

# **CLINICAL PROFILE AND OUTCOME OF CASES WITH NECROTISING SOFT TISSUE INFECTION: A PROSPECTIVE OBSERVATIONAL STUDY**



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ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR**

**In partial fulfillment of the requirement for the degree of**

**Master of Surgery (MS)**

**(General Surgery}**

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## **DECLARATION**

I hereby declare that this thesis titled **“Clinical profile and outcome of cases with necrotising soft tissue infection: A prospective observational study”** is a bonafide and original research work carried out in partial fulfilment of the requirements for the degree of Masters of Surgery in General Surgery under supervision and guidance, in the Department of General Surgery, All India Institute of Medical Sciences, Jodhpur.

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Date:

*Dedicated to My parents*

*&*

*My teachers*

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## ABBREVIATIONS

NSTI	Necrotising soft tissue infections
SOFA	Sequential Organ Failure Assessment Score
SAPS II	Simplified Acute Physiology Score II
APACHE II	Acute physiology and chronic health evaluation
GAS	Group A Streptococcus
IV	Intravenous
AKI	Acute Kidney Injury
MODS	Multiorgan dysfunction Syndrome
LRINEC	Laboratory risk indicator for necrotizing fasciitis
SIARI	Site other than lower limb, Immunosuppression, Age $\leq$ 60 years, Renal impairment, Inflammatory markers
HAI	Hospital acquired infection
ICU	Intensive care unit
HBO	Hyperbaric Oxygen therapy
IVIG	Intravenous immunoglobulins
IQR	Inter quartile range
BUN	Blood urea nitrogen

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# INTRODUCTION

Necrotizing soft tissue infections (NSTI) are life-threatening infections that involve any layer of the skin and soft tissue and are characterized by rapid progression and significant local tissue destruction, resulting in severe morbidity and mortality and affecting the quality of life (1). It is not a common disease, and the incidence ranges between 0.3 and 15 cases per 100,000 people per year.(2–4)

There are a number of descriptions and classifications of NSTI that have been put forth, such as stratification based on: (1) anatomical localization (such as Fournier's gangrene or Meleney's gangrene); (2) depth of infection (such as necrotizing cellulitis, fasciitis, or myositis); (3) severity (such as the Sequential Organ Failure Assessment Score (SOFA) or Simplified Acute Physiology Score II (SAPS II)); and (4) based on microbiological results.

It typically spreads quickly along tissue planes, and in the early stages, in the absence of obvious skin changes, the diagnosis can be challenging.(2) However, signs of systemic toxicity and pain often develop that are disproportionate to the findings of the skin examination.(5) The typical mode of entry for the pathogen is direct inoculation into the subcutaneous space. Haematogenous spread from a distant site happens infrequently. These infections may also be brought on by trivial trauma, such as minor wounds or insect bites. A number of risk factors have been associated with the pathogenesis of the diseases, including advanced age (>75 years), advanced diabetes, obesity, peripheral vascular disease, renal failure, smoking, alcohol abuse, IV drug abuse, immunosuppression, recent surgery, and traumatic wounds.(2,4,6,7)

These serious infections are among the few infectious diseases that continue to be closely linked to significant mortality and amputation, even in healthy young people. The described mortality rate ranges from 6 to 33% and the rate of amputation is considered high.(8) Early diagnosis, appropriate antibiotic therapy, prompt surgical debridement (within 24 hours) or drainage, and resuscitation when necessary are all essential components of managing patients with severe NSTIs successfully.(9) Early diagnosis and prompt surgical intervention form the first pillar of clinical management of NSTIs. It has been established that expeditious surgical removal of infected tissue is crucial and that waiting a long time before the first procedure increases the risk of mortality. (10) The second pillar in the clinical management of NSTIs is the administration of effective and adequate antimicrobial treatment, which is equally



important and of immediate importance. According to Ferrer et al. (2014), delaying the administration of antibiotics in sepsis is associated with a poor outcome, with the risk of mortality increasing linearly with each hour of delay. (11) Lastly, the need for physiological support and critical care, preferably in an ICU setup, cannot be denied.(12)

Undisputedly, survival is directly correlated with prompt diagnosis and intervention; however, diagnosis and management are challenging due to heterogeneity in clinical presentation, a multitude of associated co-morbidities, and myriads of microbiological etiologies. Geographic differences in etiology and microbiology have been shown on the national and regional levels. Given that NSTIs are relatively rare and quickly fatal, there aren't many studies on them in India. (13–16) Variability in risk factors, environmental influence, factors and exposures (like quality, quantity and timing of intervention), microbiological profile contributes to regional differences. No previous attempt has been made to characterize this entity in western India, particularly in Rajasthan, which has a dry landscape for the majority of the year. Here, we carried out a prospective observational analysis of the cases of necrotizing soft tissue infections. In an effort to pinpoint the characteristics that are different from the rest of the country, we describe the clinical profile, microbiological spectrum, and factors that affect mortality among patients with necrotizing soft-tissue infections in this region.

## REVIEW OF LITERATURE

Necrotizing soft tissue infections (NSTIs) have indeed been known since the 5th century BC, when Hippocrates first described "erysipelas" in patients with rapidly disseminating and fatal skin infection.(17) Dr Joseph Jones, a Civil War surgeon, described such a condition as "hospital gangrene" in 1871, when it was first noted in the United States.(18) These patients became infected with virulent, rapidly spreading "greyish and greenish slough." Dr B. Wilson coined the term "necrotizing fasciitis" in 1952 after observing that the infection appeared to spare the underlying muscle while still involving the fascial planes.(19) Several names have been assigned to various types of necrotising infections, in part because these names were assigned based on clinical features rather than surgical and histological findings.(2,20) Necrotizing fasciitis, suppurative fasciitis, necrotizing myositis, acute dermal gangrene, gas gangrene, Meleney's synergistic gangrene, synergistic necrotising cellulitis, Fournier's gangrene, hospital gangrene, and streptococcal gangrene are all names for different forms within the spectrum of NSTI. Fournier gangrene is a type of NSTI that affects the perineal, genital, and perianal regions.(20) Meleney's synergistic gangrene is a rare NSTI that occurs as a side effect of surgery.(21) Recent literature suggests that these severe infections should be classified as NSTI due to their extensive involvement of the soft tissue layers to varying degrees, as well as their similar clinical features and treatment strategies including antibiotics, early extensive surgery, and organ supportive care.(2,20,22,23) 'Necrotising soft tissue infections' is a new unifying term including cases of cellulitis and superficial skin infections, which may be early manifestations of necrotizing fasciitis.

Over the last decade, there have been initiatives and research that have increased our understanding of NSTI epidemiology, pathophysiology, prognosis, and treatment. The prognosis for the condition remains extremely bleak.(8) The prognosis is dependent on early correct diagnosis and the elimination of delays in surgical debridement.

These soft tissue infections are distinguished by their rapid progression, fulminant tissue destruction, systemic toxicity, and high mortality(2,13,24,25). Exotoxin-producing bacteria cause tissue ischemia and necrosis in the affected tissue in this group of infections.(26,27) The epidermis, dermis, subcutaneous tissue, fascia, muscles, and deep structures are all involved.(2,20)

NSTI has been classified based on

- (1) Anatomical localization (such as Fournier's gangrene or Meleney's gangrene)
- (2) Depth of infection (such as necrotizing cellulitis, fasciitis, or myositis)
- (3) Severity based on the Sequential Organ Failure Assessment Score (SOFA) or Simplified Acute Physiology Score II (SAPS II) or APACHE II
- (4) Microbiological results (Giuliano et al. 1977)

Necrotising fasciitis, also called flesh-eating disease, is a type of deep soft tissue infection that causes progressive destruction of the muscle fascia and overlying subcutaneous tissue. Muscles are spared due to a relatively generous blood supply as compared with fascia.(28) Because the overlying tissue can appear normal in the early stages of the disease, it is difficult to identify this entity without direct visualisation of the fascia.(2,20,25) The appearance of skin changes may be preceded by paraesthesia, indicating the presence of necrotising fasciitis.(29)

Necrotising Myositis is a rare skeletal muscle infection caused by Group A Streptococcus (GAS) and other beta-hemolytic streptococci. The antecedent cause could be blunt trauma, strenuous exercise, or skin abrasions. The most common entity in this category is Clostridial myonecrosis. (27,27,30–32)

Necrotising cellulitis is a severe form of cellulitis characterised by skin necrosis that spares the fascia and muscles. It clinically may present with crepitus and gas under the skin. Typically, symptoms of systemic toxicity are not as noticeable. It is caused by anaerobic pathogens and is classified into two types: Clostridial versus non-clostridial (caused by polymicrobial infection). (2,26,28,33)

Giuliano et al. described bacterial etiologies in sixteen patients with NSTI in a single-centered study from San Francisco, of whom nine were drug users, three were postoperative cases, and three had a history of minor trauma.(34) Using samples from within the operation, they identified 18 pathogens at the species level and a sizable number at the genus level. The study's findings led to the development of a novel system for categorizing NSTI based on microbial etiology, in which category type 1 grew facultative anaerobic bacteria and anaerobic bacteria such as Enterobacteriaceae or streptococci other than GAS. They observed that at least one anaerobic organism and a facultative anaerobe were cultured in conjunction with each instance of a type 1 infection. In category type 2 GAS was isolated. It was also

seen that type 2 GAS occurred together with Staphylococcal species, but not anaerobic bacteria or Enterobacteriaceae. This classification has been widely embraced and applied in reviews and guidelines.(1,2,9,35,36) Though the list of implicated microbes has gradually grown, it has also been suggested to add a type 3 category for monomicrobial infections brought on by marine gram-negative microbes and a type 4 category for fungi.(37) The latter is less commonly accepted because it is unclear how useful expanding necrotizing soft tissue infection entities are.(2)

