

**A PROSPECTIVE STUDY TO ASSESS THE PHARMACOTHERAPEUTIC
MANAGEMENT OF CHRONIC LEG ULCERS AT A TERTIARY CARE HOSPITAL**Afreen Fatima^{1*}, Mamatha K. R.², Sidra Shireen Zainuddin³ and Mudassir Shoeb⁴¹Assistant Professor Department of Pharmacology University of Hafr Al Batin, Kingdom of Saudi Arabia.²Professor, Department of Pharmacology Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India.³Assistant Professor, Department of Anatomy College of Medicine, Taibah University, Madinal Al Monawwarah, KSA.⁴Assistant Professor R K University, Gujarat.***Corresponding Author: Dr. Afreen Fatima**

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ABSTRACT

Introduction: A chronic leg ulcer (CLU) is a break in continuity of skin below level of knee persisting for more than six weeks. They are a major health problem affecting principally the elderly, with major risk factors being diabetes, smoking and obesity. There are three main types of ulcers, neuropathic, venous or arterial. **Objective:** The aim of this study was to evaluate efficacy and safety of drugs used in chronic leg ulcers using WHO/INRUD prescribing indicators. **Materials and method:** This was a prospective observational study, carried out in department of surgery at Victoria hospital, Bengaluru. Prescription pattern of 200 patients with chronic leg ulcer admitted to surgery ward was analysed using WHO prescribing indicators. **Results:** Out of 200 prescriptions analyzed, most common leg ulcers was diabetic (38%), followed by venous (24%) and arterial (18%). WHO prescribing indicators used for evaluating drug use, showed average number of drugs per prescription as 7, percentage of antimicrobials prescribed as 27.4%, percentage of injections prescribed as 64.5%, number of drugs prescribed from NLEM was 906 and number of drugs prescribed by generic name was 512. Percentage of antimicrobials prescribed by generic name was 46.3% and average duration of antimicrobials was 7 days. Outcome was assessed in terms of clinical cure, surgery, minor and major amputation. Out of 200 patients, 162 achieved clinical cure which was assessed using LUMT score. **Conclusion:** In this study, pharmacotherapy along with topical management of leg ulcer has achieved a clinical cure of 81% as assessed by LUMT score. All drugs used during pharmacotherapy were well tolerated.

KEYWORDS: Chronic leg ulcers, Prescription pattern, WHO indicators, Antimicrobial agents, LUMT score.**INTRODUCTION**

A chronic leg ulcer (CLU) is a break in the continuity of the skin below the level of knee persisting for more than six weeks.^[1] They are a major health problem affecting principally the elderly with a prevalence of 1% in adult population and 3-5% in population over 65 years of age.^[2] The main risk factors are diabetes, smoking and obesity. There are three main types of ulcers, neuropathic, venous or arterial.^[3,4,5]

Although the overall prevalence of leg ulcers is relatively low, the refractory nature of these ulcers increase the risk of morbidity and mortality and has a significant impact on patient's quality of life.^[6,7]

Optimum management of CLUs has large impact in prevention of foot impairment and amputation rate in patients with leg ulcers. Appropriate management of

these patients reduces the financial burden and improves patient's quality of life.^[8]

The objective in the treatment of CLU's is to avoid major limb loss and to retain function. Early recognition of lesion and prompt initiation of pharmacotherapy as well as surgical debridement of necrotic tissue are essential for controlling infection and preventing additional morbidity.

Antimicrobial agents (AMA) are the mainstay of treatment, either monotherapy with a single broad spectrum agent or combination therapy with two or more AMAs. But the objective data regarding the efficacy of treatment with various antimicrobials is not clear.^[9] Hence this study was planned to evaluate the drug use in chronic leg ulcers using WHO prescribing indicators.

1. AIMS AND OBJECTIVES

1. To evaluate drug use in chronic leg ulcers using WHO/ INRUD prescribing indicators.
2. To assess the outcome of treatment as measured by LUMT scores.

2. MATERIALS AND METHODS

A Prospective Observational Study was conducted in the Department of Surgery at Victoria hospital, Bangalore after taking approval from institutional Ethics committee. All in-patients admitted with chronic leg during the study period from November 2016 –May 2018 were enrolled in the study. Written informed consent was taken from all the patients.

