates were incubated at 35°C in a 5% CO_2 atmosphere. Thioglycolate broth was incubated at 35°C in an ordinary culture box.

The culture results were confirmed initially 18–24 hours later. Negative growth was confirmed after 48 hours. Colonies of *S aureus* were identified by Gram stain, catalase reaction, and slide coagulase test. Susceptibility testing of the isolates were performed using the Kirby-Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute. A zone size less than 10 mm around an oxacillin disk indicated methicillin resistance. All of the bacterial culture organisms from SSTIs and susceptibility were compared.

Classification of MRSA inpatients into community-associated and health care-associated MRSA

All of the inpatients with culture growth of MRSA were further classified into community-associated and health care-associated isolates based on the presence of epidemiologic criteria listed in Table 1.

Results

Baseline demographics

Of the 443 episodes with impression of SSTIs included, 264 episodes were males and 179 were females, whereas 130 episodes required hospitalization for treatment and 313 received outpatient treatment. The mean age of the inpatient group was 47.9 years ranging from 1 year to 90 years [95% confidence interval (CI): 44.8–51.7], whereas that of the outpatient group was 41.6 years ranging from 1 year to 88 years (95% CI: 44.3–38.9). For the entire cohort, the average age was 43.4 years (95% CI: 41.2–45.7).

Microbiology results

All bacterial culture growth results were analyzed (Table 2). The positive rate of bacterial culture was 77.2%. Among these SSTIs patients, 16.9% ($n = 75$) showed more than one organism growth. *S aureus* was the most dominant isolate, accounting for around 53.3% ($n = 236$). Of the *S aureus* isolates, 53.0% ($n = 125$) were methicillin-resistant.

Antimicrobial susceptibilities of MRSA isolates

In the 125 MRSA species, the susceptibility test varied for nonbeta-lactam antibiotics (Table 3). The MRSA species were 84.0% susceptible to gentamicin, 94.4% to minocycline, 95.2% to trimethoprim/sulfamethoxazole (TMP-SMX), 95.7% to levofloxacin, and 98.9% to fusidic acid. However, only 14.4% were susceptible to clindamycin.

Table 1 Defined epidemiologic criteria for health care-associated MRSA infections.[a]

Epidemiologic criteria for health care-associated MRSA infections
1. Organisms recovered from culture specimens obtained after 48 hours of hospital admission.
2. A history of recent dialysis, surgery, recent hospitalization and/or transfer from another hospital, or residence in a long-term care facility within 12 months of the MRSA culture date.
3. Presence of a permanent indwelling catheter or percutaneous medical device (e.g. tracheostomy tube, gastrostomy tube or Foley catheter, central venous line) at the time of culture.
4. A known previous isolation of MRSA from a clinical or surveillance specimen before the study period.

[a] Cases of MRSA infection among patients from healthy community without these factors are named as community-associated MRSA infection.[9]
MRSA = methicillin-resistant *Staphylococcus aureus*.

Table 2 Bacterial organisms culture results of skin and soft tissue infections.

Species	Number of isolates (%)
Staphylococcus aureus	236 (53.3)
Coagulase-negative staphylococci	37 (8.4)
β-Streptococci group A	20 (4.5)
Enterococcus	18 (4.1)
Klebsiella pneumoniae	16 (3.6)
Pseudomonas aeruginosa	14 (3.2)
Others	95 (21.4)
No growth	101 (22.8)
Multiple isolates (≥2 bacteria)	75 (16.9)

Table 3 Antimicrobial susceptibilities of methicillin-resistant *Staphylococcus aureus* isolates.

Antibiotics	Number of susceptible isolates/ number of tested isolates (%)
Minocycline	117/124 (94.4)
Gentamicin	105/125 (84.0)
Clindamycin	18/125 (14.4)
TMP-SMX	119/125 (95.2)
Levofloxacin	110/115 (95.7)
Fusidic acid	93/94 (98.9)

TMP-SMX = trimethoprim/sulfamethoxazole.

Sites of SSTIs between MRSA versus methicillin-sensitive S aureus from 73 inpatients

Of the 130 inpatients, 73 were infected by *S aureus*. Based on the susceptibility results of these 73 inpatients' episodes, 41 were resistant to methicillin, which consisted of 25 episodes of furuncles/carbuncles and 16 episodes of cellulitis. Cutaneous abscesses were present in 16 episodes (13 were furuncles/carbuncles and 3 were cellulitis resulted from furuncles/carbuncles). The 41 inpatients' episodes were further compared in terms of infected site of SSTIs. The trunk and lower extremities were the most involved sites (both 31.7%, $n = 13$). The buttocks (17.1%, $n = 7$), head and neck (12.2%, $n = 5$), and upper extremities (7.3%, $n = 3$) followed in the order of frequency. The infected sites in the rest 32 methicillin-sensitive *S aureus* inpatients were lower extremities (43.8%, $n = 14$), trunk (34.3%, $n = 11$), head and neck and upper extremities (both 9.4%, $n = 3$), and buttocks (3.1%, $n = 1$). There were no statistical significance ($p = 0.391 > 0.05$) between these two groups.

