# Cellulitis: A Study of Drug Use Evaluation in a Tertiary Care Teaching Hospital

**Shrishailgouda S. Patil[1,*], Sreekanth. S[2], Berlin Baby[2], Adireddy Sravani[2], Grandhe Geethika[2], Doddayya Hiremath[1]**

[1]Department of Pharmaceutics, N.E.T Pharmacy College, Raichur, Karnataka-584103, INDIA.
[2]Department of Pharmacy Practice, N.E.T Pharmacy College, Raichur, Karnataka-584103, INDIA.

## ABSTRACT

**Background:** Inappropriate use of drugs especially antibiotics, in the treatment of cellulitis results in therapeutic failure and recurrence of cellulitis. Drug use evaluation is a performance improvement method that focuses on evaluation and improvement of drug use processes to achieve optimal therapeutic outcomes. **Objectives:** The present work deals with the drug use evaluation in cellulitis with an aim to improve therapeutic outcomes of the disease. **Methodology:** The prospective observational study on the drug utilization evaluation in cellulitis was carried out on a total of 67 cellulitis in-patients from the departments of medicine, surgery, orthopaedics of Navodaya Medical College Hospital and Research Centre, Raichur. Relevant information was recorded in a structured proforma & data was evaluated. The drugs used in the treatment were evaluated by comparing with by using CREST (Clinical Resource Efficiency Support Team guidelines, developed by Central Medical Advisory Committee, Ireland) guidelines. **Results:** Out of 67 patients 53 patients were diagnosed with Class 2 cellulitis, 13 patients were Class 3 cellulitis and only 1 patient was Class 4 cellulitis (Class 1 cellulitis patients are treated on out-patient basis and hence not included in the study). The rank order of antibiotics prescribed in the treatment was as follows: Cephalosporins > aminoglycosides > penicillins > macrolides > fluoroquinolones. **Conclusion:** An overall deviation in 28.3% patients as been observed in the line of treatment with respect to antibiotics use as per CREST guidelines. Further, deviation was also observed in prophylactic antibiotics prescribed to prevent the recurrence of cellulitis. The study also revealed the lack of awareness in the cellulitis patients regarding the disease, its recurrence and prevention. Thus, the study intensifies the need to create the awareness among the physicians regarding the appropriate use of antibiotics and in patients to prevent its occurrence and recurrence.

**Key words:** Cellulitis, Prospective observational study, Drug use evaluation, Antibiotics, CREST guidelines.

## INTRODUCTION

Cellulitis is an infection of the skin and underlying tissues. It may follow a break in the skin or a surgical wound but may also occur without an obvious inciting event. The microorganisms most frequently involved include group A streptococci (*Streptococcus pyogenes*); groups B, C, and G β -haemolytic streptococci; and *Staphylococcus aureus*. Over the recent decades cellulitis has challenged clinicians in several ways. First, physician visits for cellulitis and soft-tissue infections have increased from 32 to 48 visits per 1000 population from 1997 to 2005.[1] Cellulitis is not always a clear-cut disease entity and may be mistakenly diagnosed for other conditions. Furthermore, there appears to be some crossover between the terms "erysipelas" and "cellulitis", the former usually reserved for a specifically streptococcal infection with a well demarcated edge, the latter being a more general description of a disease that is produced by invasive bacterial infection associated with local erythema, warmth, pain, and swelling.[2] While commonly thought to be caused by either streptococci or staphylococci, many other bacteria have also been associated with the disease. However, routine investigations such as blood cultures and wound swabs are rarely helpful in early identification of the responsible organism, and antibiotics need to be chosen to maximize efficacy from the onset.[3]

A classification system can serve as a useful guide to admission and treatment decisions. This classification was devised by Eron for skin and soft tissue infections. Class I patients have no signs of systemic toxicity, have no uncontrolled co-morbidities and can usually be managed with oral antimicrobials on an outpatient basis. Class II patients are either systemically ill or systemically well but with a co-morbidity such as peripheral vascular disease, chronic venous insufficiency or morbid obesity which may complicate or delay resolution of their infection. Class III patients may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or may have unstable co-morbidities that may interfere with a response to therapy or have a limb threatening infection due to vascular compromise. Class IV patients have sepsis syndrome or severe life-threatening infection such as necrotizing fasciitis.[4]