Inclusion criteria

1. In-patients with a chronic leg ulcer of any etiology and aged above 18 years
2. Patients willing to give written informed consent.

Data was collected and analyzed for a period of 18 months.

Assessment tools: The assessment tool used was Leg Ulcer Measurement Tool (LUMT)⁶⁷, to detect changes in the appearance of leg ulcers.

Drug data collected was analyzed for the following parameter:

WHO/INRUD prescribing indicators:

- a)Average number of drugs per encounter
- b)Percentage of encounters with an antibiotic prescribed.
- c)Percentage of encounters with an injection prescribed.
- d)Percentage of drugs prescribed from essential medicines list.
- e) Percentage of drugs prescribed by generic name.

WHO indicators for Antimicrobial agents.

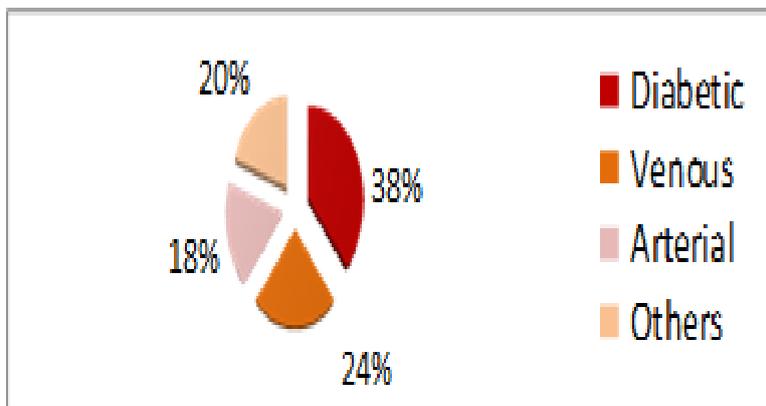
- a)Percentage of antimicrobial drugs prescribed by generic name
- b) Average duration of prescribed antimicrobial drug treatment

Statistical analysis

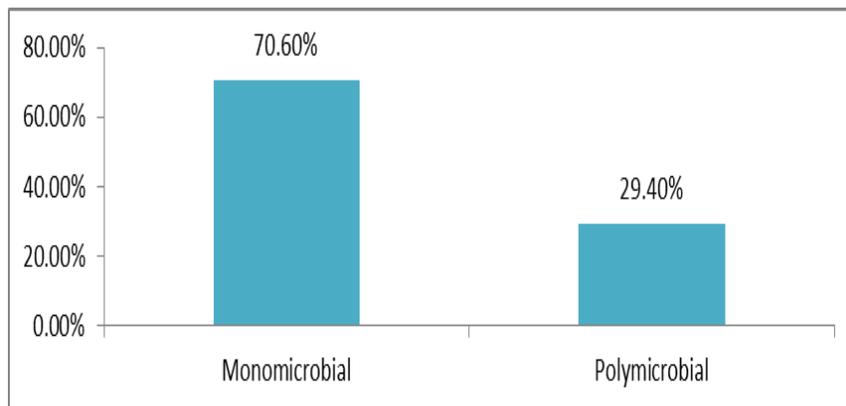
Data was analyzed using descriptive statistics viz. mean, standard deviation and percentages wherever applicable

3. RESULTS

A prospective study was conducted in 200 patients over a period of one and half year to analyze the prescription pattern of various drugs used in the management of chronic leg ulcers of all etiologies. The data was analysed using descriptive statistics



Graph 1: Types of leg ulcer.

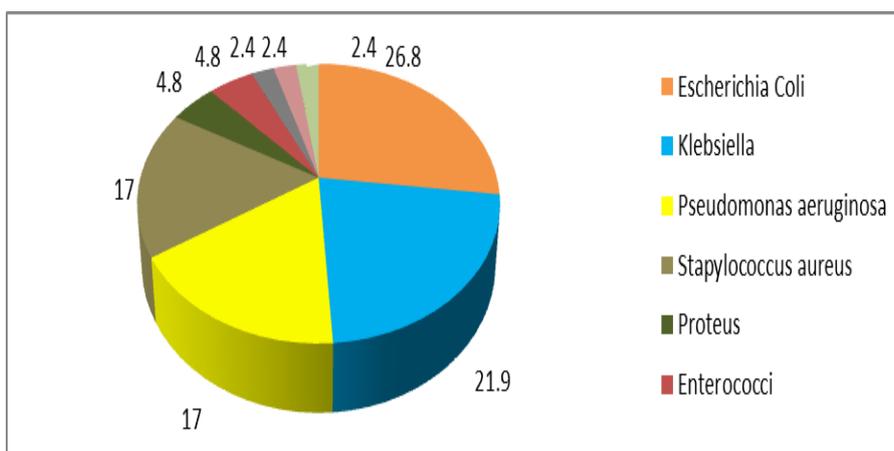


Graph 2: Wound culture characteristics.