### **Risk Factors**

NSTIs can happen in people of any age who are otherwise healthy and have no significant past medical histories.(29) Most of the time, a certain portal of entry cannot be determined. Previous research has identified several risk factors, including injuries (ranging from minor abrasions and skin/ mucosal breaches to major trauma), insect/ animal bites, IV injections/ cannulation, immunosuppression (diabetes/ cirrhosis/ neutropenia/ HIV infection), cancer, obesity, alcoholism, and drug abuse. (2,3,10,20,24,25,38–41)

Diabetes is one of the most prevalent risk factors for necrotizing soft tissue infections. Despite some disagreement, studies have shown a link between the use of non-steroidal anti-inflammatory drugs and the development of streptococcal necrotising infection in some cases. Although the precise process is still unknown, it is most likely related to the masking of inflammation's signs and symptoms, which may contribute to a delay in diagnosis.(42,43)

### **Clinical features:**

Presentation of NSTI varies considerably. It can affect almost any part of the body and up to deepest reaches. It may be preceded by a history injury (minor or major), surgery and pre-existing pathology to the site of interest.(10,20,44) However, it can arise without a clear portal of entry, and several patients come with no known predisposing event.(10,19,25,45) Cutaneous manifestations are a late symptom of NSTI because if there isn't a clear portal of entry. As a result, in the early stages of the sickness, the patient may merely exhibit pain. Other inflammatory symptoms may develop later, making it difficult to differentiate from other soft tissue infections. Edema, erythema, excruciating pain, fever, crepitus, bullae, echymosis, or necrosis are examples of clinical symptoms.(2,20) Bullae are seen in 27% of patients, whereas 32% of patients experience severe cutaneous symptoms such as skin necrosis and discolouration.(20) Even vague "flu-like" symptoms have been reported as an

early sign of NSTI.(46) Pain is typically severe and out of proportion to the disease's immediate symptoms and extent.(10,20,47) However, the use of analgesics or neuropathy may make the pain disappear. The majority of patients show systemic symptoms at presentation, such as fever, tachycardia, hypotension, and altered mental status, which point to disease progression. In Scandinavian observational research, 20% of patients developed acute kidney injury (AKI) and a few had multiorgan dysfunction syndrome (MODS), while 50% of patients met the criteria for septic shock.(20) Clinicians should have a high index of suspicion and just not exclude the diagnosis in the absence of particular symptoms because there is no pathognomonic sign or symptom for NSTI, and these vary greatly from case to case.(22)

The skin manifestations progress over several days. Process starts with changes in skin color from erythematous macules or patches to dusky bluish within a few days followed by skin breakdown with bullae formation and frank cutaneous gangrene. Subcutaneous tissue may be firm and indurated due to marked edema and inflammation.(20,28) Occasionally patients may develop compartment syndrome requiring fasciotomy. In the setting of surgical wound infection, NSTI is characterised by copious drainage, dusky and friable subcutaneous tissue and pale, devitalised fascia.(20,22) Due to thrombosis of small blood vessels and destruction of superficial nerves in the subcutaneous tissue, pain sensations diminish in the involved area.(20) It may precede the appearance of skin necrosis and provides a clue to the presence of NSTI. Subcutaneous gas is often present due to the presence of anaerobic microorganism.

However, it is often difficult to distinguish NSTI from other soft tissue infections.(48) In the early phase of NSTI, physical findings are similar to other soft tissue infections. Sometimes we can notice the difference after exacerbation of its condition. Modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and frozen section biopsy have been considered to be useful in the early recognition of NSTI, but these modalities have been limited by cost, availability, and accuracy.(10,49) The Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC) score is developed as a convenient tool to support the diagnosis of NF.(49) LRINEC is generated from six routinely performed laboratory tests including the analyses of patients' C-reactive protein, white blood cell count (10,000/ $\mu$ L), hemoglobin (g/dL), sodium (mEq/L), creatinine, and glucose. Although LRINEC scoring is not optimal, it has been used to distinguish NSTI from less severe soft tissue infections. However, there are various opinions on the usefulness of LRINEC among experts, especially

considering that LRINEC is comprised of only laboratory data. It might be possible to develop more useful diagnostic tools.(50,51)

## **SITES**

NSTI can affect any body part. NSTI. Extremities are by far the most often affected site. About one-third of cases involve the lower extremities, one-third the abdomen and anogenital region, one-sixth the upper extremities, and another one-sixth the head and neck area. (2,20)

1. Extremities: Usually affected by monomicrobial infection. GAS, Staphylococcus aureus, and Group C and G streptococci are the most typical isolates. Lower extremity odds ratios for GAS were 1.91, 95% CI 1.18-3.09, and upper extremity odds ratios were 7.80, 4.36-14.25. (20)

2. Abdomen and anogenital area: Fournier's gangrene is another name for NSTI involving the perineum. usually preceded by urogenital skin infections and frequently linked with polymicrobial infection. (20,52)

3. Cervical: Common throat infections like pharyngitis, tonsillitis, or dental infections usually precede cervical cases.(53) The incidence rate is reportedly 2 per 100,000 persons.(54) The infection can progress along the neck, skull base, and upper mediastinum fascial planes.(55) It can be complicated by suppurative thrombophlebitis of the internal jugular vein (Lemierre's syndrome) and Ludwig's angina.(56) The most prevalent isolates include streptococci, staphylococci, and a variety of anaerobic bacteria that are typically found in the oral cavity.

In the year 2009 Shah et al conducted a study on 54 patients and concluded that the most common cause of NSTI was Diabetes mellitus type II and the most common isolate was S. aureus.(57)

In 2015, Hua et al conducted a retrospective cohort study in a single tertiary care academic medical centre in France which included 109 patients with a confirmed diagnosis of necrotizing soft-tissue infections (NSTI) to identify Prognostic factors in NSTI and clinical risk factors of mortality related to it. They identified 5 independent risk factors associated with mortality which were; age older than 75 years, multifocal NSTI, severe peripheral vascular disease, hospital-acquired infection, severe sepsis, and septic shock on hospital

admission. Skin trauma was the most common source of NSTI; extremities were the most common localisation and overall mortality in study was around 30%. On microbiological examination, wound intraoperative cultures were positive for 99 of 106 patients. Most frequent bacterium isolated was *Streptococcus pyogenes*. 16 patients had a hospital-acquired infection (HAI), most frequent bacteria in HAI being *Staphylococcus aureus*. In total, 105 patients underwent surgery, most commonly procedure being surgical debridement and 15 patients underwent amputation.(25)

Krishnan et al conducted a prospective observational study in a tertiary care teaching hospital located in Pune, India, over 2 years from 2015 to 2017. A total of 100 patients were included in the study. The most common presenting complaint was pain followed by redness or blackening of the skin. The most common comorbidity associated with NSTI was diabetes mellitus. Out of the 100 patients, 43 showed positive growth on culture. *Streptococcus* was the most common organism that had grown. On multivariate analysis, only serum creatinine was found to have a significant correlation with mortality.(58)

Wong et al proposed the score Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) to differentiate between NSTI and other soft tissue infections. A score  $\geq 6$  is suspicious of necrotizing fasciitis, while a score  $\geq 8$  is strongly predictive. A higher LRINEC score also correlates with risk of mortality. (49)

A study by Kalaivani et al. demonstrated that age  $> 50$  years was associated with an a In 2016, Hadeed et al reported an observational retrospective case series done on 87 cases of NSTI and demonstrated that surgical intervention within the first 6 h after diagnosis of NSTI would improve hospital outcomes in terms of shortening both the hospital stay and ICU stay. (60)

## **TREATMENT**

### **Surgery**

The cornerstone of NSTI treatment is prompt and aggressive surgical debridement of all necrotic or non-bleeding tissue, ensuring that there remain secure essential wound edges at the completion of the procedure.(20,22,60) Therefore, until there are bleeding wound circles throughout the entire wound, a revision must be performed. Tissue samples must be removed

during the operation for microscopy and culture.(29) The subfascial tissue exploration is advised, to rule out subfascial abscess or necrosis, in situations when NSTI is suspected but the findings in the subcutis are not consistent with the NSTI.(23)

Any delay between receiving the patient and surgical debridement must be avoided since it is essential for the prognosis.(10) Therefore, the patient must be given priority on the emergency surgery schedule so that debridement can be completed as soon as feasible on the first available operating room bed. It should be emphasised that prior to being transferred to a hospital where further treatment with intensive critical care can be provided, debridement must be completed in the hospital where the patient is admitted at the time of diagnosis.(9) patient can be later transferred to a higher facility for further wound revised as soon as possible. The frequency and the total number of additional wound audits are determined by the findings of the wound and the patient's clinical condition.(9,22)

### **Antibiotic**

Beginning antimicrobial medication as soon as feasible is recommended, although surgical debridement shouldn't be postponed throughout this process.(4,11,60,61) According to the most recent recommendations, two medications should be administered every eight hours: meropenem 2 g intravenously and clindamycin 600 mg intravenously.(2,20) According to the culture results, the antimicrobial treatment needs to be regularly changed.