Cellulitis is mainly an endemic disease. Use of inappropriate antibiotics is a major drawback in cellulitis. The selection of antibiotics is empirically done. Several studies revealed that antibiotics are very often inappropriately used. Factors such as eagerness to provide quick relief to patients have promoted the misuse of antibiotics. During the past two decades, resistance to antibiotics has become a major public health concern due to the rapid spread of multi-resistant bacteria clones.[5] Appropriate use of antibiotics is central to limiting the development and the spread of resistant bacteria in hospitals and communities. Furthermore, the absence of well-established WHO guidelines for antibiotic use, protocols for rational therapeutics and infection control committees for cellulitis have led to overuse and misuse of antimicrobials in hospitals. However, the presently available CREST (clinical resource efficiency support team) guidelines developed by Central Medical Advisory Committee, Ireland are followed here as the reference guidelines.

Drug Utilization Evaluation (DUE) has been defined by the American Society of Health System Pharmacists (ASHP) as a "Criteria-based, ongoing, planning and systemic process for monitoring and evaluating the prophylactic, therapeutic and empiric use of drugs to help, assure that they were provided appropriately, safely and effectively.[6]

Thus, the present study will help in identifying any inappropriate use of drugs including antibiotics in the treatment of cellulitis, thereby rationalizing the drug therapy. The feedback of results obtained from the study may help the physicians to modify treatment regimen in cellulitis if necessary.

## MATERIALS AND METHODS

### Study design

Study type: Prospective observational study.

Study site: Navodaya Medical College Hospital and Research Center, Raichur, (1000 bedded Multi-specialty tertiary care teaching hospital).

Departments: Surgery; Orthopedics; General Medicine and Pediatrics

Sample Size: 67 patients

Study period: 6 months from November 2016 to April 2017.

### Inclusion criteria

- All in-patients of different age groups irrespective of sex diagnosed with cellulitis.
- Cellulitis patients with co-morbidities like diabetes, hypertension.

### Exclusion criteria

- Pregnant, lactating women and Oral cellulitis cases were excluded from the study.

The institutional ethical committee permission was taken to conduct the study. A specially designed data entry format was used to enter all patient details like patient's name, age, sex, weight, IP number, date of admission, reason for admission, past medical history, past medication, any surgical procedure done. Provision is given in the format to enter laboratory investigations, diagnosis made and number of drugs prescribed with duration of treatment.

### Assessing the prescriptions

Prospective data from the prescriptions were obtained with regard to patient's demographics, drugs and their dose, duration, route of administration, average number of drugs per prescription, drug interactions and ADRs. A total of 67 prescriptions were collected, observed and recorded.

### Observations for ADRs

The cellulitis patients receiving the drug therapy were observed regularly for any ADRs. The nurses were also aware of the observation. In the suspected cases, the ADRs were discussed with the respective physicians and same was recorded. Mean-while the ADRs were corrected with the help of Physicians.

## Prescription analysis

The prescriptions of the selected patients were collected from the in-patient departments of different wards paying due attention to inclusion and exclusion criteria and were evaluated prospectively for the presence and monitored for the following variables:

➢ Sex and age distribution of patients.
➢ Dose, Duration, Dosage form and Route of administration Average number of drugs per prescription.
➢ Monotherapy and combination therapy.
➢ ADRs and drug interactions associated with prescribed drugs.

## Evaluation of data

The Medscape drug interaction database and Stockley's Drug interaction book was used to assess the drug interactions in a prescription, their severity and management. The data generated in the study was analyzed using descriptive statistics namely total numbers, mean, standard deviation and percentage wherever applicable. Microsoft word and Excel have been used to generate graphs, tables etc.

