Multicentric prospective and descriptive study about community-acquired methicillin-resistant Staphylococcus aureus cutaneous and soft tissue infection (CA-MRSA)

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ABSTRACT

Community acquired methicillin-resistant Staphylococcus aureus is one of the main emergent pathogens of the last decade, being the first cause of skin and soft tissue infections in some countries. The purpose of this study is to describe the epidemiologic, clinical, and microbiological characteristics of CA-MRSA cutaneous and soft tissue infections in an ambulatory setting.

Methods. We conducted a multuicentric, prospective, descriptive study performed in 6 dermatology units at Buenos Aires from july 2008 to june 2009. Patients with documented CA-MRSA skin and soft tissue infections were included. Community acquisition was defined based on epidemiologic criteria.

Results. We included 114 patients, of which 49% were male and 51% were female. The median age was 27 years. Seventy four percent of the patients had received beta-lactamic antibiotic treatment prior to inclusion. The main clinical presentation were furuncules (59%) followed by abscesses (20%). The most frequently prescribed antibiotic was trimethoprim-sulfametoxazole (68,4%). The most frequently recovered isolates were erithromicin- (21,7%) and clindamycin-resistant (16,2%). Six patients required hospital admission, 18 had recurrent diseases, and no death was recorded.

Discussion. Demographic and clinical data obtained in this study are similar to those previously reported. Most of the patients had received antibiotic treatment before inclusion, which shows the low CA-MRSA clinical suspicious. Impetigo was frequently observed among children, and cellulitis was exclusively observed in females. As clindamycin resistance was higher than 15%, this antibiotic should not be considered a first-line treatment option. CA-MRSA infections were frequently observed in our patients, therefore its diagnosis should be considered on suppurative lesions and non responding pyodermitis (Dermatol Argent 2010;16(2):110-116).

Keywords:

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Introduction

The methicillin-resistant *Staphylococcus aureus* (MRSA) was first isolated in the 60s, after the introduction of semisynthetic penicillins, and it represents a burden for in-patients with risk factors.[1-3] For nearly 30 years, MRSA was confined tyo the nosocomial are, but since 1990 multiple cases appeared o patients without predisposing factors and any contact with the hospital or predisposing factors. This strain is called community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[1,2,4-6]

There are genetic and phenotypic differences between nosocomial MRSA (IHMRSA) and CA-MRSA.[1,7] The genes –called mecA- that confer methicillin- Resistance are different. There are six types of these and are carried o chromosome cassettes (SCCmec). The CA-MRSA presents essentially SCCmec type IV, and it confers resistance only to methicillin, while IHMRSA has SCCmec types, I, II, III, wich are related to resistance to other antibiotics[1.3 to 6]. This explains why, unlike IHMRSA, CA-MRSA is sensitive to non-beta-lactam antibiotics as sulfas, clindamycin and tetracyclines. Moreover, most CA-MRSA contain genes encoding Panton-Valentine exotoxin, responsible for skin and lung's necrotic lesions.[1-3,5-7,9,10] On the other hand, the CA-MRSA has higher rate of transmission and dissemination compared with IHMRSA.[1,7]

CA-MRSAinfections, affecting in and out-patients, have had an alarming increase worldwide in recents years, becaming one of the major emerging pathogens.[1,10-11] .It mainly affects healthy children and young adults, predominantly causing skin and soft tissue infections, and in less frequently invasive infections such as necrotizing pneumonia.[1,7,9]

The spectrum of skin lesions is similar to that caused by the community acquired methicillin-sensitive Staphylococcus aureus (CA-MSSA).[1,2,5] Although the most commonly described are boils, abscesses and necrotic lesions with perilesional erythema similar to spider bites,[3-6] it may also cause impetigo, folliculitis, paronychia, Anthrax, cellulitis, necrotizing fasciitis, pyomyositis and purple fulminans.[1,4,5,7,10] The overcrowding and poor sanitation conditions facilitates transmission, as it may be spread by person to person, or by contaminated fomites.[1-4,6,10] CA-MRSA risk groups include prisoners, military, sports, homeless, IV drug addicts, men who have sex with men, pregnant and postpartum women, as well as contact with hospitalized patients or health care staff.[1-2,5-6,10] Anyway, we emphasize that CA-MRSA infections are not limited to these groups.