### **Hyperbaric oxygen therapy (HBO)**

Increased oxygen pressure in necrotic tissue, increased capillary formation, facilitation of leukocyte function with bacteriostatic/cidal effect and phagocytosis, decrease in exotoxin production and pro-inflammatory cytokines, improved antibiotic efficacy, and prevention of platelet-leukocyte complexes are a few of the potential advantages that have been noted with HBO therapy.(62–64)

Insufficiently high-quality trials of HBO treatment could not be found, according to a recent systemic review study.(65) Due to their retrospective nature or limited sample sizes, the studies are prone to bias. Emphasis can be placed on the fact that HBO therapy is a safe operation without any significant adverse effects.



### **Immunoglobulins (IVIG)**

Immunoglobulins are no longer included in the treatment guidelines for NSTI. No evidence of efficacy has been found in, among other things, a recently published Danish randomised controlled trial. There is still some doubt as to whether immunoglobulins have a possible effect against GAS, but regular use is not recommended.

Takei et al. conducted a study in 1993 which proposed IVIG therapy which is based on the fact that the immunoglobulin can bind and neutralize streptococcal and staphylococcal exotoxin. The hypothesis is mainly based on retrospective studies and case reports. A randomized control study INSTINCT compared the effect of placebo vs IVIG on self-reported physical function in ICU patients. The study, however, failed to show any beneficial effect and further large-scale trials would be required before any treatment recommendation for the IVIG in NSTI is made.(66)

## **AIM AND OBJECTIVES**

### **AIM**

To study clinical profile and outcome of cases with necrotising soft tissue infection

### **OBJECTIVES**

#### **Primary Objective:**

- To determine the influence of surgical procedure timing on the mortality of patients admitted with NSTI.

#### **Secondary Objectives:**

- To determine the etiology, presentation and outcome of cases with NSTI
- To study the microbiological flora of NSTI.
- To determine the major co-morbidities in patients admitted with NSTI.

## **MATERIAL AND METHODS**

### **1. STUDY SETTING**

All patients of NSTI meeting inclusion criteria during the study period were recruited from the Department of General Surgery, AIIMS Jodhpur.

### **2. STUDY DESIGN**

A hospital-based cross-sectional descriptive study.

### **3. STUDY PARTICIPANTS**

#### **a) Inclusion Criteria:**

- a. All patients above 18 years of age with NSTI diagnosed initially on clinical parameters and later confirmed based on operative findings and tissue diagnosis if required.
- b. Diabetic foot and Peripheral vascular disease with NF

#### **b) Exclusion Criteria:**

- a. Patients having any of the following were excluded from the study.
- b. Cases of only cellulitis, abscess, lymphedema, diabetic foot, peripheral vascular diseases and anasarca

### **4. SAMPLE SIZE CALCULATION**

All cases diagnosed as NSTI, admitted in the Department of General Surgery from Jan 2021 to June 2022 based on the inclusion and exclusion criteria were included in the study.

### **5. 5. SAMPLING**

All patients presenting with NSTI to AIIMS Jodhpur were included in the study based on inclusion and exclusion criteria.

### **6. STUDY DURATION**

1.5 years from date the of the Institutional Ethics Committee (IEC) approval (January 2021 – July 2022).

## **7. STUDY PROCEDURE**

This descriptive study was conducted in the Department of General Surgery AIIMS, Jodhpur after obtaining the approval of the institutional research committee & institutional ethics committee. Diagnosis of NSTI was based on medical history, physical examination, operative findings and laboratory work.

All patients were investigated soon after reaching the emergency department. Once the patient is stabilized, the patient was started on broad-spectrum antibiotics, later converted as per culture reports. All cases of NSTI diagnosed based on clinical grounds and subjected to the operative intervention were included in the study. The cases with only cellulitis, abscess and peripheral vascular disease were excluded from the study. Excised tissue specimens were sent for microbiological and histopathologic (if required) evaluation.

Appropriate surgical interventions were done after initial resuscitation. An operative diagnosis was made based on intraoperative findings. Post-operative tissue viability was assessed. NPWT was utilized as and when required. Patients were discharged when satisfactory clinical status was achieved.

## **8. STATISTICAL ANALYSIS**

Data were entered and analysed using SPSS version 23. Nominal data were described using frequency and percentages and compared using the chi-square test or Fischer Exact test. Ordinal Data was described using the median and the Interquartile Range (IQR) and compared using the Mann-Whitney U test. Continuous data were described using mean  $\pm$  SD and compared using the unpaired t-test. A P-value of  $<0.05$  was considered statistically significant.

## **9. ETHICAL CONSIDERATION**

The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC) before commencing the study. All patients enrolled in the study received standard care management and their participation in the study did not lead to changes in their usual diagnostic workup and management. All personal data collected during the study was kept confidential.

## RESULTS

During the study period, a total of 359 patients presenting to the Emergency Department of AIIMS Jodhpur were screened for eligibility (a suspected case of NSTI meeting inclusion criteria). Out of which 34 were ineligible (age <18 years and outside operated cases) and 247 were eligible but not recruited due to various reasons as mentioned in Figure 1. One patient withdrew from the study after recruitment on day 3 of admission. Consequently, 87 patients with NSTI were enrolled in this study.

There were 65 male and 22 female patients with an age range of 18 years to 88 years (median age 58). Males were more commonly affected than females. The majority of the patients were residents of Jodhpur, Rajasthan.

Table 1: Patient Characteristics

	TOTAL n=87	GROUP I (Survivor) n=69	GROUP II (Non-survivor) n=18	
Age (years)	58 (48-66)	56 (43.7-68.5)	60 (43.7-68.5)	0.659
Sex				0.784
· Male	65	52	13	
· Female	22	17	5	
Timing of presentation (days)	3 (2-4)	3 (2-4)	3 (2-4)	0.960
Time from admission to first operation (hours)	6 (4.3-9.4)	5.9 (4.2-9.2)	6.1(5-9.4)	0.575

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.