## RESULTS AND DISCUSSION

Cellulitis is a severe infection of the soft tissues, with a variable aetiology from Gram-positive to Gram-negative bacteria and deep fungal infections, whose early recognition is mandatory to avoid potentially life threatening complications[7]. Inappropriate use of antibiotics specifically, the broad-spectrum antibiotics in hospital results in resistance to antibiotics. Assessment of antimicrobial use can be performed by evaluating their use. Drug use evaluation is a performance improvement method that focuses on evaluation and improvement of drug use processes to achieve optimal patient outcomes. Thus, the present work was undertaken to study the drug utilization evaluation in the cellulitis patients as the successful therapeutic outcome mainly depends on the appropriate use of antibiotics in this disease.

## Patient demographics

The gender distribution of our study population showed that among 67 patients, 82.08% were male and 17.91% were female. Similar findings were also reported by Simonsen SME *et al*.[8] regarding the higher incidence rate of cellulitis among males compared to female. With respect to age and sex, 53.7% of males (n=55) and 53.3% of females (n=12) in 41–60 years age-group were predominantly diagnosed with cellulitis followed by patients who were in the age group of 61 – 80 years (23.6% male and 8.3% female). Our observations were found to be similar to another study on cellulitis conducted in South Korea by Park SI *et al*.[9] and by Kremer M *et al*.[10] Table no 1 and 2 shows the gender wise distribution and age distribution of the study population respectively.
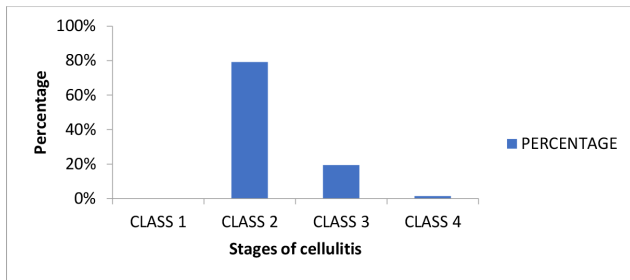
## Occupational status and social habits

In the study population majority of the patients were from agriculture sector i.e., 38.80% followed by 28.35% working in industries. The higher incidence of cellulitis in the patients with these occupations could be due to their susceptibility for cuts and scrapes during the work and also due to the negligence and poor health care facilities after the injury. Thus, wounds are more prone to bacteria and may get converted to cellulitis.
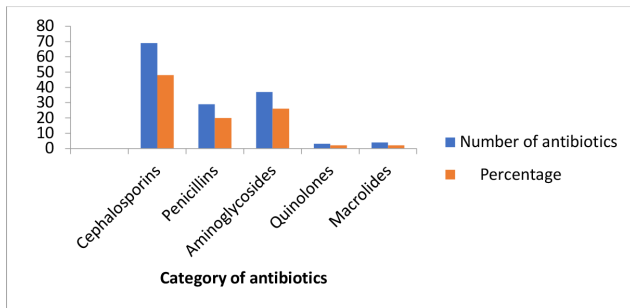
Among the study population, 59.7% patients were alcoholic and 40.29% were non-alcoholic. Smoking habits were found in 65.67% and the remaining 34.32% were non-smokers. It is reported that nicotine reduces the healing of the infectious wounds and decline the effect of drug therapy. The results of our study were in accordance with the study conducted by Pitché P.V *et al*.[11] On the other hand, alcohol consumption in the patients may also lead to drug interactions. Thus, counseling of the patients for these social habits is important in order to improve the therapeutic effects of drugs. However, in a study carried out by Alain Dupuy *et al*. revealed that, alcohol has no significant effect on the healing of infections.[12]

## Comorbidities in study population

In the study population, majority of the patients have no comorbidities (77.61%) and few patients (22.38%)

### Table 1: Gender wise distribution.

| Sl.no | Gender | Total No. of patients (n=67) | Percentage |
|---|---|---|---|
| 1. | Male | 55 | 82.08% |
| 2. | Female | 12 | 17.91% |

### Table 2: Age distribution of patients.

| S.NO | Age group | NO of patients (n= 67) | Percentage |
|---|---|---|---|
| 1. | < 20 | 03 | 4.47% |
| 2. | 21- 40 | 13 | 19.4% |
| 3. | 41 – 60 | 36 | 53.73% |
| 4. | 61 – 80 | 14 | 20.89% |
| 5. | > 80 | 01 | 1.49% |