CA-MRSA is the most common cause of skin infections and soft tissue in many countries.[1.3] It has been described that skin and soft tissue infections by CA-MRSA are very common in children.[8]

Considering its high prevalence, it is necessary to know the diverse clinical presentations, demographic characteristics and profile of local sensitivity, in order to adopt criteria and treatment strategies due to the lack of existent data in our country on skin and soft tissue infections regarding the general population.

Materials and methods

Study population. We included patients with documented skin and soft tissue infections caused by CA-MRSA evaluated between July 2008 and June 2009 from 6 Dermatology Services of University Hospitals of Buenos Aires and the suburbs of Buenos Aires province. The infection was considered to come from the community when they did not meet the CDCs' hospital infection criteria.

Study design. We performed a prospective and descriptive study. Patients were evaluated at 0 and 2 weks. The attending physician completed a record of each patient that included age, sex, comorbidities, clinical manifestation, lesions localization, risk factors, household contacts, antibiotic sensitivity of isolation, previous antibiotic therapy, treatment performed, decolonization, recurrences (before and after day 15) and hospitalization. We considered the following risk factors: age (less than 5 and more than 60 years old), men who have sex with men, athletes, homeless, intravenous drug addicts, prison inmates, military personnel, pregnancy, childbirth, overcrowding, contact with healthcare staff, contact with hospitalized patients and antibiotic therapy during the past year.

Cultures were taken from the site of infection at the time of the consultation by aspiration or punch biopsy.

Staphylococcus aureus was detected by routine microbiological tests. Methicillin sensitivity was determined by oxacillin disk diffusion tests. A determination of halos smaller than 20 mm was considered as resistance.

Tests were conducted to determine the sensitivity to the following antibiotics: vancomycin, gentamicin, rifampicin, teicoplanin, ciprofloxacin, trimethoprim-sulfamethoxazole, clindamycin, erythromycin and tetracycline and minocycline. All patients received empiric antibiotic treatment prescribed by the attending physician. Treatments were re-evaluated and modified according to the antibiogram.

Statistical analysis. To describe the variables we calculated statistical averages and standard deviation for continuous variables as well as the number and percentage of categorical variables.

We used the Fisher test to compare categorical variables. We performed a multiple logistic regression model to assess predictors of poor prognosis. Were included in the model those variables with statistical significance under univariated analysis and those with clinical relevance. The model was constructed using the method of steps forward with input probabilities of 0.05 and output of 0.10. We used SPSS 16.0 software, 2004 (SPSS, Inc, Chicago, IL, USA).

TABLE 1. Risk factors.

Risk factor	Patients (%)	Patients (n)
Antibiotic therapy during the previous year	10,5	12
Under 5 years old	11,4	13
Over 60 years	2,6	3
Prison	0,9	1
Men who have sex with men	0,9	1
Homeless	0,9	1
Contact with hospitalized patients	3,5	4
Contact with health personnel	2,6	3
Military personnel	0,9	1
Sportsman	3,5	4
Overcrowding	6,1	7
Pregnancy	1,8	2

FIGURE 1. Distribution of injuries by age of the patients.

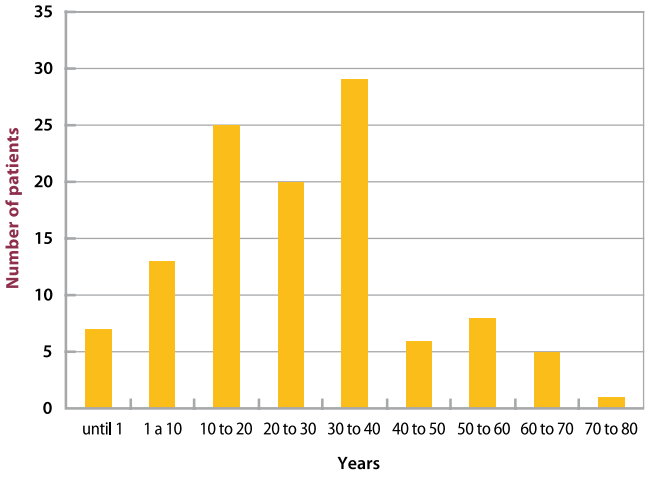
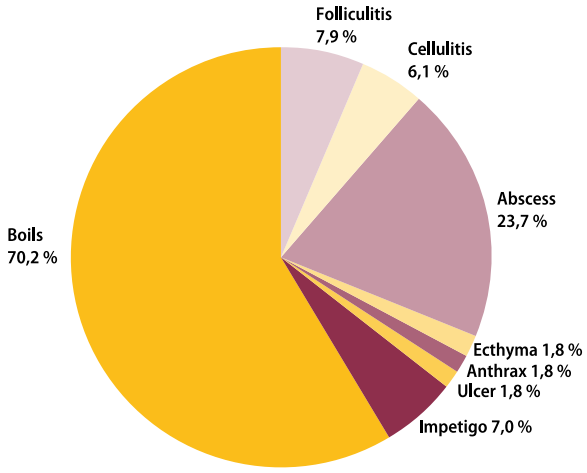


TABLE 2. Patterns of microbial sensitivy and resistance.