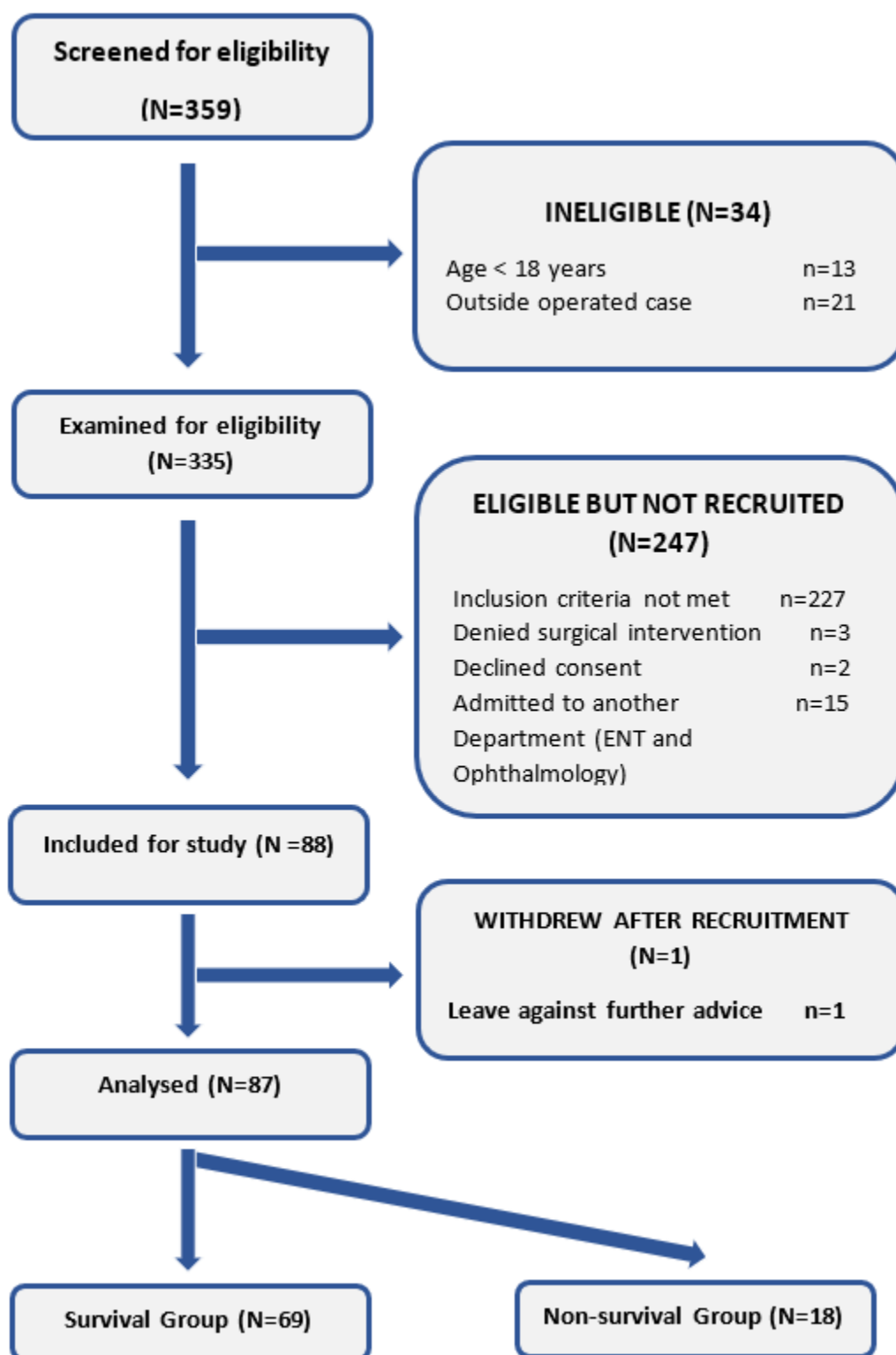
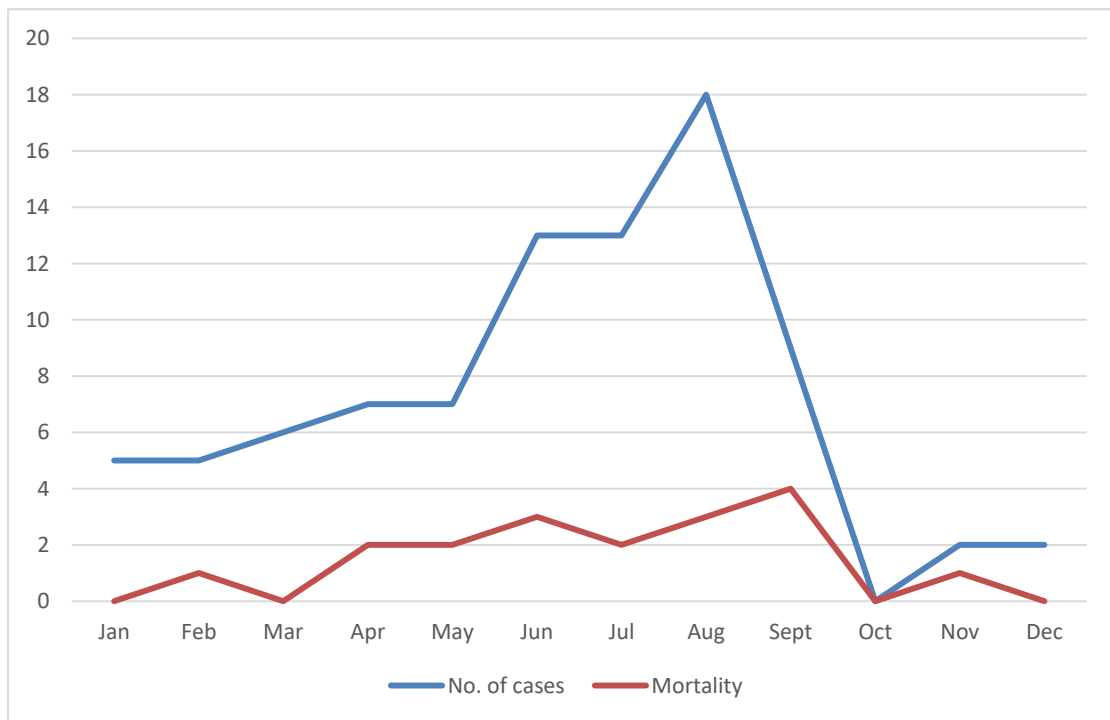


Figure 1: STROBE Study flow diagram

Data are presented as number of patients. ENT- Department of otorhinolaryngology

## Aetiology

NSTI was most commonly seen during the summer season post monsoon with peak incidence during the month of July and August.



Graph 1: Month of presentation

Data are presented as number of patients.

21 patients (24.1%) gave a history of injury (both major and minor) before the onset of symptoms. Minor skin infections such as furuncles were present in 2 patients (2.3%) and abscesses in 3 patients (3.4%). One patient developed an infection postoperatively after drainage of a perianal abscess in the lower anterior abdominal wall. No predisposing cause could be found in 60 patients (68.9%).

Table 2: Precipitating Event

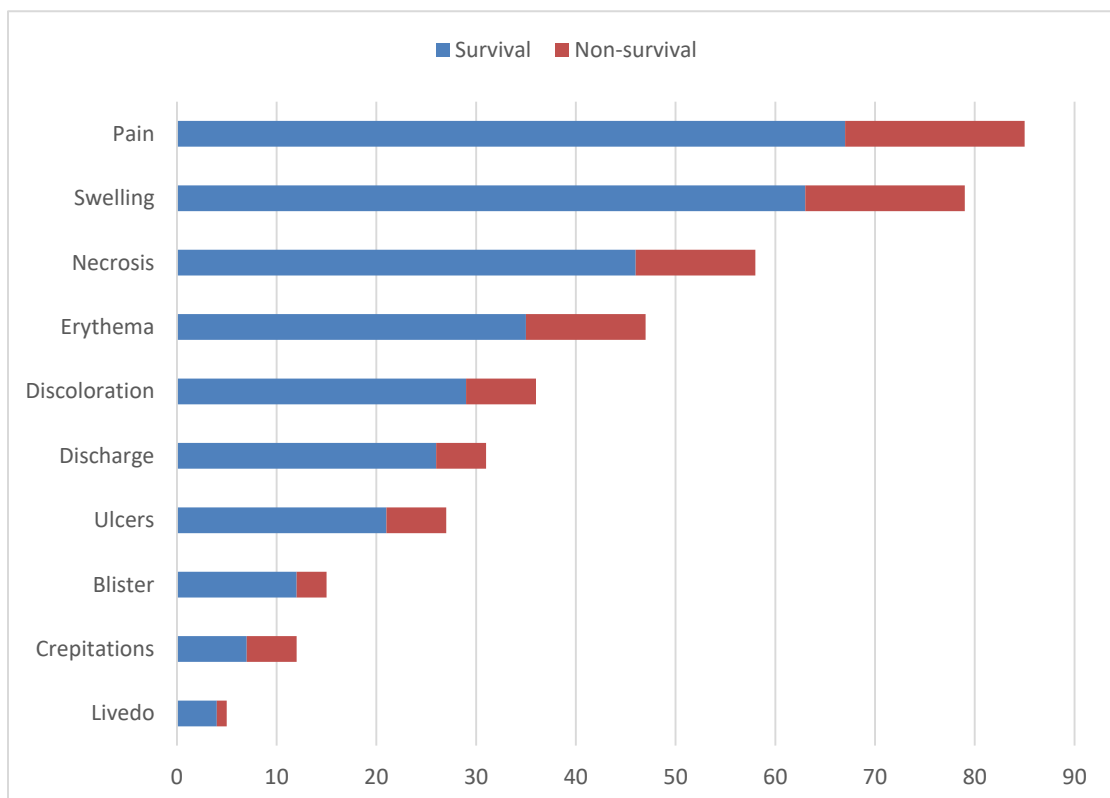
	GROUP I (Survivor) n=69 (Median/IQR)	GROUP II (Non-survivor) n=18 (Median/IQR)
a. Injury		
· Trauma	9	3
· IV injection/ cannulation	1	1
· Bite- animal/ insect/unknown	4	0
· Thorn prick	2	1
b. Pre-existing soft tissue infection	4	0
c. Post-surgical intervention	1	0
d. Not known	48	13

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.



## Coexisting conditions

Diabetes mellitus was the most commonly associated illness ( $n = 34$ , 39.1%) followed by hypertension (18, 20.7%). Nine patients had PVD. Prolonged corticosteroid therapy for bronchial asthma ( $n = 2$ ), rheumatoid arthritis ( $n = 2$ ), thrombocytopenic purpura ( $n = 1$ ), Morvan syndrome ( $n=1$ ), chronic dermatitis ( $n = 2$ ), radiotherapy for CA buccal mucosa ( $n=1$ ) and chemotherapy for acute lymphocytic lymphoma ( $n = 1$ ) were assumed to have caused appreciable immunosuppression. Two patients had a history of cerebrovascular accidents and 2 had myocardial ischemia in the recent past. 3 patients were obese, 2 patients had congestive heart failure and 3 patients had pneumonia at the time of presentation. 15 patients (17.2%) had a history of smoking, 9 were opium users and 6 were alcohol users. There were no intravenous drug misusers. DVT, acalculous cholecystitis and chronic lymphedema of the lower limb were present in single cases.



**Graph 2: Co-morbidities**

Data are presented as number of patients.

## Site

Although no area of the body was spared, the lower extremities were the most common sites involved. The upper and lower limbs were involved in 9 (10.3%) and 53 (60.9%) patients, respectively. The trunk was involved in 12 (13.7%) patients and the perineum in 13 (16.1%). There was only one instance of infection of the head and neck in which NSTI of the left arm extended to the neck region. Similarly, in many cases, the infection had spread to more than one anatomical region, perineum and lower limb, trunk and gluteal region or perineum, and groin and trunk.