**Figure 1: Stages of cellulitis in the study population (n= 67).**



**Figure 2: Category and percentage of antibiotics prescribed in the treatment of cellulitis.**
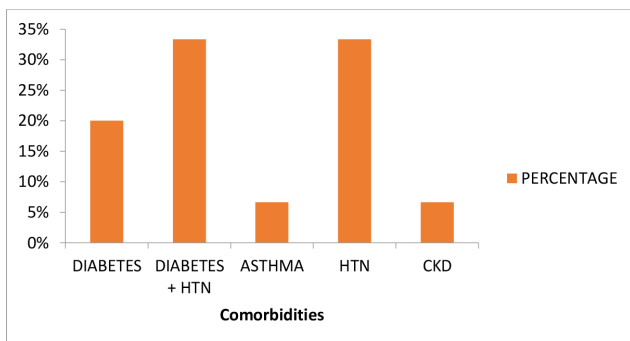


**Figure 3: Types of comorbidities observed in the study population.**

were found with comorbid conditions. The common comorbid condition found in the study population was diabetes with hypertension (33.33%). This is one of the important risk factor of cellulitis which would prolong the rate of healing and also interfere with prescribed regimens. The type of the comorbidities in the study population is depicted in Figure 3.

### Incidence of fresh and recurrent cellulitis

Out of 67 patients 92.53% were freshly diagnosed with cellulitis and 7.46% patients were admitted with recurrence. The history of cellulitis is the major risk factor for subsequent recurrence. Taking the antibiotics for a period of 6 months can effectively prevent the recurrence of cellulitis. The patient counselling and medication history revealed that, the incidence of recurrence was



**Figure 4: Photographs of selected patients suffering from cellulitis (Class III).**

mainly due to poor compliance in taking the prescribed antibiotics for the specified time period. In fact, the condition of cellulitis was still worse than what it was at the first time. Similar findings have been reported in another study conducted by Karppelin M *et al.*[13]

### Stages of cellulitis

Based on the severity of the cellulitis, CREST guidelines classifies the disease into four stages: Class 1, Class 2, Class 3 and Class 4. In the study population class 2 cellulitis (79.10 %) was found to be more predominant than class 3 (19.40%) and class 4 (1.49 %.). As class 1 cellulitis patients are treated on the outpatient basis, they are not included in the study as per our exclusion criteria. The number of patients belonging to different class of cellulitis is depicted in Figure 1. As class 1 cellulitis patients are treated on the outpatient basis, they are not included in the study as per our exclusion criteria. Figure 4 shows the photographs of selected patients suffering from class III cellulitis.

### Laboratory investigations

The levels of C reactive proteins (C-RP) is increased in case of inflammation, infections and long-term diseases. Hence, some of the patients were recommended for C-RP test. Out of 67 patients only 20 patients were recommended for C-RP test and out of 20 only 10 patient had abnormal C-RP values. ESR was tested for only 52 patients, out which 21 had higher value. A very high ESR usually has an obvious cause, such as a severe infection, marked by an increase in globulins, polymyalgia rheumatic or temporal arteritis. WBC of every patient was found to be higher which is due to the severity of infection. The laboratory investigations also revealed that 79.10% of study population was anemic. Among 67 patients,

8 patients were found to be diabetic as witnessed by high RBS values. Similar results were reported by Matti Karppelin *et al*.[13]

## Antibiotics prescribed

About 37.31% patients were prescribed with single antibiotic, 34.32% were prescribed with two antibiotics. Further 23.88% and 4.47% patients were prescribed with three or more than three antibiotics respectively. Generally, more number of antibiotics were prescribed for the patient with class 3 and class 4 cellulitis. The correlation between the number of antibiotics prescribed and the stage of cellulitis corroborated well as per the CREST guidelines.