Antibiotic	Sensitive	Resistant	n
Vancomicina	100	0	114
Gentamicina	88,8	11,2	105
Rifampicina	96,3	3,7	105
Teicoplanina	100	0	105
Ciprofloxacina	87	13	105
TMS	94,6	5,4	105
Clindamicina	83,8	16,2	111
Minociclina	93,9	6,1	99
Eritromicina	78,3	21,7	111

FIGURE 1. Distribution of injuries by age of the patients.



Results

Demographic characteristics. The study included 114 patients, of whom 56 (49%) were male and 58 (51%) women. The age range was from 6 months to 77 years, with an average of 27.3 years **(Figure 1)**.

Risk factors were detected in 47 patients (41%), listed in Table 1, and 8 patients (17%) presented more than one risk factor at the time of consultation.

Most of the patients were healthy young adults. Only 21% of patients had comorbidities: hypertension, atopic dermatitis, HIV, smoking and mellitus diabetes.

Half of the patients (n = 57) had affected contacts, some of them lived together and some not.

Of the 114 patients, 91 received treatment prior to consultation: 74% (n = 84) received β-lactam antibiotics, 4.4% (n = 5) trimetoprima-sulfametoxasol, 3.5% (n = 4) ciprofloxacin, 1, 8% (n = 2) clindamycin, and 1% (n = 1) received topical fusidic acid, topical mupirocin, clarithromycin and levofloxacin. 2.6% of patients reported prior drainage (n = 3).

Clinical manifestations (Figure 2). In order of decreasing frequency were: foruncules in 80 cases (70%) **(Photo 1)**, abscess in 27 (24%) **(Photo 2)**, folliculitis in 9 (8%) **(Photo 3)**, impetigo in 8 (7%) **(Photo 4)**, cellulitis in 7 (6%), and ecthyma, ulcer and Anthrax **(Photo 5)** each accounted for 1.8%. 19% of patients had more than one clinical manifestation at the time of diagnosis. Cellulitis was an infrequent manifestation and was only present in females, affecting 12% of these patients (p = 0.013). 75% of impetigo (n = 6) occurred in the pediatric population (defined as under 18 years old), with a statistically significant trend (p = 0.009).

The greatest number of lesions was observed in the lower limbs (40.4%), followed by upper limbs (34.2%), trunk (27.2%), head (25.4%), perianal and genital regions (10.5%) and neck (7.9%).

Microbiology and treatment

All isolates were sensitive to more than one non-bethalactam antibiotic, similar to that reported previously for CA-MRSA **(Table 2)**. All isolates were sensitivity

to vancomycin and teicoplanin, and 94.6% for trimethoprim-sulfamethoxazole (TMS). Minocycline resistance was of 6%, but it is noteworthy that all cases of resistance came from a single center. Resistance to clindamycin for the entire sample was 16.2% and 18% in the pediatric population. Most patients were treated with TMS (68.4%). Clindamycin was administrated to 19.3% of the patients, 15.8% received minocycline, 4.4% rifampicin, 3.5% ciprofloxacin and 0.9% doxycycline. The drainage of the lesion was performed in 14.9% of the cases (17 patients). In 6 patients this was the only therapeutic modality, while the other cases also received antibiotics-therapy. The average duration of antibiotic treatment (n=108) was 11.7 days (SD=3.4), with a minimum of 7 days and a maximum of 21.

87 patients (76.3%) were indicated topical decolonization, 71 received mupirocin (62%), 31% (36 patients) chlorhexidine and 7% (8 patients) iodine.

Clinical Evolution. Six patients required hospitalization (5.3%). There were no serious complications or deaths. Recurrence was recorded within 15 days prior the first consultation in 7% (n=8) of the patients and after 15 days in 9.7% (n=11) of patients (loss of follow-up on 1 patient). One patient had a recurrences 15 days before and after the consult. Twenty-two patients (19.35%) had recurrence or hospitalization. We performed univariate and multivariate analysis to identify predictors factors of poor prognosis. In both the location (perianal/genital) was the only variable that showed a statistically significant difference (univariate: OR = 4.04, 95%CI: 1.13-14.4, p = 0.03) (multivariate OR = 5.289, 95%CI:1,36-20, 44, p = 0.016).