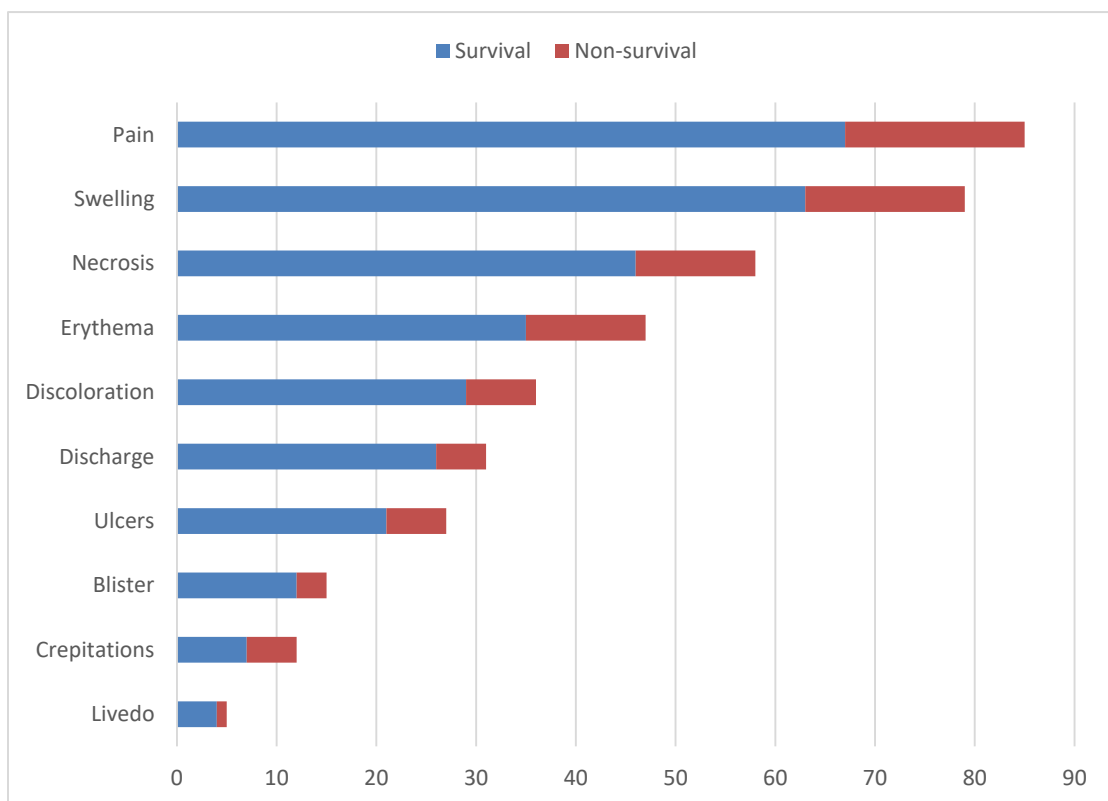
Table 3: Site

	GROUP I (Survivor) n=69	GROUP II (Non-survivor) n=18	
Head and Neck	1	0	0.607
Upper limb	5	4	0.063
Lower limb	45	8	0.209
Torso	9	3	0.239
Perineum	11	3	0.607

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.

## Clinical features

The diagnosis was suspected if there was gross or microscopic evidence of tissue necrosis. The clinical features are summarised in graph 2 The pain was the most common manifestation (n=85, 97%), followed by swelling, redness and discolouration. Severe skin manifestations like crepitations, livedo, bullae, necrosis, discharge and ulcers were seen in 86.2% of cases. Most patients met the criteria for sepsis, which was seen in 60.9% of cases (n=53). Furthermore, 24.1 % of cases had acute renal failure and 5.7% were in septic shock at the time of diagnosis. The median APACHE II score was 6 (5-11). The median APACHE II score among the non-survival group was 10 and was statistically significant with a p-value of 0.036. The median LRINEC was 4 (3-6) overall and 6 among the non-survival group which was statistically significant (p-value = 0.004). The median SIARI score was 3 (2-5) and there was no statistically significant difference between the two arms.



**Graph 3: Clinical features**

Data are presented as number of patients.

## Investigations

All patients had abnormal haematological and biochemical tests, refer to table 3. Anaemia, Leucocytosis, hypoalbuminemia, increased blood urea concentrations and dyselectrolytemia were present in varying degrees. Haemoglobin and albumin were significantly lower in the non-survivor than survivor group ( $p=0.0007$  and  $p=0.0002$ , respectively) (Table 2). Mortality was significantly higher in the patients with a high serum creatinine level ( $p<0.038$ ).

Table 4: Laboratory Parameters

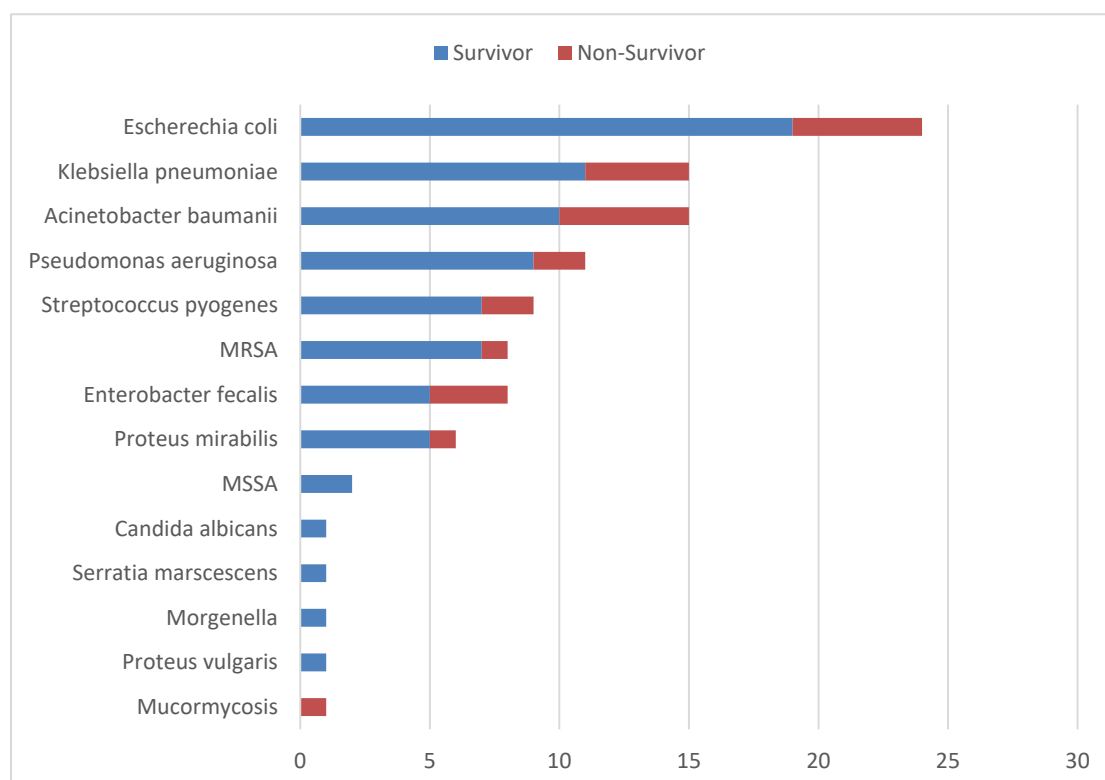
	GROUP I (Survival) n=69	GROUP II (Non-survival) n=18	p-value
Haemoglobin (g/dL)	11.2 (9.7-13.15)	9.1 (7.1-9.8)	<b>0.0007</b>
TLC ( $10^3$ /uL)	13.7 (9.7-20.9)	16.6 (11.4-22.1)	0.5418
Creatinine (mg/dL)	1.03 (0.8-1.57)	1.5 (0.9-2.3)	<b>0.0384</b>
Na (meq/L)	131 (127-134)	130 (124-132)	0.1336
K (meq/L)	4.27 (3.8-4.7)	4.6 (3.9-4.8)	0.3575
Albumin (g/dL)	2.75 (2.3-3.3)	2.0 (1.8-2.6)	<b>0.0002</b>
ALP (IU/L)	138 (96-226.5)	118.5 (108-148.5)	0.3953
APACHE II	6 (5-9)	10 (5.5-15.2)	<b>0.0366</b>
LRINEC	4 (2-6)	6 (4-10.2)	<b>0.0046</b>
SIARI	2 (1-5)	4 (2.7-5)	0.0536

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.

## Microbiology

All patients underwent tissue culture at an early stage of admission with a positive rate of 82.7 %. No bacteria were isolated from 15 patients. Mixed bacterial growth (defined as the growth of at least three organisms, each equally dominant, with no further identification being made) was present in 19 patients. Among these 19 patients, pathogenic bacteria were identified in 10 patients upon further sampling. Pathogenic bacterial isolates were therefore identified in 71 patients. The rest of the 9 cases were considered sterile as no pathogenic microorganism could be identified.

A single pathogenic organism was isolated in 45 cases (65.4%), whereas the remaining 26 patients (34.5%) sample revealed polymicrobial growth and one case showed growth of mucormycosis. *Candida albicans* was found in one of the polymicrobial growth. Details of the bacterial isolates are given in Table III. None of the isolates revealed any significant difference in mortality rate except for the case of mucormycosis.



**Graph 4: Microbiological isolates**  
Data are presented as number of microorganisms identified

Table 5: Type of NSTI by Giuliano classification

PARAMETERS	GROUP I (Survival) N = 69*	GROUP II Non- survival) N = 18	
Polymicrobial	19	7	0.392
Monomicrobial	36	9	0.869
Fungal	1*	1	0.373
No growth	14	1	0.179

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.

One patient in survival group had polymicrobial infection with one of isolate being *Candida albicans*, and is included in fungal category as well.

