Empirical hospital treatment regimes for skin and soft tissue infections. Clinical guidelines and real empirical practice

Tratamiento empírico de pacientes ingresados con infección de piel y partes blandas. Guías clínicas y práctica clínica real

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Resumen

Objetivos: Existen diferentes guías de tratamiento de la infección de piel y partes blandas (IPPB), sin embargo el tratamiento de estos pacientes es muy variable. Los objetivos fueron analizar las pautas antibióticas, así como su duración en pacientes con IPPB que precisaron ingreso.

Pacientes y métodos: Se revisaron los pacientes con IPPB ingresados entre enero y diciembre de 2009. Se recogieron las pautas de tratamiento antibiótico empleadas antes, durante y tras el ingreso, así como su duración.

Resultados: De un total de 131 pacientes con IPPB ingresados, se identificaron 41 pautas diferentes de tratamiento antibiótico. En 61 pacientes (47%) se emplearon dos o más fármacos y en 21 (16%) antibióticos de amplio espectro. En 25 pacientes (19%) se modificó la pauta antibiótica por mala evolución y se utilizaron 16 regímenes antibióticos diferentes. En los pacientes con fracaso del tratamiento antibiótico, ni la duración del ingreso (12 ± 9.0 días vs. 14 ± 8.7 días, p = 0.31), ni la duración del tratamiento antibiótico (12 ± 8.2 días vs. 14 ± 6.8 días, p = 0.33) fueron superiores a la de aquellos en los que la respuesta al tratamiento empírico inicial fue adecuada. Al alta, 95 pacientes (73%) recibieron tratamiento antibiótico, se identificaron 25 regímenes diferentes; 22 pacientes (23%) recibieron dos o más antibióticos y antibióticos de amplio espectro se pautaron en 10 casos.

Conclusiones: La IPPB es una causa creciente de hospitalización y, a pesar de existir guías recientes de tratamiento, las pautas de tratamiento antibiótico son altamente variables.

Palabras clave: Celulitis; infección de piel y partes blandas; absceso cutáneo; tratamiento antibiótico.

Abstract

Objetives: There are several clinical guidelines for the management of skin and soft tissue infections (SSTI); however, the empirical treatment of patients with this common cause of hospital admission is highly variable. The aims of this study were to determine the empirical antibiotic treatment regimes and the duration of antibiotic treatment of SSTI requiring hospitalization.

Patients and methods: Cases admitted for SSTI were reviewed. We evaluated antibiotic therapy before, during and after hospitalization, as well as duration of treatment.

Results: From the 131 patients, 41 different antibiotic regimes were identified. Antibiotic combinations were used in 61 patients (47%) and broad-spectrum antibiotics were used in 21 patients (16%). Modification of the antibiotic regimen was required in 25 patients (19%) due to poor clinical response, and 16 different regimes were prescribed. For patients with treatment failure, neither duration of hospitalization (12 ± 9.0 days vs. 14 ± 8.7 days, p = 0.31) nor duration of antibiotic treatment (12 ± 8.2 days vs. 14 ± 6.8 days, p = 0.33) were greater than for those who responded to the initial empirical treatment. On discharge, antibiotic treatment was prescribed for 95 patients (73%), with 25 different regimes, including a combination of drugs in 22 patients (23%) and broad-spectrum antibiotics in 10.

Conclusions: SSTI is an increasing cause of hospitalization and, despite recent relevant formal guidelines, management is greatly variable.

Key words: Cellulitis; skin and soft tissue infection; skin abscess; antibiotic treatment.

Introduction

The term skin and soft tissue infection (SSTI) includes a group of diseases which vary widely in clinical severity. They range from folliculitis to necrotising fasciitis. Since the infections are in general mild and respond satisfactorily to oral treatment, most patients are managed in the outpatient setting. However, in recent years, a significant increase has been observed in the number of hospitalisations due to this disease[1-3]. The emergence of particularly virulent microorganisms has contributed to this, including community-acquired methicillin-resistant *S. aureus* (MRSA), which causes more serious SSTIs that frequently require surgical drainage[4].

On the one hand, the clinical variability leads to complex and heterogeneous management of this disease. On the other hand, treatment guidelines establish their recommendations either on the basis of the isolated microorganism[5] or according to a clinical classification[6]. However, most patients receive empirical treatment, since the causative etiological agent is isolated in less than 20% of aspirates[7,8], and only 2% of blood cultures are positive[9]. Only in the more serious infections, such as necrotising fasciitis, the proportion of positive blood cultures is significantly greater; rising to 80%[10]. In addition, the severity scores are not always useful for determining the type of management and empirical treatment in each particular case[11].