Discussion

Pyodermitis are frequent infections, with an annual incidence of 24.6 per 1,000 habitants.[12] Traditionally they have been attributed to Staphylococcus and Streptococcus and consequently medicated with penicillin or first generation cephalosporins.

In recent years it has been shown that CA-MRSA has emerged as a new pathogen acquiring pandemic proportions.[10] Much has been published about it in the international literature, but in our country there had only been only isolated case reports and one retrospective multicenter study on general pediatric population reported by Paganini et al.[9]

Skin and soft tissue infections are the most frequent diseases produced by CA-MRSA, but this agent may be responsible for varied and potentially fatal infections such as pleural empyema, pyomyositis, osteomyelitis and arthritis, endocarditis, liver, brain abscesses and necrotizing pneumonia. These infections occur mainly in healthy young patients without comorbidities where one or more risk factors are present. The most common risk factors are overcrowding, poor hygiene, sports, intravenous drug addicts and men who have sex with men.[10,13-15]

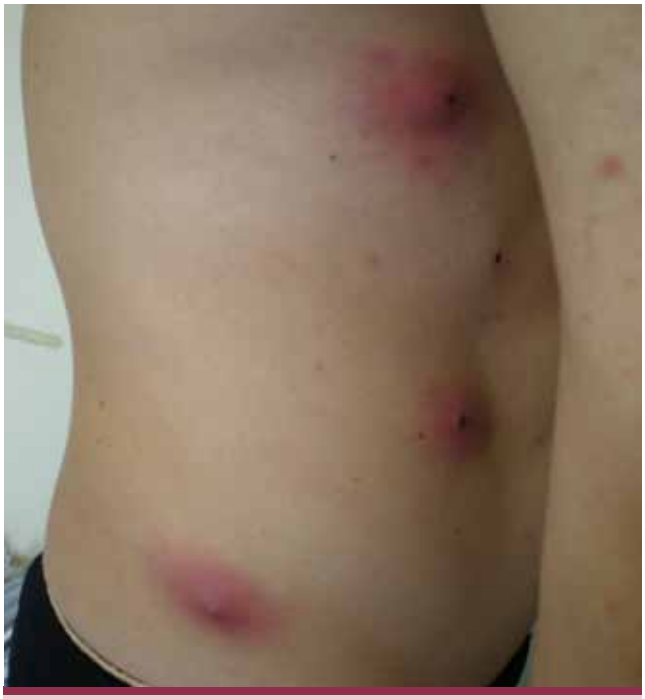


PHOTO 1. Multiple boils on the trunk.

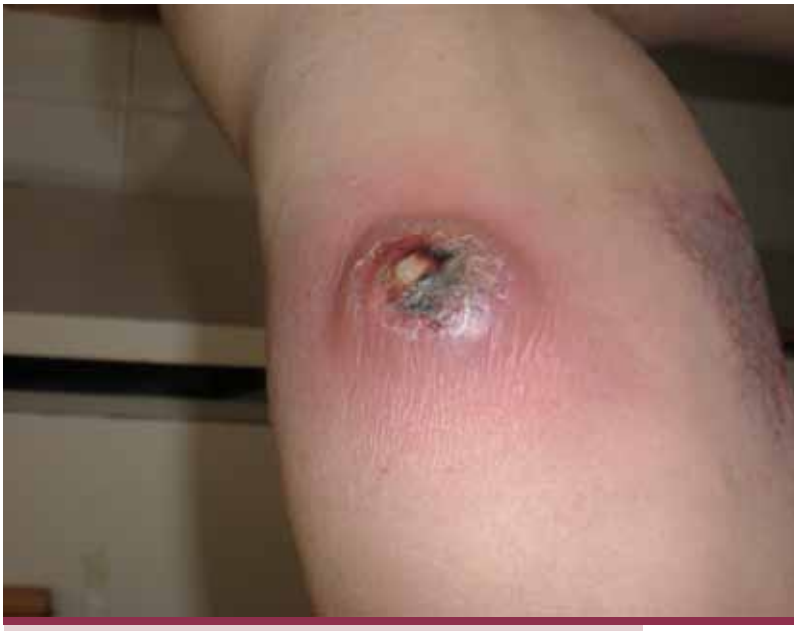


PHOTO 2. Large size abscess with a necrotic center located on the forearm.