Table 6: Microbiological isolates

ISOLATES	TYPE I	TYPE II
<i>E. coli</i>	11	14
<i>Acinetobacter baumannii</i>	9	6
<i>Klebsiella pneumoniae</i>	9	7
<i>Pseudomonas</i>	7	4
<i>Enterobacter</i>	8	1
<i>Proteus mirabilis</i>	6	0
<i>Proteus vulgaris</i>	0	1
<i>Morgenella</i>	1	0
<i>Serratia marcescens</i>	0	1
<i>Streptococcus pyogenes</i>	5	4
MRSA	4	5
MSSA	0	2
<i>Candida albicans</i>	1	0
Mucormycosis	0	0

Data are presented as number of microorganisms identified

Table 7: Antimicrobial sensitivity of gram-negative isolates (n=84)

	E. coli N=24 (%)	K. pneumoniae N=16 (%)	E. cloacae N=9 (%)	P. mirabilis N=6 (%)	P. vulgaris N=1 (%)	M. morganii N=1 (%)	S. marcescens N=1 (%)	A. baumannii N=15 (%)	P. aeruginosa N=11 (%)
Piperacillin-tazobactam	16 (66.6)	7 (43.7)	5 (55.5)	4 (66.6)	1	1	1	2 (13.3)	8 (72.7)
Cefoxitin	7 (29.1)	1 (6.2)	0	4 (66.6)	0	1	0	0	0
Ceftriaxone	0	4 (25)	3 (33.3)	0	0	0	1	0	0
Ceftazidime-avibactam	0	3 (18.7)	-	0	0	0	0	1 (6.6)	4 (36.6)
Cefoperazone-sulbactam	13 (54.1)	3 (18.7)	5 (55.5)	3 (50)	0	1	1	1 (6.6)	2 (18.1)
Cefepime	4 (16.6)	4 (25)	5 (55.5)	1 (16.6)	0	1	1	-	6 (54.5)
Aztreonam	4 (16.6)	1 (6.2)	4 (44.4)	1 (16.6)	0	0	0	0	5 (45.4)
Imipenem	16 (66.6)	8 (50)	5 (55.5)	1 (16.6)	1	1	-	1 (6.6)	4 (36.3)
Meropenem	20 (83.3)	6 (37.5)	5 (55.5)	3 (50)	1	1	-	2 (13.3)	6 (54.5)
Ertapenem	4 (16.6)	1 (6.2)	0	0	0	0	0	0	1 (9.1)
Teicoplanin	.	.	1 (11.1)	.	.	.	.	.	.
Colistin	22 (91.6)	10 (62.5)	6 (66.6)	1 (16.6)	.	.	.	13 (86.6)	10 (90.9)
Linezolid	.	.	1 (11.1)	.	.	.	.	.	.
Gentamicin	14 (58.3)	2 (12.5)	7 (77.7)	5 (83.3)	1	0	0	3 (20)	2 (18.1)
Amikacin	19 (79.1)	5 (31.2)	7 (77.7)	3 (50)	1	1	0	3 (20)	5 (45.4)
Netilmicin	5 (20.8)	2 (12.5)	1 (11.1)	0	0	1	0	2 (13.3)	1 (9.1)
Tetracycline	2 (8.3)	.	.	.	.	.	.	.	.
Minocycline	0	3 (18.7)	2 (22.2)	0	0	0	0	4 (26.6)	1 (9.1)
Tigecycline	16 (66.6)	5 (31.2)	5 (55.5)	2 (33.3)	0	0	0	4 (26.6)	0
Cotrimoxazole	9 (37.5)	5 (31.2)	4 (44.4)	3 (50)	1	0	1	1 (6.6)	0
Ciprofloxacin	2 (8.3)	1 (6.2)	1 (11.1)	3 (50)	1	-	-	-	3 (27.2)
Levofloxacin	-	3 (18.7)	4 (44.4)	3 (50)	1	1	1	1 (6.6)	2 (18.1)

Data are presented as percentage. E. coli, Escherichia coli. K. pneumoniae, Klebsiella pneumoniae. A. baumannii, Acinetobacter baumannii. E. cloacae, Enterobacter cloacae. P. aeruginosa, Pseudomonas aeruginosa. P. mirabilis, Proteus mirabilis. P. vulgaris, Proteus vulgaris. M. morganii, Serratia marcescens.

Table 8: Antimicrobial sensitivity of gram-positive isolates (n=20)

	Streptococcus pyogenes N=9 (%)	MRSA N=9 (%)	MSSA N=2 (%)
Penicillin g	9 (100)	.	.
Ampicillin	7 (77.7)	.	.
Piperacillin- tazobactam	.	.	.
Cefoxitin	0	.	2 (100)
Cefuroxime	0	.	.
Cefotaxime	1 (11.1)	.	0
Ceftriaxone	3 (33.3)	0	0
Ceftazidime- avibactam	0	0	0
Cefoperazone- sulbactam	0	0	0
Cefepime	0	0	0
Aztreonam	0	.	.
Imipenem	0	1 (11.1)	.
Meropenem	0		1 (50)
Ertapenem	0	0	0
Vancomycin	6 (66.6)	7 (77.7)	2 (100)
Teicoplanin	1 (11.1)	8 (88.8)	1 (50)
Linezolid	6 (66.6)	9 (100)	2 (100)
Gentamicin	1 (11.1)	8 (88.8)	2 (100)
Amikacin	0	2 (22.2)	2 (100)
Netilmicin	0	1 (11.1)	.
Tetracycline	.	3 (33.3)	2 (100)
Tigecycline	.	8 (88.8)	2 (100)
Erythromycin	1 (11.1)	2 (22.2)	0
Clindamycin	6 (66.6)	1 (11.1)	1 (50)
Cotrimoxazole	0	8 (88.8)	2 (100)
Ciprofloxacin	3 (33.3)	3 (33.3)	1 (50)
Levofloxacin	3 (33.3)	2 (22.2)	1 (50)
Moxifloxacin	.	1 (11.1)	.

Data are presented as percentage. MRSA, methicillin resistant *Staphylococcus aureus*. MSSA, Methicillin sensitive *Staphylococcus aureus*



## OUTCOME

All patients underwent at least two surgeries (Median 2, IQR: 1-3 in the survival group and 1-4.25 in the non-survival group). 84 patients underwent debridement of which 11 patients (all falling in the non-survival group) required multiple debridement (IQR:1-6). A total of 19 patients landed up with amputation after initial debridement (17 in the survival group and 2 in the non-survival group). 3 patients underwent amputation as a primary procedure due to extensive myofascial compartment involvement. 27 patients had NPWT applications for wound management and 12 patients required multiple sitting (2-3). The rest of the patients were managed by daily dressing and bedside debridement.

Table 9: Outcomes Parameters

PROCEDURES	GROUP I (Survival) n=69 (percentage)	GROUP II Non- survival) n=18 (percentage)	
Debridement	66 (95.6)	18 (100)	1
NPWT	22 (31.8)	5 (27.7)	0.737
Amputation	19 (27.5)	2 (11.1)	0.146
Number of Procedures done (median/IQR)	2(1-3)	2 (1-4.25)	0.303
Hospital Stay (median/IQR)	9(7-15)	4 (2-12.3)	<b>0.007</b>
ICU Stay (n)	3	15	<b>0.00001</b>
Requirement of ventilatory support	3	17	<b>0.00001</b>

Data are presented as number of patients, median (interquartile range) or.  $p < 0.05$  was considered statistically significant.

The median time from admission to the first operation was 6 (4-9) hours. However, there was no statistically significant difference between the survivor and the non-survivor group ( $p = 0.575$ ). The median total duration of hospital stay was 9 days (IQR: 6-15 days). A total of 18 patients (20.7%) required ICU care with a median

ICU stay of 2 days (IQR: 1-4.25). Statistically, a significant difference was found in the total duration of hospitalization, ICU stay and requirement of ventilatory support between the survivor and the non-survivor groups with p values 0.007, <0.00001 and < 0.00001 respectively.

Table 10: Outcomes

<b>OUTCOMES</b>	<b>n=87 (percentage)</b>
<b>Death</b>	18 (20.6)
<b>Amputation</b>	21 (31.8)
<b>Primary closure</b>	5 (5.7)
<b>Wound coverage</b>	26 (29.8)
<b>Secondary healing</b>	19 (21.8)

Data are presented as number of patients and percentage

## DISCUSSION

Necrotising soft tissue infections are fulminant infections of the soft tissue compartment with relative sparing of skin and underlying muscles, associated with widespread necrosis and systemic toxicity.(2) Any layer (dermis, subcutaneous tissue, superficial fascia, deep fascia) in any part of the body can essentially be involved in NSTI.(20) NSTI has been described as various entities (e.g., necrotizing fasciitis, suppurative fasciitis, necrotizing myositis, acute dermal gangrene, gas gangrene, Meleney's synergistic gangrene, synergistic necrotising cellulitis, Fournier's gangrene, hospital gangrene and streptococcal gangrene).(2,20) However, given the extensive involvement of the soft tissue layers to a variable extent as well as their similar clinical features and treatment strategies (antibiotics, early extensive surgery, and organ supportive care), recent literature suggests that these severe infections should be classified as NSTI.(2,38,67) The incidence of necrotizing fasciitis ranges from 0.3 to 15 cases per 100,000 population.(2) The incidence of all causes of NSTI is not clear. Though such infections are relatively rare, as surgeons who practise at a tertiary referral centre, we see more than most. We present a cross-sectional study with an analysis of the clinical profile, microbiological spectrum, and factors that affect mortality among patients with necrotising soft-tissue infections. The present study is one of the largest prospective studies to date dealing with the topic in this part of the country.