This has given to the use a wide variety of treatment regimes, depending on the hospitals, the antibiotic preferences of the clinician, and the clinical picture in each specific case[1,12]. It also implies a heavy use of healthcare resources (lengthy hospital stays, the cost of drugs and complementary tests); in addition to inconvenience for the patients. The aim of this study was to determine the empirical antibiotic regimes and the duration of antibiotic treatment in a tertiary hospital.

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Patients and methods

The Complejo Hospitalario de Vigo is a third-level hospital with 1,250 beds attending a population of 435,000 inhabitants. We identified patients discharged from the hospital with a principal diagnosis of SSTI from 1st January through 31st December 2009 using the *International Classification of Diseases, 9th Revision* (ICD-9), coding data. The search codes were cellulitis and skin abscesses of the toes or fingers (681.*), other cellulitis or abscesses (682.*), erysipelas (035), other skin and subcutaneous tissue infections (686.*) and necrotising fasciitis (728.86).

The clinical records were reviewed and the following data were collected: demographic characteristics, co-morbidities, microbiological and radiological examinations; antibiotic regimen before admission, during admission and at discharge; duration of admission, need for surgical procedures, and subsequent evolution. Patients less than 18 years of age, those with surgical wound infections, or those transferred to an outside hospital were excluded.

Infections were classified in three groups: cellulitis, abscess and soft tissue infection with additional complicating factors (cSSTI). The criteria for inclusion in the latter group were hospitalization, or surgery within the previous 90 days, long-term care facility residence, deep tissue infection, bacteraemia, intensive care unit admission, diabetic ulcer or chronic ulcer, peripheral artery disease, recurrent cellulitis (<90 days), animal or human bite, severe cellulitis requiring surgical debridement or fascial biopsy, necrotising fasciitis[1].

The following markers for clinical failure were established: recurrence or re-admission due to soft tissue infection within 30 days following discharge from the hospital, need for a second surgical debridement or treatment failure. This was defined as a change in antimicrobial therapy, or the need for additional drainage or debridement >7 days after the initiation of therapy due to inadequate clinical response.

The statistical analysis was performed using SPSS 17.0 software. Qualitative variables were expressed as number and frequency, and quantitative variables as mean and standard deviation (SD). Differences between the qualitative variables were established using the χ^2 test or Fisher's exact test, as appropriate. Quantitative variables were compared using the Student's t-test. Statistical significance was considered at $p< 0.05$.

Results

One hundred and thirty-one patients were identified (3.5 per 1 000 admissions/year), classified according to infection type as cellulitis (75 patients), abscess (13 patients) and cSSTIs (43 patients). The clinical characteristics of the patients in each group can be seen in the Table 1.

Outpatient treatment failure was the most common reason for admission in the three groups. Patients with cSSTI more frequently presented co-morbidities, such as diabetes mellitus, liver disease, cancer, (49% in cSSTI, 28% in cellulitis and 7% in abscesses, $p = 0.009$), and the need for surgery was more common in patients with abscesses (46% in abscesses, 0% in cellulitis and 9% in cSSTI, $p < 0.001$). Seventy-seven percent (77%) of patients were admitted to the Internal Medicine Department, and the rest to the Geriatric Unit (8%), Traumatology Department (5%), Plastic Surgery Unit (1%) and others (9%).

The average age of patients with abscesses was significantly lower (45±20.5 years) compared to patients with cellulitis (63±17.1 years) or cSSTI (65±18.8 years), $p = 0.001$. Intravenous drug user was more prevalent in the group of patients with abscesses (15% in patients with abscesses, 1% in cellulitis and 0% in cSSTI, $p = 0.004$), also infection in the upper limbs was most common in this group, although the difference was not statistically significant (31% in abscesses, 15% in cellulitis and 14% in cSSTI, $p = 0.31$).

Table 1. Characteristics of patients hospitalised with skin and soft tissue infections.