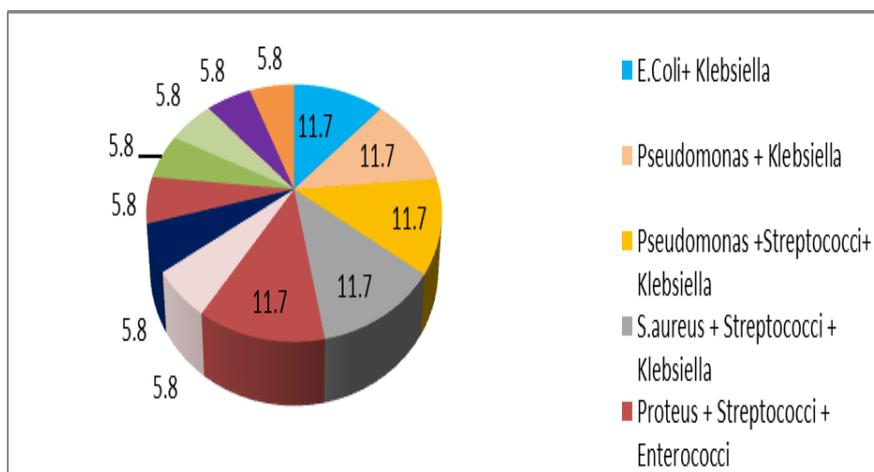
Organism isolated

Out of 92 organisms isolated, Escherichia Coli was the most frequent (17.3%), followed by Klebsiella species (16.3%) and Pseudomonas aeruginosa (14.1%). Among

the Gram positive organism isolated, Staphylococcus aureus (14.1%) was the most predominant. MRSA were isolated in 2 cultures.



Graph 3: Monomicrobials.



Graph 4: Polymicrobials.

WHO prescribing indicators

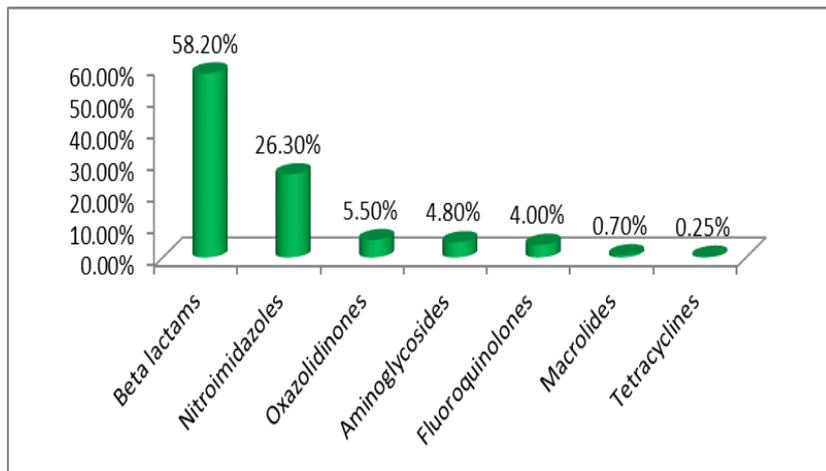
Table 1: WHO prescribing indicators.