Our study was based on the evaluation of a general population who consulted the Dermatology Service of the city of Buenos Aires and suburbs, taking into account patients of all ages and social strata. In agreement with the available literature, we note that most patients are young persons without comorbidities (mean = 27 years). Most of them (69%) did not present any described risk factor. Of these, the most frequently observed was pre-treatment with antibiotics during the previous year, followed by overcrowding.

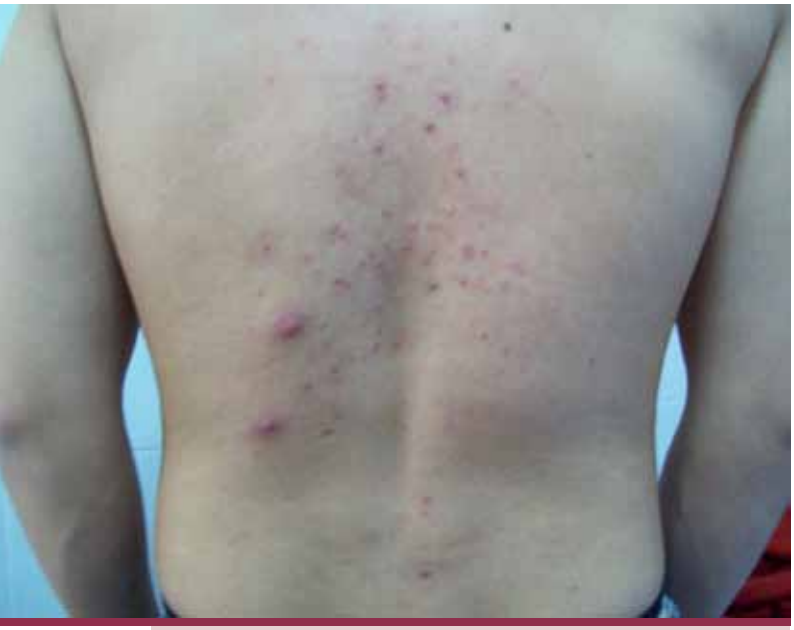


PHOTO 3. Folliculitis on the back.

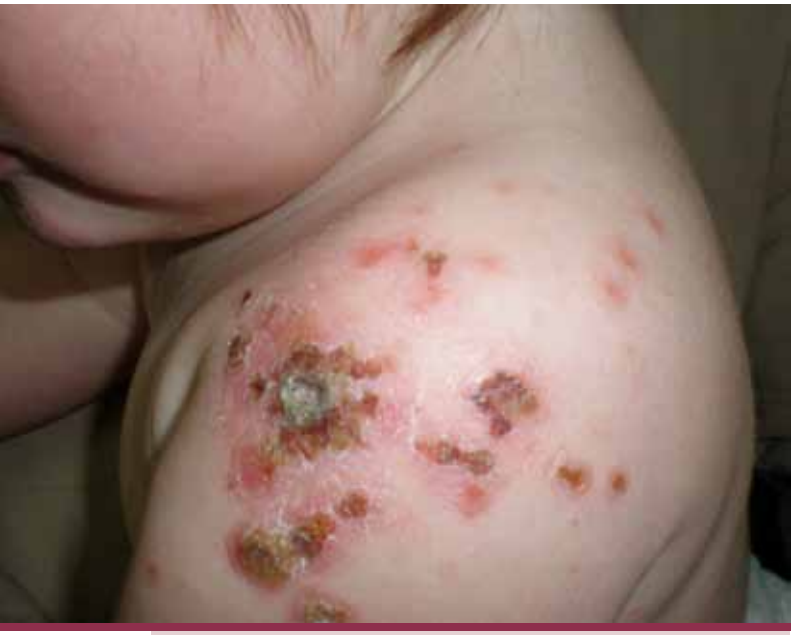


PHOTO 4. Impetigo on a child's shoulder.

Despite being considered as a risk factor for CA-MRSA infection, it is noteworthy that the use of antimicrobials would not be the main form of acquisition of methicillin resistance proposed for this bacterium. Horizontal transfer of chromosomic cassette *SCCmec* to methicillin-sensitive Staphylococcus aureus strains would be the main mechanism of resistance.[13]

Half of the patients (n = 57) had affected associates, some of them lived together and some not. This might explain the tendency of physicians to indicate decolonization, mainly with mupirocin. About 80% of the patients received an empirical treatment for their current infection. Beta-lactam antibiotics, mainly in the form of first-generation cephalosporins were the most appropriate antibiotics. This might probably be because there are no conclusive data in our environment on the incidence of CA-MRSA, and the suspected diagnosis is still low.