Proportion of community-associated and health care-associated MRSA from inpatients database

Based on the presence of epidemiologic criteria, 41 MRSA inpatients were divided into two groups of either community-associated ($n = 31$) or health care-associated infection ($n = 10$). In the MRSA infected inpatients, 75.6% were community-associated.

A concise report of the experience of minocycline application in 15 MRSA SSTIs inpatients with poor response to beta-lactam antibiotics

Based on the susceptibility, we presented our experience of the minocycline application in the treatment of MRSA SSTIs inpatients. In our treatment protocol, inpatients with MRSA SSTIs were treated with empirical antibiotics initially and bacterial culture of wound or pus was performed before antimicrobial therapy. Performance of an incision and drainage procedure or surgical drainage was required if an abscess or purulent lesion were present. After 3 days, when bacterial culture and susceptibility results revealed MRSA isolates, and there were no satisfactory clinical improvement, second-line antibiotics, such as minocycline, were added as combination therapy based on the susceptibility results. Children younger than 8 years were not recommended for the use of minocycline. Totally, 37 inpatients received beta-lactam antibiotics consisting of intravenous agents (e.g. first-generation cephalosporins or oxacillin in standard doses) as empirical antimicrobial therapy. Of which, 15 from 18 inpatients with poor clinical response to beta-lactam empirical therapy received minocycline (oral/intravenous form, at standard dose of 100 mg twice daily) as combination therapy with beta-lactam agents based on the susceptibility results, all of which obtained satisfied clinical remission after minocycline therapy.

Discussion

This study is conducted in 2003–2007 in Hualien County, which is located in eastern Taiwan, where distinct geographic location and ethnic populations are illustrated. In this study of a dermatologic setting in eastern Taiwan, 53.3% of SSTIs are because of *S aureus*. In all of the bacterial culture from skin infections in one study in an emergency department in the United States, around 76% of bacterial culture obtained were caused by *S aureus* species.[2] The results here are consistent with other reports, with *S aureus* still as the leading causative bacteria for SSTIs.[2]

The prevalence of MRSA SSTIs varies widely among different studies, which involves different geographic locations and patient characteristics. In several recent studies in SSTIs, methicillin-resistant strains accounts for 26.7–59% of *S aureus* in North America[2–5,14] and 22.5% in European countries.[1] Risk factors for MRSA have already been constructed,[10,15–17] including masculine sex, advanced age, previous isolation of MRSA from a clinical or surveillance specimen, presence of a permanent indwelling catheter or percutaneous medical device at the time of culture, recent dialysis, surgery, recent hospitalization and/or transfer from another hospital, or residence in a long-term care facility during the recent 12 months preceding the culture, chronic disease, previous antibiotic therapy, and injection drug use, although there is no consensus yet. In our study, 53% of *S aureus* strains are methicillin-resistant, which is clinically significant for dermatologists when facing SSTIs. Screening for risk factors is helpful and important to choose the initial empiric antibiotics.

Traditionally, MRSA is considered a health care-associated pathogen. However, the CA-MRSA strain has already been described worldwide and defined by specific epidemiological and molecular criteria.[18] The used epidemiologic criteria to differentiate CA-MRSA from HA-MRSA are relatively simple and practical. However, *S aureus* can persist as a colonizer for months or years, and some "community-onset" infections may actually be caused by hospital-acquired strains and, vice versa, CA-MRSA may invade hospitals, leading to misclassification of the source.[18] Nevertheless, family and personal histories are still the only identified risk factors for CA-MRSA.[10] Skin and soft tissue are the predominant sites of infection for CA-MRSA.[19] In the present study, CA-MRSA strains accounts for 75.6% of MRSA isolates among SSTIs inpatients. On reviewing the literatures, the ratio of community-associated strains variances from all kinds of MRSA infections in different areas ranged from 8% in Japan[20] to 12–74% in United States.[8,17] The result that the prevalence of CA-MRSA is higher in ratio than other studies may be related to the acquisition from SSTIs and indicates that more MRSA SSTIs from the dermatological settings in eastern Taiwan can be caused by strains related to the community.