Prescribing indicators	Frequency
Total number of prescriptions analyzed	200
Total number of drugs prescribed	1439
Average number of drugs per encounter	7
Total number of antibiotics prescribed	395 (27.4%)
Total number of injections prescribed	929 (64.5%)
Drugs prescribed from essential medicines list	906 (62.9%)
Drugs prescribed by generic name	512 (35.5%)

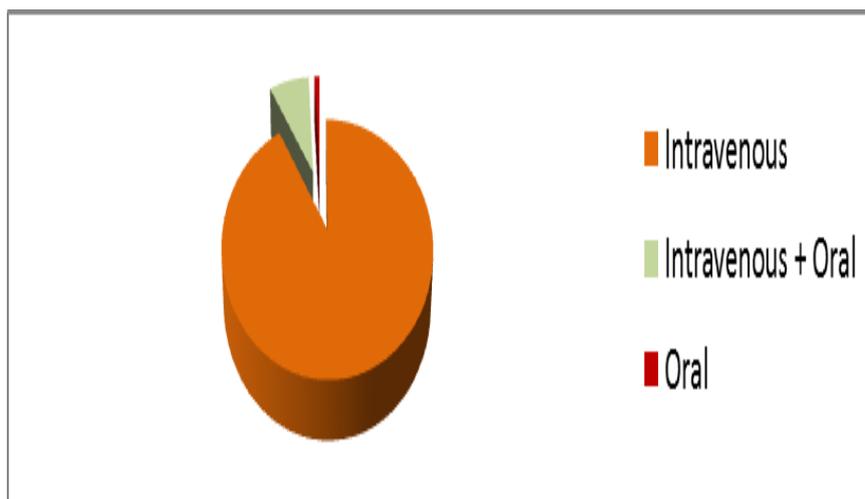
WHO prescribing indicators for antimicrobial agents (AMAs)

Table 2: WHO indicators for antimicrobial agents.

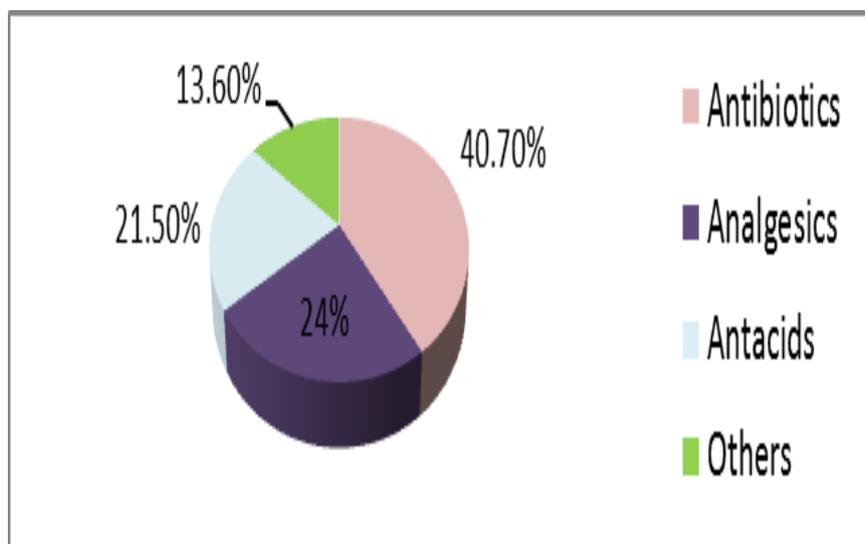
Number of AMAs prescribed by their generic name	183 (46.3%)
Average duration of AMA therapy (in days)	7



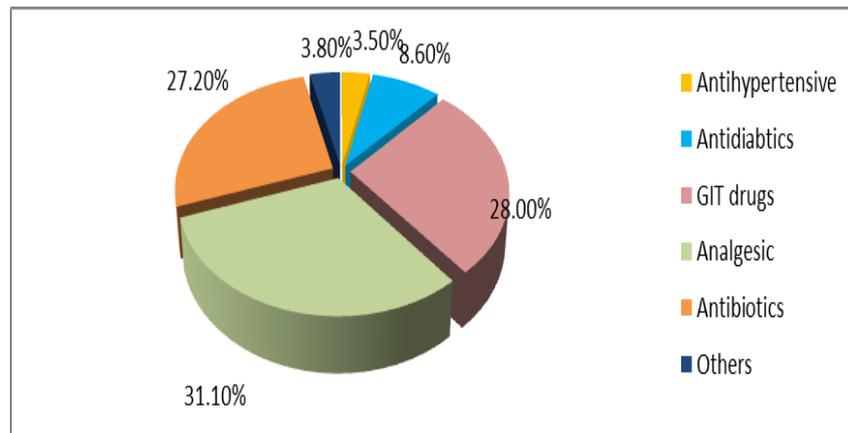
Graph 5: Antibiotics prescribed.



