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Epidemiologic Factors and Treatment Responses on Patients Infected with Cellulite: a Case Study of Iran

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Introduction:

Cellulite is an acute infection of the dermis and hypoderm layers of the skin, characterized by swelling, warmth, redness and local pain (Shiffman, 2012). The annual worldwide incidence of cellulitis is about 200 cases per 100,000 individuals and is common in middle-aged and elderly adults. The predisposing factors include the breakdown of the traumatic skin barrier (insect bite, age, penetrating ulcers and the use of injectable drugs), inflammation (eczema, radiotherapy), skin infections (yellow fever or foot fungus infection), chicken pox and edema (caused by Intravenous dysfunction) (Kasper & Fauci, 2010). Lymphatic obstruction is also susceptible to cellulitis after surgery. Such therapeutic measures include saphenous vein removal, axillary lymph nodes in cancer and

Abstract

Cellulite is an acute infection of dermis and hypoderm layers of the skin. Most patients are treated with oral antibiotics. This descriptive-analytic study aimed to evaluate the epidemiologic factors and treatment response to different antibiotics in patients suffering from cellulitis hospitalized in Ahvaz Razi Hospital, Ahvaz, Iran. The epidemiologic factors, predisposing factors as well as the therapeutic response to different antibiotics were recorded and analyzed. The antibiotic treatment was defined successful if the target antibiotic was administered for 7 to 14-day treatment period, and during this period skin redness decreases, body temperature normalize and the patient gets released based on the diagnosis of an infectious expert. The most frequent involved organs in cellulitis were respectively lower and upper extremity, buttocks, head, neck, and trunk. The rate of treatment failure in male was higher than the females (31.8% Vs 27.2%), but the difference was not statistically significant. The two distinct age groups of the patients revealed statistically treatment failure (51.32 Vs 37.9 years). More than 50% of the patients with an underlying disorder showed treatment failure, whereas the treatment failure rate was statistically lower (18.3%) in the patients with no underlying disease. The mean hospitalization duration in the patients with treatment failure was statistically longer than the patients with successful treatment (12 days Vs. 5 days). In comparison with a similar study conducted a decade ago on cellulitis on this hospital, our findings showed that the treatment with the presently available antibiotics is good for cellulitis.

the removal of lymph nodes in pelvic malignancies (Mzabi *et al.*, 2017). The gap between the two toes is perhaps the most important place for the introduction of pathogens, but the gaps in the skin may be small and clinically not obvious (Mzabi *et al.*, 2017). The most common pathogens of cellulitis are Group A *Streptococcus* and *Staphylococcus aureus* (*S.aureus*) or golden staph. The bleak infectious include Erysipelothrix Rhusiopathiae (in individuals dealing with meat, fish, and leather), Aeromonas hydrophila (after swimming in freshwater), Vibrio species (after swimming in salt water or contact with raw seafood) *Pasteurella multocida* (following bites or scratching by animals) (Collazos *et al.*, 2018). The symptoms of cellulitis vary, depending on the etiology, underlying disease, and the location of the infection. Cellulitis is usually formed with red, warm, and stiffened macules with an uncertain