## Category of antibiotics prescribed

Figure 2 shows the category of antibiotics prescribed in the treatment of cellulitis. The majority of antibiotics prescribed were from cephalosporins (48.59%), aminoglycosides (26.05%) and penicillin (20.42%) class compared to the macrolides (2.81%) and fluoroquinolones (2.11%). In contrast to our findings, Athena Ferreira *et al*.[14] reported the greater effectiveness of beta-lactam and macrolide antibiotics in treatment of cellulitis. However, the CREST guidelines recommend the use of cephalosporins and penicillins as the first line drugs in the treatment of cellulitis. Among the cephalosporins, 19.71% were prescribed with ceftriaxone + salbactum and 5.63% prescribed with only ceftriaxone. Thus, according to CREST guidelines, ceftriaxone is the first line treatment for class 2 cellulitis. Other cephalosporins prescribed were cefaperazone + salbactum, cefotaxime, cefixime, cefuroxime, cefuroxime + clavulanic acid.

Among the study population 20.42% were prescribed with penicillin's. The most common penicillins prescribed were amoxicillin (33.33%), amoxicillin + clavulanate (29.16%), piperacillin + tazobactum (29.16%) and the least prescribed was ampicillin (8.33%). On the other hand, 22 patients were prescribed with aminoglycosides. Within the aminoglycoside category, 90.9% patient were prescribed with amikacin followed by 9.09% with gentamycin. However, there is a lack of literature indicating the prescribing of aminoglycosides in the treatment of cellulitis. This might be due to the severe side effects like ototoxicity and nephrotoxicity of aminoglycoside antibiotics. Among the miscellaneous antibiotics/antimicrobials prescribed, common were the Metronidazole (68.18%) Azithromycin (18.18%) and Ciprofloxacin (13.6%). The details of the antibiotics prescribed is depicted in Figure 3.

## Drug interactions

Drug interactions usually results when the patients are on multiple drug therapy. The details of the concomitant drugs prescribed apart from the antibiotics is given in Table no 3. Out of 67 patients prescribed with the drugs, the incidence of drug-drug interactions were observed in 33 prescriptions (49.25%) whereas 34 prescriptions had no drug interaction. The drug interactions were reported to the physicians for needful correction in the therapy. The possible reason for high incidence of drug-drug interactions may be due to the polypharmacy used in treatment of comorbid conditions along with cellulitis. Majority of drug interactions were moderate in severity. Major drug interactions were found in 8 prescriptions and drug therapy have been suitably modified. Some of the interacting drugs that caused moderate and major interactions were gentamicin ó piperacillin, tramadol ó meropenem and cifiximeó amikacin. T

## Appropriateness of therapy

Appropriateness of therapy in the study population was analysed with respective to the CREST guidelines. In Class 2 cellulitis, out of 53 patients, 12 patients had deviation from the therapy mentioned as per the guidelines. The Patients were prescribed with Cefoperazone + salbactum, Metronidazole, Cefpodoxime+clavulanic acid, Cefoperazone+salbactum, Amikacin, Cefotaxime,

### Table 3: Concomitant drugs prescribed in the treatment of cellulitis.

| Drugs | Number of drugs (n=286) | Percentage |
|---|---|---|
| Anti-ulcer Drugs | 63 | 22.02% |
| NSAID's | 65 | 22.72% |
| Analgesics | 27 | 9.44% |
| Vitamins | 42 | 14.68% |
| Probiotics | 2 | 0.69% |
| Antifungal | 3 | 1.04% |
| Corticosteroids | 1 | 0.34% |
| Mucolytics | 1 | 0.34% |
| Anti-asthamatics | 4 | 1.39% |
| Diuretics | 5 | 1.74% |
| Cream (Clonate) | 3 | 1.04% |
| Opioid analgesics | 30 | 10.48% |
| Anti-Emetics | 7 | 2.44% |
| Anti-Epileptics | 9 | 3.14% |
| Anti Hypertensives | 6 | 2.09% |
| Calcium Supplements | 7 | 2.44% |
| Cardiac Drugs | 7 | 2.44% |
| Anti-Diabetics | 4 | 1.319% |