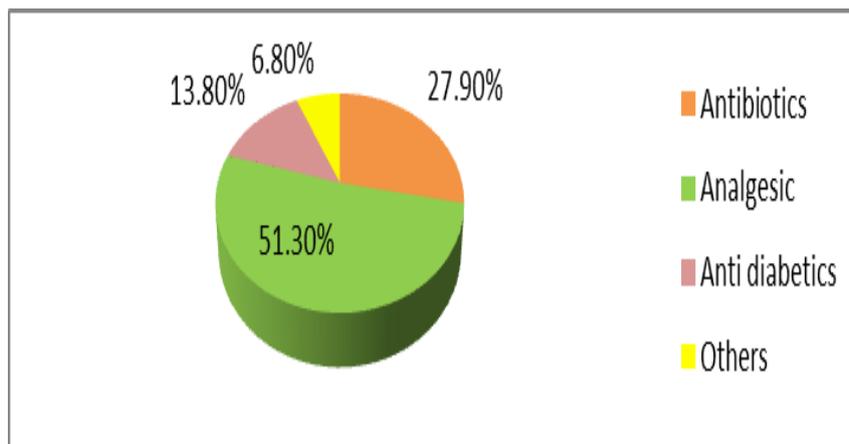
Graph 6: Routes of administration of antibiotics.



Graph 7: Injections prescribed.

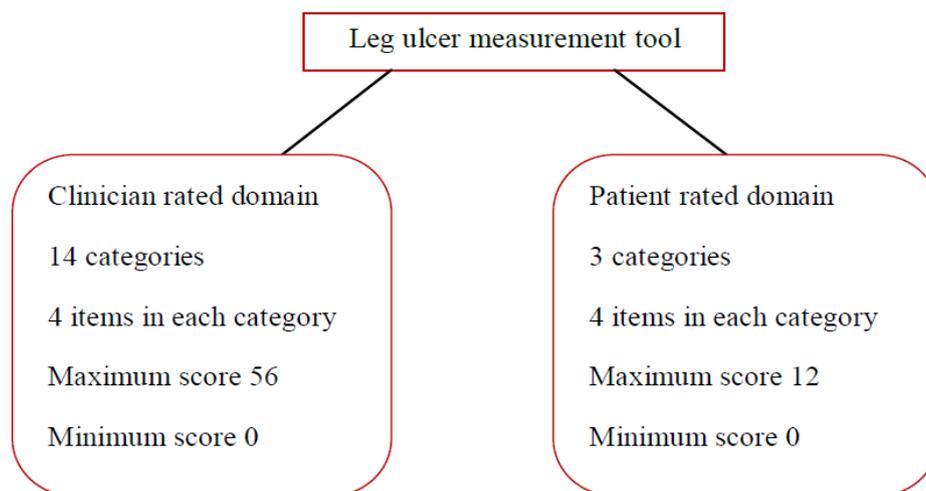


Graph 8: Drugs from essential medicine list (EML).

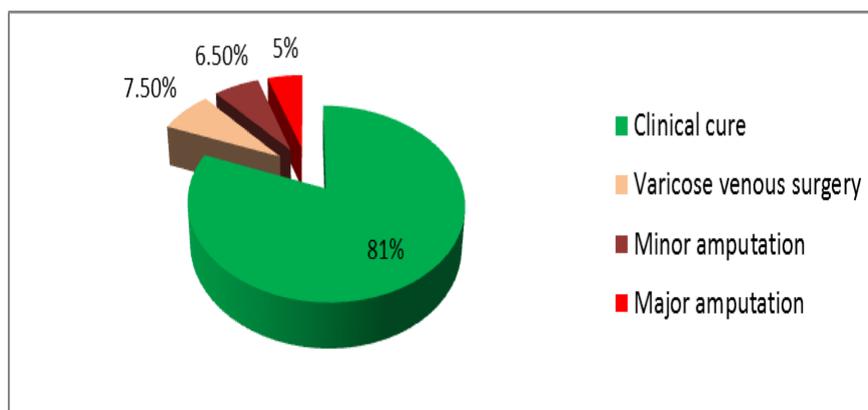


Graph 9: Drugs prescribed by generic name.