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border that expands rapidly. Other manifestations usually include fever, lymphangitis, and regional lymphadenitis (Collazos *et al.*, 2018). Cellulitis complications include abscess, myositis, osteomyelitis, septicemia, septic arthritis, deep vein thrombosis, glomerulonephritis, endocarditis, lupus erythematosus, meningitis and gangrene of the limbs. The most common complications include abscesses (20-30%), myositis (20-40%), osteomyelitis (9-7%), and septicemia (3-5%), while other complications are not significant (Njim *et al.*, 2017). The most vulnerable groups to cellulitis are the patients already suffering from diabetes, cirrhosis, kidney failure, malnutrition, immune deficiency, and alcohol and drug users. Cellulitis is diagnosed by biopsy, observation, and examination of skin findings and examination of laboratory findings (mild to moderate leukocytosis with a slight increase in the rate of erythrocyte sedimentation) (Cook, 2016). The average recovery time after treatment is ~12 days. Most patients are treated with oral antibiotic therapy. Those who do not respond to the treatment should be reassessed and administered with intravenous antibiotics. The antibiotics that cause an effective treatment for *S.aureus* such as the first generation cephalosporins (cephalexin, injectable cefazolin), or penicillins that are effective on *S. aureus* (dicloxacillin or cephalexin) are also an effective treatment for cellulitis cases (Rayner & Munchof, 2005). Cellulitis is most commonly observed in the limbs, especially the lower extremity. In general, in 53% of the cases, the involved organs are upper and lower extremities, 20% are hips and perineum, 18% is the trunk and in 9% of the cases, the involved organs are head and neck (Karppelin *et al.*, 2010). The first line treatment for cellulitis is oral antibiotics that in most cases, effectively treat the infection within 10 to 14 days (Dalal *et al.*, 2017). If the face or the end part of the organs is involved, or the cellulitis involved area is wide, the patient should be hospitalized for the administration of injectable antibiotic therapy (Karppelin *et al.*, 2010). Experimental therapy should start immediately which is effective in most cases. Conducting epidemiologic studies on the prevalence of cellulitis and the treatment response to different antibiotics for a geographical location is necessary. To our knowledge, there is one study conducted on this important infection that was conducted by Nikkhoy *et al.* (2012) on the patients referred to Ahvaz Razi Hospital from 2001 to 2004. They observed the history of animal bites and the type of trauma have a significant relation with the frequency of the clinical complications. The main limitations of their study were based on small sample size (n=150) and a short period of assessment (four years).

The aim of this study was to re-evaluate the absolute frequency of patients suffering from cellulitis and to evaluate epidemiologic and predisposing factors as well as the therapeutic response to different antibiotic types in

patients with cellulitis hospitalized in Ahvaz Razi Hospital as the referral center for infectious diseases in Khuzestan province, Iran. Indeed a similar study was conducted a decade ago on cellulitis on this hospital. Thus, with the advancement in medical science, it has been felt again to recheck the results with some additional factors. Underlying disorders such as diabetes decrease treatment response. Increasing age particularly above 20 years old, increases the rate of treatment failure that consequently increases the imposed costs over the healthcare systems. The findings of this study could be used to prevent the onset of this disease and to develop appropriate antibiotics for treatment of cellulitis.

Methodology:

This was a descriptive-analytic study based on hospital records. The medical records of 400 patients (n=400) who were admitted to Ahvaz Razi Hospital in between the year 2011 to 2015 due to cellulitis. The study variables included epidemiologic factors such as age, sex, occupation, and place of residence, predisposing factors such as any underlying disease as well as a therapeutic response to different antibiotics. In this study, the antibiotic treatment was considered as a successful measure, if the antibiotic was administered for a 7 to 14-day treatment period and during this period skin redness decreases, the patient's body temperature normalized and the patient is released based on the diagnosis of an infectious expert. Otherwise, antibiotic therapy was considered unsuccessful or failed. Inclusion criteria include the definitive diagnosis of cellulitis confirmed by the specialist(s) infectious expert. Exclusion criteria include all patients whose medical records are incomplete or illegible.

Statistical analyses: descriptive analyses of quantitative variables were used as mean $\pm$ standard deviation (SD) and for qualitative variables as percentages, tables, and charts. The normality of the data was verified using Kolmogorov-Smirnov test. Further, to compare the mean differences between the two groups, for the quantitative and qualitative variables the t-test and Chi-square test were respectively used. The statistical analyses were conducted with statistical package of SPSS (Windows, version 22).

Results:

The male/female ratio of this study was 198 (49.5%)/202 (50.5%). The mean age of the subjects was 41.8 ± 18.6 years (range 10-86 years), the distribution pattern is in Fig-1. Most of the patients (59.5%) were residents of the urban areas compared with the rural residents (40.5%).

Figure-1: Frequency distribution of patients by age group

ORIGINAL ARTICLE

In this study, 34.5% of the subjects had a history of underlying disorder whereas as the frequency distribution of patients by the cellulitis involved organ has been shown in Fig.-2.

Figure-1: Frequency distribution of patients by the cellulitis involved organ

As per the definition of the successful treatment response, 282 (70.5%) of the patients revealed successful treatment.

Our results showed that in the male subjects, the rate of treatment failure was more than the females (31.8% Vs 27.2%). However, this difference was not statistically significant ($p > 0.314$). The mean age of the patients who showed the treatment failure was higher than the others (51.32 years Vs 37.9 years). This difference was statistically significant ($p < 0.005$). After the age of 20, as age increases, the rate of treatment failure increases (Table-2).