There are several classifications for NSTI. The one commonly followed is based on the bacteriological spectrum of growth proposed by Giuliano et al.(34) Three types of NSTI are included in this classification. Type I infections are polymicrobial with mixed growth of gram-positive cocci, gram-negative cocci, and anaerobes. Type II infections are monomicrobial and are caused by group A  $\beta$  haemolytic *Streptococcus* or *Clostridia* group. Type III infections are caused by gram-negative marine organisms like *Vibrio vulnificus*. Some authors have also described a type IV infection which is caused by *Candida* and other fungi.(61) The incidence of type I and II is typically very similar.(68) The most common pathogens involved in type I infection are *Escherichia coli* and *Enterococcus* species, whereas *Streptococcus pyogenes* and methicillin-resistant *Staphylococcus aureus* are the most common pathogens involved in type II infection.(2) In the present case series, types I and II

infection were found in 45(65.4%) and 26 (34.5%) patients, respectively. *E. coli* was the most common isolate in both types I and II NSTI. Though in literature polymicrobial growth is the most common cause,(61,68) few studies also show *E. coli* as the predominant growth.(68) Antibiotic resistance pattern revealed high resistance to third generation cephalosporins and fluoroquinolones in general for Enterobacteriaceae group as whole and *E. coli* in particular, as shown in Table 7. Moreover, the difference in mortality between the two groups was not statistically significant in our study contrary to previous pieces of evidence ( $p = 0.562$ ).

M-protein is the major virulence factor for GAS. But the key mediator of the immunopathogenesis of NSTI is the extracellular superantigens, among others. The treatment of choice for GAS is undisputedly penicillins. However, isolates with reduced susceptibility to beta-lactam antibiotics have recently been reported. In addition, increasing resistance to clindamycin has been reported and is of more immediate concern mainly due to functional antimicrobial resistance caused by GAS biofilm formation. In our study all isolates were sensitive to Penicillin. Most of them showed sensitivity to ampicillin, vancomycin and linezolid. Resistance was high for third generation cephalosporins, aminoglycosides and moderate for macrolides. (Table 8)

Though not an established cause of NSTI in isolation, *S. aureus* is a major pathogen isolated in our study. Its success to cause such extensive disease can be attributed to several microbial traits. Firstly, 30% of the human population is carriers in the upper respiratory tract. In addition, it produces a multitude of virulence factors that helps in adherence, local and systemic spread and host responses. Many strains of *S. aureus* have attained Panton–Valentine leukocidin (PVL) toxin-producing capabilities by exchanging PVL-producing phages. Most of these strains are methicillin-resistant *S. aureus* (MRSA). These PVL-toxin-producing MRSA is associated with severe skin and soft tissue infections consistent with NSTI. Antibiotic resistance is rampant in this group and resistance to almost all of the relevant antibiotic classes has been reported. The majority of *S. aureus* strains produce penicillinase, this can be appreciated in our study which shows high resistance to third generation cephalosporin. All isolates were sensitive to Linezolid. Most showed high sensitivity to vancomycin, gentamicin and cotrimoxazole. (Table 8)

The most common presenting symptom in our study was pain followed by erythema. Pain is often out of proportion to the external lesion. The small necrotic patch of skin often masks the widely spread underlying infection. This can be noted in the operative photographs, in which the extent of debridement exceeded the area of skin necrosis, Figure 2. The presence of bullae is a characteristic sign of this disease but is seen at a later stage of the disease after the infection has set in.



**Figure 2: Case of NSTI left lower limb – extent of involvement**

Necrotizing soft tissue infection in a patient without obvious causal event. A 24-year-old lady presented with complaints of pain in the left leg for the last 2 days and generalised weakness and difficulty in breathing for the past 1 day. She was admitted with a working diagnosis of septic shock with acute lung injury with disseminated intravascular coagulopathy. She was managed with multiple debridement, NPWT applications and daily dressing. Skin changes, preoperative. A long incision extending along the longitudinal axis revealed necrotic fascia and muscles. A large amount of dishwater-grey exudate was encountered. The extent of the disease is far more than the visible skin changes and requires extensive debridement.





**Figure 3: Case of NSTI left thigh – extent of involvement**

A 42 years old male who is a known diabetic for past 8 years (uncontrolled), developed NSTI following a history of trauma. The extent of involvement exceeds the skin changes as can be appreciated in this case.

Despite advances in the understanding of NSTI, the mortality rate of NSTI is still high at 18% to 34%.(6,44,69)In the present study, a mortality rate of 20.7% was noted. A review of the literature shows that the mortality rate for NSTI varies widely from study to study. Comparative Indian studies showed a mortality rate of 25%.(59,70) The relatively lower rate of mortality can be explained by the fact that the hospital in which this study was conducted is a tertiary care centre in this region and deals with cases of NSTI on a routine basis. A high index of suspicion while dealing with cases of soft tissue infection has been ingrained into skills of treating surgeons.



**Figure 4: Case of NSTI left lower limb – wound coverage**

A 40 years old man developed NSTI post snake bite. Presented with signs and symptoms of envenomation with septic shock, AKI and wound over foot and leg. He underwent serial debridement followed by wound coverage by STSG.

In our study 31.8% patients landed up in amputation and 21.8 % required wound coverage in the form of skin grafting (split thickness skin grafting), see figure 3. In previous studies, factors associated with high mortality included older age, delayed surgery, low body mass index, and abnormal laboratory test parameters (white blood cells, haemoglobin, creatinine, sodium, BUN, and platelets).(2,6,20) Wong et al. proposed the LRINEC score, which is the most widely used predictive system for NSTI diagnosis. The LRINEC scoring system uses the total white blood cell count and the haemoglobin, sodium, glucose, creatinine, and C-reactive protein concentrations to differentiate NSTI from other mild infections. However, the positive predictive value of the LRINEC score ranges from 57% to 92%.(20,71) In addition, some new predictive scoring systems have been proposed (e.g., SIARI score and NAS).(50,51) High APACHE II and LRINEC scores were associated with mortality in our study. Also, non-survival was not associated with previously established risk factors like older age, a higher BUN or creatinine concentration, coagulation disorder, lower sodium concentration, and longer duration from admission to the first operation compared with patients in the survivor group in our study. However, parameters like low hemoglobin, low albumin and high creatinine levels showed a significant difference between survival and non-survival groups (p values of 0.0001, 0.0007 and 0.0382 respectively).

Surgical exploration is an indispensable method for the diagnosis of NSTI. It is also essential for determining the extent of infection and controlling the source of infection.(22,71) Typical findings include grey necrotic tissue, lack of bleeding, thrombosed vessels, dishwater-grey exudate, non-contracting muscle, and a positive finger test result.(2) Minimizing the time from admission to the first operation is critical for reducing mortality. In one study, the survival rate of patients who underwent surgery within 24 hours after admission was significantly higher than that of patients who underwent surgery after 24 hours.(20) In the present study, the median time from admission to the first operation was 6 hours (IQR, 4.3-9.4 hours), which was significantly shorter than that in previous studies (19-35 hours). This discrepancy can be explained by the fact that our institution is a tertiary referral centre, thus the diagnosis of NSTI may be made elsewhere before admission to AIIMS hospital. Secondly being a tertiary care centre in the whole region draining 4-5 districts in western Rajasthan with poor medical infrastructure, surgeons and

physicians are relatively more experienced in identifying NSTI, which helps avoid delayed diagnosis and thus misdiagnosis.

In addition to surgical debridement and antibiotic treatment, the roles of organ support, standardized antishock therapy, and multidisciplinary collaboration have also been recognized. Moreover, multidisciplinary collaborative management is an effective modality to reduce the mortality rate of NSTI.(20,72) In our setting, the patient is primarily managed by the admitting surgical department and the intensivists participate in the treatment of patients with NSTI on a call basis. Resuscitation is guided by clinical, physiological and laboratory parameters. After the operation, patients are transferred to wards or the ICU based on clinical grounds in order to further manage septic shock and provide organ and nutritional support. The surgeons oversee daily wound care. Finally, patients are transferred to the parent surgical department for wound repair if their clinical condition is stable.

At present, very few reports about NSTI exist in this part of the region. In this study, we analysed the characteristics and prognosis of 87 patients with NSTI. We introduced our experience in treating NSTI and highlighted the variations in the clinical presentation, risk factors, multitudes of associated comorbidities, myriads of microbiological isolates and outcomes. We emphasized on the importance of multidisciplinary collaborative management as an effective modality to reduce NSTI-related mortality and morbidity.