**Table 4: Deviation in the line of treatment as per CREST guidelines.**

| CELLULITIS STAGE | No. of Patients with deviation in therapy(n=67) | Type of drugs prescribed | Drugs to be prescribed according to guidelines (CREST Guidelines) | Percentage |
|---|---|---|---|---|
| CLASS 1* (n=0) | 0 | -- | -- | -- |
| CLASS 2 (n=53) | 12 | Cefoperazone + salbactum Metronidazole, Amikacin Cefpodoxime+clavulanic acid Cefoperazone+salbactum Cefoperazone, Cefotaxim Cefixime, Meropenem | Flucloxacillin/Ceftriaxone/ Clarithromycin/clindamycin | 22.64% |
| CLASS 3(n=13) | 06 | Ceftriaxone, Cefixime Ciprofloxacin, Metronidazole Cefoperazone Cefoperazone+salbactum | Flucloxacillin/Clarithromycin/ clindamycin/ piperacillin+ tazobactum | 46.15% |
| CLASS 4 (n=1) | 01 | Amikacin Piperacillin+tazobactum | Benzyl penicillin+ciprofloxacin+clind amycin Empirical Rx Vancomycin+piperacillin/tazobactum | 100% |

*Class 1 cellulitis patients are treated on out patients basis and hence not included in the study

Cefoperazone. Instead, patients could have been prescribed with Flucloxacillin/Ceftriaxone/Clarithromycin/clindamycin as per the CREST guidelines. In Class 3 cellulitis, out of 13 patients 6 patients had deviation from the guidelines. They could be prescribed with Flucloxacillin/Clarithromycin/clindamycin/piperacillin+tazobactum. However, these patients were advised with Ceftriaxone, Cefixime, Ciprofloxacin, Metronidazole, and Cefoperazone, Cefoperazone + salbactum. In class 4 cellulitis, the patients should be prescribed with vancomycin and piperacillin + tazobactum combination but was prescribed with amikacin + piperacillin + tazobactum combination. The details of the antibiotics prescribed the deviation in the line of treatment as per the CREST guidelines is given in Table 4.

The discharge medication chart also revealed the deviation in the prescription of drugs. The prophylactic therapy should be for 6months and as per the available literatures,[15-16] penicillin V which is more economic and therapeutically effective is generally recommended to prevent the recurrence of cellulitis. However, the patients were prescribed with amoxicillin with potassium clavunate and cefeperazone which is costlier and less effective in the treatment of cellulitis. The prescribing of more costly antibiotics may also lead to non-compliance of the patients as most of them were from rural area with poor financial conditions. This may also become a reason for the recurrence of cellulitis.

## CONCLUSION

The results of the study revealed that, cellulitis is more prevalent in rural area and male were more affected than the female. Deviation in the line of treatment with respect to antibiotics use has been observed as per CREST guidelines and overall deviation in 28.3% patients has been observed. The discharge medication charts revealed that amoxicillin+clavulanic acid and cefoperazone were prescribed instead of the more economic and more effective penicillin V, which also indicates the deviation in the prophylactic antibiotics prescribed to prevent the recurrence of cellulitis. Overall, from the study it can be concluded that, rationalization of the antibiotics in the treatment as per the available guidelines is needed for the better management of cellulitis.

## ACKNOWLEDGEMENT

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ADRs:** Adverse Drug Reactions; **ASHP:** American Society of Health System Pharmacists; **CREST:** Clinical Resource Efficiency Support Team; **C-RP:** C Reactive Proteins; **DUE:** Drug Utilization Evaluation; **WBC:** White blood Cells; **WHO:** World Health Organization.

## SUMMARY

Cellulitis is a bacterial infection of the deeper layers of the skin which can become serious if not treated properly. Often the therapy for cellulitis is empirical which may lead to poor therapeutic outcomes. The present study revealed the ignorance of the patients towards the minor injuries which has eventually led to the development of cellulitis and also the non compliance and the poor follow up post discharge of patients resulted in recurrence of cellulitis. The present study also showed the deviation in the line of treatment as per the available guidelines. Overall, the study intensifies the need to rationalize the use of antibiotics and patient education about the cellulitis is needed for the better management of cellulitis.

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