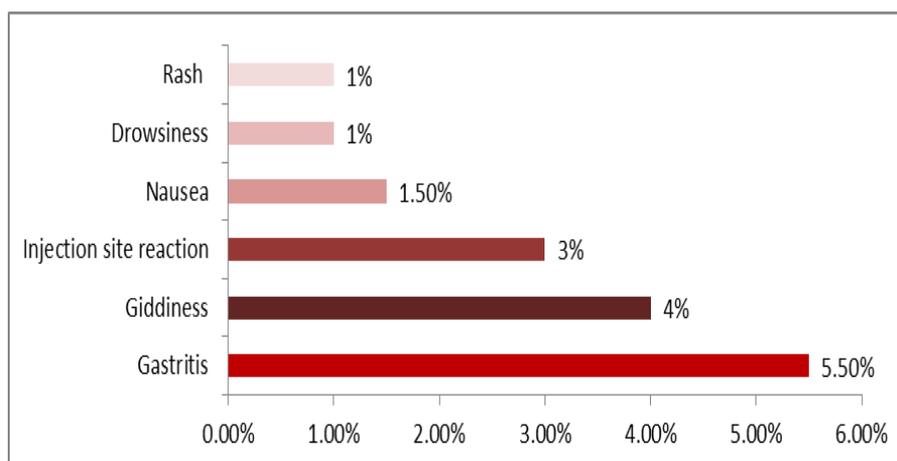
Outcome (LUMT score): Assessment was done using Leg Ulcer Measurement Tool



LUMT score	Clinician rated domain (Mean ±SD)	Patient rated domain (Mean ±SD)
Baseline	23±6.42	10±1.11
At 1 st week	13±1.35	6.8±1.18
At 2 nd week	5±4.93	4.1±1.71
Change at 2 weeks from baseline (baseline – 2 nd week)	17.8±6.26	5.9±1.67



Graph 10: Outcome Graph.



11: Adverse drug reaction.

4. DISCUSSION

Chronic leg ulcers (CLU) are defined as those that show no tendency to heal after 3 months of appropriate treatment or are still not fully healed at 12 months.¹¹ Leg ulcers are highly painful and debilitating, greatly reducing patient's quality of life.

Apart from treating precipitating factors and alleviation of symptoms, improving circulation and venous return by vasodilators and compression therapy, promoting healing of ulcer by good wound care, and preventing recurrences by lifestyle changes are the basic principles of management. Therefore the management of chronic leg ulcers presents a therapeutic challenge.

The researchers are inventing novel modalities of treatment for patients with chronic leg ulcers, so that they can have better quality of life and reduction in personal financial burden.

As the available literature is limited regarding the pharmacotherapy of leg ulcers in India, this study was taken up to assess the various treatment approaches and their outcomes.

Results of the current study revealed that the most common types of leg ulcers were diabetic (38%), followed by venous (24%) and arterial (18%). Leg ulcers

due to other etiology were found to be 20%. Among 200 patients with CLU, 123 had co-morbidities, most common being diabetes (n=76), followed by hypertension (n=24).

In the current study, majority of the wound culture were mono-microbials (70%) and rest were poly-microbials (30%). This finding is akin to the studies done by Dhanasekaran et al., Saraswathy KM et al, Tiwari et al. Out of 92 bacterias isolated from 58 culture positive cases, Gram negative organisms (67.3%) were more prevalent than Gram positive organisms (32.6%). Previous studies done by Shankar EM et al. and Abdulrazak A et al showed the predominance of Gram-positive infections. However, when individual isolate was concerned, *Staphylococcus aureus* was highest among the gram positive organisms, which is similar to our study (14.1%), and also in accordance with the studies done by Yoga R et al and Dang CN et al. These discrepancies could be partly due to the differences in geographical variation, the types of ulcers, causative organisms, immunity and the severity of the infections.

WHO prescribing indicators

Average number of drugs per encounter

Using the WHO prescribing indicators, this study provides a better understanding of the prescribing practice. In our study, the total number of prescriptions

analyzed was 200 and the total number of drugs prescribed was 1439. The average number of drugs per encounter is the most commonly measured index that is used to assess the extent of polypharmacy. In the year 2004, WHO published "The world medicines situation" which reported that the average number of drugs per encounter of 35 countries was 2.39 (ranging from 1.3 to 4.4). The study done by Das N *et al*, Nawabshah *et al*, and Elhassan A M S A *et al* reported the average number of drugs per prescription was 4.51, 3.97 and 3.4 respectively. In the present study, the average number of drugs per prescription was 7, but this cannot be considered as polypharmacy, as more than 50% of the total drugs prescribed were analgesics and antibiotics which is necessary for treating severely ill in-patients and most of the patient presented with co-morbidities, for which they were on medications, and hence no irrational prescription was seen.