Table-2: Distribution of patients by age group and the outcome of antibiotic therapy

Age group	Treatment outcome			
	Failure: N	%	Success: N	%
Below 20	11	23.9	35	76.1
Between 21-30	8	8.2	89	91.8
Between 31-40	14	20.3	55	79.7
Between 41-50	17	30.9	38	69.1
Between 51-60	26	49.1	27	50.9
Between 61-70	22	50	22	50
over 70	20	55.6	16	44.4

The frequency distribution of patients by location and outcome of antibiotic therapy was revealed as the percentage of failure was slightly higher than the failure rate among the rural residents (29.8% Vs 29%) which statistically didn't differ. Further, the results showed that more than 50% of the patients with a history of underlying disorder showed treatment failure, whereas in the patients with no underlying disease the treatment failure rate was 18.3%. The difference was statistically significant.

Results showed that the treatment outcome significantly differed with respect to the involved organs, the patients with the involved organ of buttocks showed the lower treatment failure rates, whereas the patients with the trunk involvement showed the higher rates of successful treatment than the rest of the patients (Table-3).

Further, we found that the mean duration of hospitalization in the patients with treatment failure was higher than other the patients (12 days Vs 5 days) and the difference was statistically significant (Table-4).

Table-3: Frequency distribution of patients by involved organs and outcome of antibiotic therapy

Age group	Treatment outcome			
	Failure: N	%	Success: N	%
Upper extremity	48	30.7	104	69.3
Lower extremity	53	29.8	125	70.2
Buttocks	8	21.1	30	78.9
Trunk	5	33.3	10	66.7
Head and neck	6	31.6	13	68.4

Table-4: Average, minimum, and maximum hospitalization period by the outcome of antibiotic treatment

Outcome	Average	Minimum	Maximum	p value
Failure	12	3	27	<0.005
Success	5	2	16	<0.005

Discussion:

In this study, conducted on 400 patients revealed the most common site of infection of cellulite was in the lower extremities, upper extremities, head, neck and trunk. Earlier, Nikkhoy *et al.* (2012) in a cross-sectional study investigated the epidemiologic factors of the patients admitted with a final diagnosis of cellulitis in the infection ward of Ahvaz Razi Hospital during 2001-2004, but their sample size was smaller ($n=150$) and also the study period was for only three years. However, we could compare their findings in some aspects of our findings. They found 25.3% of the patients were inflicted with complications. They assessed the age, sex, occupation and underlying diseases and the prevalence of clinical complications. They reported that 25% of the patients showed complications, 18.7% of them were an abscess, 3.3% necrotizing fasciitis, 0.7% sepsis, and 2.7% were osteomyelitis. There was no significant relationship between total cellulitis complications with age, sex, occupation, history of the immunosuppressive disease, consumption of immunosuppressive drugs and narcotics injection in the patient, whereas there was significant relation between total complications and type of trauma and history of animal bites. In conclusion, considering a significant relationship between cellulite complications and the history of bites or trauma in the cellulitis area, physicians should pay more attention to these two important factors in the history of the disease which is important for effective management of the patients (Nikkhoy *et al.*, 2012). Sarvghad *et al.* (2013) in a descriptive-analytic cross-sectional study assessed the signs, symptoms and treatment protocols of soft tissue infections in patients of Mashhad, Iran. They studied 300 patients and the most common underlying disorder was intravenous drug injection in 85 patients (28.5%). In 254 patients (84.6%), the primary diagnosis was cellulitis. They concluded that the most common soft tissue infection was in patients with cellulite and more than half of the patients were treated with amniotic antibiotic therapy.

Park *et al.* (2016) diagnosed with lymphedema

evaluated the prevalence and associated factors involved in cellulitis with lymphangitis among 1,246 Korean patients out of which 99 cases suffered from cellulitis such as lymphangitis and in 49 patients, more than one lower extremity was involved. The main findings of this study were ninety-nine lymphedema patients experienced complications such as lymphangitis associated cellulitis whereas forty-nine cases had more than two recurrences of cellulitis with lymphangitis. The incidence and recurrence of cellulitis with lymphangitis were significantly higher in patients with lower-extremity lymphedema. They observed a significant trend toward higher cellulitis prevalence in the lower-extremity lymphedema group according to the time of lymphedema onset. Among the cellulitis with lymphangitis cases, 62 cases were diagnosed through blood-cell culture; 8 of them showed positive β -hemolytic streptococci.