The CA-MRSA strains from various communities are usually not the multidrug-resistant phenotype,[21,22] which always contains Type IV staphylococcus cassette chromosome mec and a major portion carries the genes for Panton-Valentine leukocidin.[23,24] PVL-positive strains of *S aureus* are associated with tissue necrosis and abscess formation, although it is unclear whether PVL is mediating these effects, indicating a role for PVL as a major virulence factor.[18] Most CA-MRSA strains are identified from the skin and compared with health care-associated cases, they are more likely to be susceptible to clindamycin, tetracycline, erythromycin, and fluoroquinolones.[8,9,16,25]

Therapeutic options for SSTIs include incision and drainage in combination with antimicrobial therapy, which may be oral, topical, or parenteral. The effect of antimicrobial drugs between *in vitro* susceptibility data and clinical effectiveness could be possibly disconcordance and the inflammation, microenvironment, and immune system are still the major factors when humans

encountering infections. Of note, performance of incision and drainage of abscess-like lesions remains the mainstay of therapy.[9,26] In two cohort studies from emergency departments, MRSA strains were 94–95% susceptible to clindamycin, 86–92% to tetracycline, 60% to fluoroquinolones, and 100% to rifampicin and TMP-SMX. Only 6% were susceptible to erythromycin.[2,27] However, the MRSA isolates in the present study were only 14.4% susceptible to clindamycin, which was lower than those of the aforementioned studies. This made clindamycin to be an unfavorable choice against MRSA in eastern Taiwan. On the other hand, in this study, minocycline, TMP-SMX, levofloxacin, and fusidic acid were still the major susceptible antimicrobial agents to MRSA. This result may be related that more MRSA SSTIs from the dermatological settings in eastern Taiwan can be possibly caused by strains related to the community. Thus, dermatologists in Taiwan could still have many choices of antibiotics against MRSA SSTIs.

Several alternative (nonvancomycin) anti-MRSA agents, that is, TMP-SMX, expanded-spectrum tetracyclines (doxycycline and minocycline), and fluoroquinolones, can be used successfully with few and minor adverse drug effects to treat nonlife-threatening MRSA infections in appropriate patients. Usage of these alternative drugs may help avoid the use of newer, more costly, antimicrobials, which should be reserved for more severe infections. In several studies of *S aureus* SSTIs, TMP-SMX appears to be an appropriate agent.[28,29] Nonetheless, TMP-SMX has side effects and may result in bone marrow suppression or hypersensitivity reactions. TMP-SMX may also not provide adequate activity to empirically cover Group A streptococcus, another common causative organism.[30] Although fusidic acid possesses good antimicrobial activity against *S aureus* (including MRSA) and has been in clinical use worldwide, it is found not to be effective for eradication of MRSA colonization and the emergence of fusidic acid-resistant strains was detected more common in the world and significantly higher in dermatology patients compared with other hospital patients and primary-care patients.[31,32] Continued restriction of fusidic acid is recommended by some authors.[31]

Expanded-spectrum tetracyclines appear to be a promising treatment option for patients who present with suspected CA-MRSA skin infection.[33] Adverse effects are less likely with doxycycline than minocycline.[34,35] However, minocycline achieves much higher concentrations in the tissues where it does its work in reducing swelling and killing germs than doxycycline does.[36] Besides, the demonstration of doxycycline-inducible efflux pump mediated resistance and *in vitro* data suggesting that doxycycline has less intrinsic anti-*S aureus* activity than minocycline does,[37–40] indicating a role for minocycline as a choice against MRSA infections. In our experience, minocycline is still sensitive to MRSA in dermatological settings and prescribed by physicians as an alternative choice, indicating minocycline a clinical application for antimicrobial therapy. About 15 MRSA SSTIs inpatients were recruited during the study period and altogether received satisfactory effect to combination therapy with beta-lactam antibiotics and minocycline. Combination therapy can be used to expand the antimicrobial spectrum, to enhance the susceptibility level of resistant strains, to minimize toxicity, and to obtain synergistic antimicrobial activity, resulting in more pronounced inhibition of microorganism growth than either drug alone.[41] Based on this clinical experience, we also obtained excellent response clinically in other patients afterward.

This study has several limitations. First, its retrospective analysis lacks reliable and complete data for parameter estimates and clinical evaluation. Second, SSTIs patients without available bacterial culture have been excluded. However, bias will be unavoidable although this group of patients may possibly have less severe conditions not warranting wound culture. Third, the minocycline combination therapy as an alternative choice is estimated from the limited number of inpatients and our clinical experience rather than from the randomized control study. Future prospective clinical studies evaluating large number of SSTIs may more certainly elucidate the clinical role and effect of minocycline therapy.

In conclusion, from epidemiology and microbiology of SSTIs in dermatologic settings in eastern Taiwan, *S aureus* remains the leading causative bacterial organism. Methicillin-resistant strains are increasing and among which most are community-associated in eastern Taiwan. MRSA strains are still susceptible to other nonbeta-lactam antibiotics, such as minocycline, TMP-SMX, levofloxacin, and fusidic acid, in dermatological settings, of which minocycline is an alternative choice in our clinical experience.

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