	Cellulitis (n= 75)	Abscess (n=13)	cSSTI (n=43)	p
Age (years ± SD)	63 ±17.1	45 ± 20.5	65 ± 18.8	0.001
Sex (female, %)	41 (55)	4 (31)	26 (61)	0.17
Risk factors (n, %) *				
Diabetes mellitus	14 (19)	2 (15)	14 (33)	0.18
Obesity	12 (16)	1 (8)	7 (16)	0.73
CVI	16 (21)	0	7 (16)	0.17
Previous cellulitis	13 (17)	0	5 (12)	0.22
Alcoholism	6 (8)	2 (15)	4 (9)	0.70
Cirrhosis	3 (4)	0	0	
Injury	23 (31)	5 (39)	13 (30)	0.84
Tinea pedis	28 (37)	2 (15)	2 (5)	<0.001
IDU	1 (1)	2 (15)	0	0.004
Immunodeficiency	9 (2)	0	6 (14)	0.37
Site (n, %)				
Lower limbs	60 (80)	9 (69)	36 (84)	0.39
Upper limbs	11 (15)	4 (31)	6 (14)	0.31
Causes of hospitalization (n, %) *				
Oral treatment failure	31 (41)	6 (46)	15 (35)	0.70
Extension of the infection	13 (17)	1 (8)	4 (9)	0.38
Comorbidities	21 (28)	1 (8)	21 (49)	0.009
Sepsis syndrome	1 (1)	0	3 (7)	0.18
Need for surgery	0	6 (46)	4 (9)	<0.001
Radiological studies (n, %)				
Plain film radiograph	22 (29)	5 (39)	12 (28)	0.76
CT	10 (13)	0	6 (14)	0.37
MRI	5 (7)	2 (15)	6 (14)	0.35
Ultrasound	2 (3)	4 (31)	8 (19)	0.001
Doppler	22 (29)	3 (23)	9 (21)	0.59
Failure of empirical treatment (n, %)	12 (16)	2 (15)	11 (26)	0.52
Duration of hospitalisation (days ± SD)	10 ± 7.5	8 ±4.2	14 ± 9.2	0.003
Treatment duration (days ± SD)				
Outpatient	5 ± 13.9	8 ± 4.9	7 ± 7.6	0.12
Inpatient	9 ± 5.6	8 ± 4.4	14 ± 8.6	0.001
Discharge	5 ± 4.4	7 ± 7.9	5 ± 8.1	0.42
Total	17 ± 7.9	19 ± 10.2	22 ± 15.5	0.016

Note: cSSTI: complicated skin and soft tissue infection; CT: computed tomography; CVI: chronic venous insufficiency; IDU: intravenous drug user; MRI: magnetic resonance imaging;

* Some patients presented ≥1.

Cultures of superficial wound swab or pus or blood cultures were positive in 28 patients (21%): 19 *S. aureus* (2 MRSA, neither of which were community-acquired), 2 *S. pyogenes*, 4 Gram negative bacilli (2 *Pseudomonas aeruginosa*, 1 *Enterobacter cloacae*, 1 *Proteus mirabilis*) and 2 mixed flora. Blood cultures were positive in 2% of patients (1 methicillin-sensitive *S. aureus* and 2 *S. pyogenes*). The microorganism was recovered more frequently among patients with abscess (15% vs 8%) or cSSTI (56% vs 25%) than in patients with uncomplicated cellutitis (29% vs 67%, p = 0.001). Patients with positive microbiology results had longer duration of treatment (median [IQR]: 18 [15-29.5] vs 15 [12-19] days, p = 0.003) and longer hospital stay (11 [7-17] vs 8 [5-13] days, p = 0.014).

The most common SSTI site was the lower limbs (80%), followed by the upper limbs (16%), facial area (3%) and the perianal region (1%).

Duration of hospitalization was significantly longer in patients with cSSTI (14±9.2 days) compared to patients with cellulitis (10±7.5 days) and patients with abscesses (8±4.2 days), p = 0.003. The duration of antibiotic treatment was also greater in patients with cSSTI (22±15.5 days for cSSTI, 17±7.9 days for cellulitis and 19±10.2 days for abscesses, p = 0.016), according to a longer duration of antibiotic treatment during admission (14±8.6 days in patients with cSSTI, 9±5.6 days in cellulitis and 8±4.4 days in abscesses, p = 0.001).