The average number of drugs per encounter should be kept as low as possible to avoid the unfavorable outcomes of polypharmacy such as increased risk of drug interactions, increased cost of therapy, non-compliance and emergence of resistance in case of use of antimicrobials.

Percentage of encounters with an antibiotic prescribed

Appropriate use of antibiotics is necessary to prevent emergence of drug resistant bacteria. Overuse of antimicrobials is wide spread across geographical areas throughout the world. However, in developing countries, antibiotics are the most common drugs sold and frequently misused. 'The world medicine situation' reported that the percentage of encounters with an antibiotic prescribed was 44.8% (ranging from 22% to 76.5%). In the present study, the prescribed antibiotics constitute 27.4% which include both empirical and definitive antibiotics. In contrast, a study done by Nikhil Peter *et al* reported that the prescribed antimicrobials were 34.9%. The discrepancies could be due to various reasons such as the severity of ulcer, prevalence of microorganisms and the study setting. In addition, lack of hospital guidelines, prevailing socio-cultural factors and demand are known to influence irrational antibiotics use. Indiscriminate use of antibiotics backed by no diagnostic certainty can contribute to the development of drug resistance leading to significant morbidity. High use of antibiotics is also costly and the development of resistance can further aggravate treatment cost by requiring the use of more powerful and expensive antibiotics which are likely to be unavailable.

Percentage of encounters with an injection prescribed

Patient preference and socio-cultural beliefs is known to influence prescribing behaviors. 'The world medicine situation' reported that the percentage of encounters with an injection was 22.8% (ranging from 0.2% to 74%).. In the present study, the injectables used were 64.5%. The reason could be that the study population was in-patients

with serious conditions and co-morbidities. Injections are expensive as compared to other dosage forms and require trained health personnel for their administration. Moreover, the use of injections is accompanied with variety of disadvantages like sepsis, local irritation and cost.

Percentage of drugs prescribed from Essential Medicines List (NLEM 2015)

The WHO introduced the model list of Essential drugs for the first time in 1977 containing about 250 drugs. India introduced its first list of essential drugs (NLEM) in 1996 which has been revised four times. The latest revised list was issued in December 2015 and contains 376 drugs. However, the number of drugs registered with the drug control authority of India (DCGI) is far more, which makes it extremely difficult for the prescriber to know them all and to identify the better amongst them.

'The world medicine situation' reported that the percentage of drugs prescribed from NLEM was 71.7% (ranging from 12% to 99.6%). Essential drugs aim to satisfy the health care needs of majority of the population and they should therefore be available at all times, in adequate amounts and in the appropriate dosage forms. The percentage of drug prescribed from NLEM in the present study was 62.9%. This value is lower than that reported by 'The world medicine situation'. The reasons behind this could be lack of awareness about NLEM among the drug prescribers and variations in the study setting. Additionally, few antibiotics were prescribed based on culture and sensitivity report, which may not be available in the NLEM.

Total of 106 drugs were added in the new updated NLEM. Piperacillin + tazobactam, Linezolid, Levofloxacin are among the added drugs noted in our study. These drugs were not accounted in analysis of the results which would have increased the percentage of prescribed drugs to 69% from NLEM.

Percentage of drugs prescribed by generic name

The generic prescribing rate attained in this study was 35.5% and lower than that reported by 'The world medicine situation' (60.3%, ranging from 24.6% to 99%). A study done by Satish Kumar BP *et al* also demonstrated that the use of drugs by their generic names was 39%. Prescribing the drugs with their brand name increases the cost of therapy to the patients. On the other hand, prescribing by generic name would rationalize the use and offers several advantages including less cost of therapy and less dispensing errors.

WHO prescribing indicators for antimicrobial agents

The WHO prescribing indicators for Antimicrobial agents (AMAs) take into consideration the average number of AMAs prescribed by their generic name and the duration of antimicrobial therapy. In our study, out of 395 antimicrobials prescribed, 183 (46.3%) were

prescribed by their generic names and the average duration of antimicrobial therapy was 7 days.