Wijayaratna *et al.* (2016) in a retrospective case-control medical record of an urban hospital in New Zealand where the case group included cellulitis patients with type 2 diabetes and the case group included cellulitis patients without diabetes mellitus found the association between type II diabetes and length of stay in hospital and also increasing the rate of readmissions in the patients with lower limb cellulitis. Subsequent hospitalization after 1 month with the same diagnosis was also investigated in the hospitalization group. They studied 4600 cases of admissions with lower limb cellulitis in 3636 patients, and out of which 719 (20%) was having type II diabetes. The hospital stay was statistically higher for patients with type II diabetes, regardless of age, ethnicity, and HbA_{1c}. Lower limb ulcers were more frequent in diabetic patients as compared with other patients (50% vs. 17%; $p < 0.001$). Further, the length of stay in the hospital for diabetic patients without ulcers was higher (Median 4.4 Vs 8.2; $p < 0.001$). In addition, the readmission rate was higher for diabetic patients than non-diabetic patients ($p < 0.001$), even when there was no ulcer ($p < 0.001$). Interestingly, the age, HbA_{1c}, and ethnicity had no effect on the readmission rate of diabetic patients. One-fifth of all admissions and one-third of the estimated costs were for diabetic patients. This study concluded that a large percentage of patients with type II diabetes suffered from lower limb cellulitis. They have a longer hospitalization period and higher readmission rate. Age, HbA_{1c} and ethnicity had no effect on hospital stay or readmission rate in these conditions. However, our study showed that in 29.5% of patients the treatment was successful which supports the findings of the previous similar studies. Miller *et al.* (2015) comparatively assessed treatment outcomes of clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) in cellulitis patients with uncomplicated skin infections and found that the treatment failure for clindamycin was 19.1%, whereas in the TMP-SMX-treated

patients the treatment failure rate was 23.6%. Pertel *et al.* (2009) compared the treatment efficacy of daptomycin and vancomycin in the treatment of cellulitis patients and reported that the clinical success rates were 94.0% for daptomycin and 90.2% for vancomycin, which didn't differ statistically. Prokocimer *et al.* (2013) compared the treatment effectiveness of tedizolid phosphate with linezolid in treating acute bacterial skin and skin structure infections and reported that tedizolid phosphate had the failure rate of 20.5% and linezolid showed the treatment failure rate of 20.6%. As per them the Tedizolid phosphate was a statistically non-inferior treatment to linezolid in early clinical response at 48 to 72 hours after initiating therapy for the acute bacterial skin and skin structure infections. Tedizolid phosphate may be a reasonable alternative to linezolid for treating acute bacterial skin and skin structure infections. In a retrospective cohort study during 2003 to 2004 evaluated the consequences of failure of initial antibiotic therapy in the patients ($n=47219$) who were admitted to the hospital for complicated skin and skin structure infections and received intravenous antibiotics during the first 2 hospital-days (Edelsberg *et al.*, 2008). They reported that 10,782 (22.8%) of the patients showed the failure of initial antibiotic therapy. The findings of our study are in line with the results of previous studies. The previous studies have reported the same level of treatment failure rates that were comparable to our findings. However, the Pertel *et al.* (2009)'s study reported a lower rate of treatment failure compared with other studies. Moreover, the reason for the difference in treatment failure rates in different antibiotic regimens than the previous reports may be attributed to the outbreak of underlying diseases in patients, the complications of cellulitis as well as the delay in referring patients to treatment. In this study, there was no significant relationship between treatment failure and gender, place of residence, place of engagement. However, with increasing age and underlying disorder, the degree of treatment failure increased. Further, the patients had the treatment failure, the duration of hospitalization was found greater in them (12 days Vs. 5 days).

Conclusively, the findings of our study showed that antibiotics are a good treatment for cellulitis, and the rate of treatment failure is higher in patients who are older in age and have an underlying disorder such as diabetes. With the failure of treatment, the average length of hospitalization increases that consequently increases the imposed costs over the healthcare systems. It is suggested future studies to investigate the cause of treatment failure in patients with cellulitis in a prospective clinical trial focusing on the factors such as the causative microorganism, antibiotic outcomes for these microorganisms, tissue perfusion in these patients, and other effective factors.

ORIGINAL ARTICLE

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