The most frequent clinical presentation in studied patients were foruncules and abscesses, where the clinical suspicion for CA-MRSA is greater, but we have also isolated the causative agent in patients with cellulitis, folliculitis and impetigo, where there is usually no suspicion on the presence of germs resistant to commonly used antibiotics. Clinical cellulitis was observed more frequently in women, a result that cannot be adequately explained, but should be taken into account when choosing a treatment for cellulitis in women.

With regard to the chosen treatment, the combination of trimetroprimasulfametoxazol was the most used, followed by minocycline and clindamycin. While in the literature clindamycin is usually preferred, the choice of treatment could be explained by the familiarity of the dermatologist with tetracyclines and accessibility to these and to TMS. It is noteworthy that no adverse events were noted due to antibiotic treatment.

Drainages were performed only in 14.9% of patients, and in 6 of them as the only therapeutic treatment; we can explain this by not being a common practice among dermatologists, who may not entirely rely on the drainage as the only therapy despite being widely validated in the literature.[4,6]

Although the CA-MRSA is an aggressive bacteria and there are many reported cases of fatal complications and developments, we observed a high rate of cure, and only 20 patients had recurrences in the short or long term or require hospitalization, sometimes due to social reasons. The location of perineal/genital regions showed worse outcome, probably where factors such as heat, humidity and occlusion can adversely interfere with the healing process.

None of the studied patients presented infections at sites other than skin and soft tissue, with a survival of 100%. This suggests that, according to our study, CA-MRSA is a locally aggressive type of agent presenting itself with purulent collections and necrosis, but with little systemic impact. This is consistent with a pediatric study conducted by Mongkolrattanothai et al., which revealed that invasive staphylococcal infections were caused mostly by MSSA, while in skin and soft tissue infections CA-MRSA prevailed.[16] In spite of this, those patients with invasive infections of CA-MRSA had a history of prior skin and soft tissue infections.

In addition to beta-lactam antibiotic resistance, CA-MRSA may be resistant to other antibiotic families. In this case it would be through the exchange of plasmids. It is important

to know the resistance profile of the local strains of CA-MRSA as several studies show that different bacterial clones differ in their sensitivity profile. Thus, the European clone is resistant to tetracycline, kanamycin and fusidic acid, while the predominant U.S. strain is resistant to macrolides but not clindamycin.[4]

In contrast to the results of Paganini et al.,[9] we observe a 16% of general resistance to clindamycin and an 18% for the pediatric population, a figure that would place it as a second-line agent and not as a first line treatment as suggested in that study.

The findings of this work, allow us to conclude that CA-MRSA is present in our environment and constitutes already a real public health problem that should be suspected of not only due to necrotic infections and abscesses on skin and soft tissue but also in cases such as impetigo and folliculitis. The presence or absence of comorbidities and risk factors described in the literature are not enough to make treatment decisions, but the dermatologist should consider CA-MRSA in the presence of skin and soft tissue infections regardless of its severity at the initial assessment of the patient, and also know the local resistance profile in order to implement an effective therapeutic strategy.

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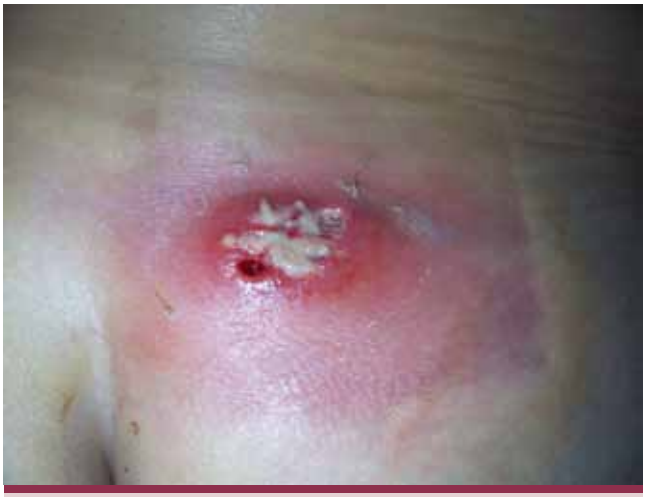

PHOTO 5. Anthrax. Lesion with multiple drainage outlets on butt-cheeck.

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