All patients in our study received antimicrobials empirically, either monotherapy or combination therapy. The most commonly prescribed antimicrobial agent was beta lactam (58.2%), followed by nitroimidazole (metronidazole 26.3%). The high usage of these antimicrobials is attributed to the culture and sensitivity reports. Other antimicrobials prescribed were oxazolidinones (5.5%), aminoglycosides (4.8%), fluoroquinolones (4%), macrolides (0.7%) and tetracyclines (0.25%).

Most commonly prescribed analgesic in the present study was paracetamol followed by diclofenac and tramadol as the patients with chronic leg ulcers presents with pain and inflammation. The use of NSAIDS could lead to gastritis and hence pantoprazole, ranitidine and ondansetron were prescribed. Other drugs prescribed in this study were antidiabetic agents like insulin, metformin, glibenclamide as majority of the patients were diabetics. Antihypertensives such as atenolol, amlodipine etc. were prescribed as hypertension was the second most co-morbidity seen in our study.

Peripheral vascular diseases (PVDs) are either primarily occlusive (Buerger's disease with intermittent claudication of legs), or mainly vasospastic (Raynaud's phenomenon with episodic blanching \pm cyanosis of fingers followed by hyperaemia), or both as in arteriosclerotic/diabetic vascular insufficiency, ischaemic leg ulcers, frost bite, gangrene, cerebrovascular inadequacy, etc. Antibiotics have effect on ulcer healing when presented with clinical infections and surrounding cellulitis whereas ulcers without any signs of clinical infection are better treated with vasodilators like pentoxifylline and cilostazol as they increase the blood flow to the ischaemic areas by reducing whole blood viscosity and by improving the flexibility of RBCs ("rheological property") and hence helps in healing ulcer. In our study, 18% of the patients were prescribed with pentoxifylline and 12% with cilostazol. A placebo controlled, double blind, randomized clinical trial by De Sanctis MT *et al* (n= 80) showed that 88% of ulcers were healed with use of pentoxifylline for a period 12 months as compared to placebo.^[92]

In the present study, the outcome was assessed in terms of Clinical cure, Surgery, Amputation- minor and major. Majority of the cases achieved clinical cure (162) with pharmacotherapy and this cure was assessed by LUMT score. Varicose veins stripping surgery was conducted on 15 patients. Thirteen patients underwent minor amputation (toe, forefoot and below ankle amputation) and ten patients underwent major amputation (below and above knee amputation). Amputation was performed as a last resort if there was no improvement in ulcer healing despite consistent pharmacotherapy or if there was a risk of a severe systemic infection arising from the wound.

Leg ulcer measurement tool (LUMT)

This is a novel assessment tool specifically designed and validated for clinical or research use on chronic leg ulcers. The changes in the appearance of leg ulcer during the course of treatment were assessed. The mean score at baseline for clinician rated domain and patient rated domain was 23 ± 6.4 and 10 ± 1.1 respectively. After two weeks of treatment, the mean score reduced to 5 ± 4.9 and 4.1 ± 1.7 respectively. There was a significant reduction in LUMT score after 2 weeks of treatment, which showed that healing of leg ulcer increased gradually after starting medication.

Adverse drug reactions (ADRs) monitoring was done by using ADR proforma. All of the drugs used during the study period were well tolerated, with commonly encountered ADRs such as gastritis, injection site reaction, nausea etc.

Strengths and limitations

To the best of our knowledge, this is the first study evaluating drug use in chronic leg ulcers of any etiology using WHO prescribing indicators, and also the first study which assessed the outcome of leg ulcers using a validated leg ulcer measurement tool (LUMT) score.

Incomplete follow up data of the patients after discharge from hospital, leading to lack of information on recurrence or relapse of leg ulcer.

5. CONCLUSION

In the present study, evaluation of prescription pattern in chronic leg ulcers, using WHO prescribing indicators showed that use of AMAs for the treatment of CLUs were adequate. However the total number of drugs prescribed by their generic names as well as from EML was less as compared to the WHO reference level. In this study, pharmacotherapy along with the topical management of leg ulcers has achieved a clinical cure of 81% as assessed by LUMT score.

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