Antibiotic regimes

The most frequently used antibiotic in the outpatient setting was amoxicillin-clavulanate (72%), followed by quinolones (26%), either as a single agent or in combination. On admission to hospital, 41 different antibiotic regimes were employed. Amoxicillin-clavulanate was the most common (37%). In 61 patients (47%) more than one drug was used and in 21 patients (16%) antibiotics with activity against resistant microorganisms were used as first line therapy (linezolid, vancomycin, daptomycin, tigecycline, carbapenems, piperacillin-tazobactam). The antibiotic regimen had to be changed in 25 patients (19%) due to inadequate clinical response, with 16 different antibiotics or combinations of antibiotics: 8 carbapenems, 5 tigecycline, 4 quinolones, 4 linezolid, 2 piperacillin-tazobactam. No relationship was observed between treatment failure and the type of antibiotic initially used. In patients with treatment failure, although the period of hospitalization (14 ± 8.7 vs. 12 ± 9.0 days, p = 0.31) and the duration of antibiotic treatment (14 ± 6.8 vs. 12 ± 8.2 days, p = 0.33) were greater than in patients who responded adequately to their initial antibiotic treatment, no statistically significant difference was demonstrated.

On discharge, 95 patients (73%) received antibiotic, and 25 different treatment regimes were prescribed. This included combinations of two drugs in 22 patients (23%) and drugs active against resistant microorganisms (linezolid or daptomycin) in 10 patients. The duration of this treatment was 8 ± 5.8 days.

None of the patients presented recurrent infection within 30 days following discharge. A second intervention was required in 4 of the 10 patients. Two patients (2%) died, one due to a disease not directly related with the infection, and another due to septic shock.

Discussion

Skin and soft tissue infection is a highly common disease with an increasing number of hospitalisations[1-3], most of them resulting from previous treatment failures[6,13]. However, there is very little evidence regarding what is the best antibiotic treatment. Accordingly, some authors have found better clinical response in patients who received beta-lactams, even without MRSA cover, compared to quinolones or other broad-spectrum antibiotics[14]. However, a double-blind study comparing amoxicillin-clavulanate with moxifloxacin, initially administered intravenously and then orally, did not find any differences[15].

Current guidelines for treatment of SSTI[5,6] do not provide clear recommendations for some common clinical scenarios, such as empirical management or treatment of patients with previous treatment failure. Moreover, the treatment regimes recommended are confusing, with more than 10 different antibiotic combinations[6]. Sometimes, the first line treatment suggested for uncomplicated SSTI is oral cloxacillin, a drug with poor oral bioavailability, and which is considered by many clinicians as an inappropriate choice[6]. This has meant that only 26% of the treatments prescribed by clinicians are in accordance with the guidelines[12,16]. Although single agent treatment or combinations of 2 drugs are recommended in the guidelines, over 50% of patients receive combinations of 3 or more antibiotics[1]. As a result, the possible combinations are so varied that some studies have found between 35 and 46 different regimes for the treatment of SSTI[12,14]. These data are similar to those found in our study.

In our study, patients with positive microbiologic results were more commonly those with abscess and cSSTI, as previously reported[9,10]. This could explain the longer treatment duration and also the longer hospital stay of these patients.

A treatment duration of 7-14 days may be sufficient in the majority of patients, but those patients with lymphoedema, chronic venous insufficiency, peripheral artery disease or more complicated infections, such as diabetic foot, may require between 3 and 4 weeks of treatment[6]. In several studies, the mean duration of treatment is around two weeks[1,13], which is inferior to that observed in our study. However, in the study of Jenkins et al, the rate of recurrence was 6%, which can be explained by the antibiotic selected at discharge (trimethoprim-sulfamethoxazole, which has poor *Streptococcus* cover), and by the short duration of treatment[1]. In our study, none of the cases presented recurrence of their infection, which may be explained by the fact that our patients had a higher percentage of uncomplicated SSTI and a longer duration of treatment.

In this study, 19% of patients had treatment failure, a rate similar to that found in other series (12-23%)[1,14]. This has been associated with an increase in in-hospital mortality, a longer duration of antibiotic treatment and hospital stay and, higher costs[14]. Factors associated with treatment failure are age, severity, bite wounds and the Charlson index[17]. However, in our study, no factor was found to be associated with a higher failure rate, and although the duration of hospitalisation and time of antibiotic treatment were greater in these patients, no significant difference was demonstrated.

Our study has some limitations. It was a retrospective cohort study, where cases were identified according to the discharge report coding, which may have led to an underestimation of the number of admissions for this disease. In addition, although the subsequent admissions of the patients were reviewed, as was any attendance in the emergency room, the rate of treatment failure may also have been underestimated. The study was carried out in a single hospital complex, which also has its limitations.

Despite recent relevant formal guidelines, a highly variable empirical antibiotic treatment has been observed. An elevated percentage of patients received, after oral treatment failure, antibiotics with activity against multi-resistant microorganisms or combinations of more than three drugs.

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