## **LIMITATIONS**

Researching NSTIs is challenging because they are uncommon and difficult to distinguish from other soft tissue infections due to their uncanny clinical resemblance. Our research was not without flaws. Similar to the majority of clinical studies in this area, our study has largely ignored pathogens and their interactions with hosts in favor of concentrating more on patient characteristics and outcomes. In order to improve patient outcomes, it is crucial to strengthen the microbiological diagnostic handling of patients with NSTI. (68) Survival rates in many severe infections are correlated with the discovery of the microbial cause and the presence of antimicrobial resistance in that cause. The prevalence of microbes causing NSTI in clinically oriented studies, one like ours, is difficult to assess, as reporting on microbiological data even from relevant cohorts in general holds low precision. It is also difficult to quantify the impact of a particular microorganism to whole disease pathogenesis and manifestations. Since the majority of NSTIs are polymicrobial, there is a risk of the emergence of antibiotic resistance. Second, this was a single-center study. To demonstrate statistical significance and the strength of associations and correlations, the small sample size was underpowered. Finally, since it was challenging to determine the length of time between the patient's injury and admission, the duration between their admission and the first operation was used. Since the majority of earlier studies used this parameter as well, the results are still comparable. (2,50,60)

## **CONCLUSION**

Clinicians should fully understand the clinical characteristics and mortality-related factors of NSTI. Patients presenting with AKI and septic shock are at high risk of mortality. High APACHE II and LRINEC scores, anaemia, hypoalbuminemia and high creatinine may also be at higher risk of death and thus more attention should be given to this group of patients. The avoidance of delayed intervention, though not statistically significant in our study, is age-old evidence that cannot be overlooked. In addition to early diagnosis, rational use of antibiotics and multidisciplinary cooperation is essential for the improvement of the clinical outcome of NSTI

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All India Institute of Medical Sciences, Jodhpur  
संस्थागत नैतिकता समिति  
Institutional Ethics Committee

No. AIIMS/IEC/2021/3525

Date: 12/03/2021

**ETHICAL CLEARANCE CERTIFICATE**

Certificate Reference Number: AIIMS/IEC/2021/3360

Project title: "Clinical profile and outcome of cases with necrotising soft tissue infection: A prospective observational study"

Nature of Project: Research Project Submitted for Expedited Review  
Submitted as: M.S. Dissertation  
Student Name: Dr. Piyush Sharma  
Guide: Dr. Ashok Kumar Puranik  
Co-Guide: Dr. Poonam Elhence, Dr. Ashwini Agarwal & Dr. Pawan Kumar Garg

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma  
Member Secretary

Member secretary  
Institutional Ethics Committee  
AIIMS, Jodhpur

**ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR,  
RAJASTHAN**

**DEPARTMENT OF GENERAL SURGERY**

**PARTICIPANT INFORMED CONSENT FORM**

Participant identification number: \_\_\_\_\_

**Title:** Clinical profile and outcome study of patients with necrotising soft tissue infection admitted in surgery department at AIIMS jodhpur.

Name of PG resident: Dr Piyush Sharma

Tel.No(s). 8294699389

The contents of the information sheet dated ..... that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

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(Signatures / Left Thumb Impression)

Date:

Place:

Name of the Participant: \_\_\_\_\_

Son/Daughter/Spouseof: \_\_\_\_\_ Address: \_\_\_\_\_

This is to certify that the above consent has been obtained in my presence.

Signatures of PG resident:

Date:

1) Witness– 1

2) Witness –2

Signatures:

Signatures:

Name:

Name:

Address:

Address:

ऑल इंडिया इंस्टीट्यूट ऑफ मेडिकल साइंसेज

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस / निबंध का शीर्षक: " एम्स जोधपुर में जनरल सर्जरी विभाग में भर्ती नरम ऊतक संक्रमण के साथ रोगियों के रोगविषयक प्रोफाइल और परिणाम अध्ययन "

पीजी छात्र का नाम: डॉ. पीयूष शर्मा (8294699389)

रोगी / स्वयंसेवी पहचान संख्या: \_\_\_\_\_

मैं, \_\_\_\_\_ पुत्र/पुत्री

निवासी \_\_\_\_\_ इस अध्ययन का हिस्सा बनने के लिए पूरे सहमति देता/देती हूँ

"जिसकी प्रक्रिया और प्रकृति मुझे मेरी भाषा में मेरी संतुष्टि तक समझा दी गई है। मैं पुष्टि करता हूँ कि मुझे प्रश्न पूछने का पूरा अवसर मिला है, जिनके जवाब से मैं संतुष्ट भी हूँ।

मैं समझता हूँ कि मेरी भागीदारी स्वैच्छिक है और मुझे किसी भी कारण के बिना, किसी भी समय अध्ययन से बाहर निकलने का अधिकार है।

मैं जानता हूँ कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी को गुप्त: रखा जायेगा I

दिनांक : \_\_\_\_\_

स्थान: \_\_\_\_\_ हस्ताक्षर / बाएं अंगूठे की छाप

यह प्रमाणित करने के लिए कि उपर्युक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

पीजी छात्र के हस्ताक्षर: \_\_\_\_\_

दिनांक: \_\_\_\_\_

स्थान: \_\_\_\_\_

साक्षी 1

साक्षी 2

हस्ताक्षर: \_\_\_\_\_

हस्ताक्षर: \_\_\_\_\_

नाम: \_\_\_\_\_

नाम: \_\_\_\_\_

पता: \_\_\_\_\_

पता: \_\_\_\_\_

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RAJASTHAN  
DEPARTMENT OF GENERAL SURGERY  
INFORMATION TO PARTICIPANTS**

**Title:** Clinical profile and outcome study of patients with necrotising soft tissue infection admitted in surgery department at AIIMS jodhpur

**Name of Participant:** .....

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in AIIMS, Jodhpur because you satisfy our eligibility criteria.

**What is the purpose of research?**

This study aims to provide a complete epidemiological description of necrotising soft tissue infection. If you enrol in it you will be benefitted by better perioperative outcomes. We have obtained permission from the Institutional Ethics Committee for conducting this study.

**The study design:**

The study will be a hospital based prospective descriptive study and patients will be recruited from Department of General Surgery, AIIMS Jodhpur.

**Study Procedures:**

The study involves evaluation of the outcomes of operative intervention in patients of NSTI. You will be counselled about the entire perioperative care before surgery. You will be started on broad-spectrum antibiotics, later converted as per culture reports. All cases of NSTI will be diagnosed based on clinical grounds and operative findings. Excised tissue specimens were sent for microbiological and histopathologic (if required) evaluation.

Appropriate surgical interventions will be done after initial resuscitation. Post-operative tissue viability will be assessed frequently. NPWT will be utilized as and when required. You will get discharged when satisfactory clinical status is achieved. All the events will be recorded. The laboratory/ microbiological/ histopathology specimen shall be processed and all findings shall be recorded. Complications, if any shall be prospectively recorded.

**Possible risks to you:**

There is no added risk other than the risk involved due to surgery and disease.

**Possible benefits to you:**

You shall have all the benefits of early operative intervention for NSTI and the proven benefit of critical care protocol.

**Compensation:** Nil.

**Reimbursement:**

You will not be paid to participate in this research study.

**Possible benefits to other people:**

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

**The alternatives you have:**

If you do not wish to participate, you still will get the standard treatment for your condition.

**What should you do in case of injury or a medical problem during this research study?**

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment.

**Confidentiality of the information obtained from you:**

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

**How will your decision to not participate in the study affect you?**

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

**Can you decide to stop participating in the study once you start?**

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons.

**Can the investigator take you off the study?**

You may be taken off the study without your consent if you do not follow instructions of the investigators or the research team or if the investigator thinks that further participation may cause you harm.

**Right to new information**

If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

**Contact persons**

For further information / questions, you can contact at the following address:

Dr Piyush Sharma  
Post Graduate Resident (Academic),  
Department of General Surgery,  
AIIMS, Jodhpur  
Mobile No-829469938

## आल इंडिया इंस्टिट्यूट ऑफ़ मेडिकल साइंसेज

जोधपुर, राजस्थान

जनरल सर्जरी विभाग

### रोगी की सूचना पत्र

**शीर्षक:** " एम्स जोधपुर में जनरल सर्जरी विभाग में भर्ती नरम ऊतक संक्रमण के साथ रोगियों के रोगविषयक प्रोफाइल और परिणाम अध्ययन "

#### नाम:

आपको इस शोध अध्ययन में भाग लेने के लिए आमंत्रित किया गया है। इस दस्तावेज़ की जानकारी यह तय करने में आपकी मदद करने के लिए है कि भाग लेना है या नहीं। कृपया बेझिझक पूछें कि क्या आपके पास कोई प्रश्न या चिंता है।

आपको एम्स, जोधपुर में आयोजित किए जा रहे इस अध्ययन में भाग लेने के लिए कहा जा रहा है क्योंकि आप हमारी पात्रता मानदंड को पूरा करते हैं।

#### अनुसंधान का उद्देश्य क्या है?

इस अध्ययन का उद्देश्य नेक्रोटाइजिंग सॉफ्ट टिशू संक्रमण का एक पूर्ण महामारी विज्ञान विवरण प्रदान करना है। यदि आप इसमें दाखिला लेते हैं तो आप बेहतर परिधीय परिणामों से लाभान्वित होंगे। हमने इस अध्ययन के संचालन के लिए संस्थागत आचार समिति से अनुमति प्राप्त की है।

#### अध्ययन डिजाइन:

अध्ययन एक अस्पताल आधारित भावी वर्णनात्मक अध्ययन होगा और रोगियों को जनरल सर्जरी विभाग, एम्स जोधपुर से भर्ती किया जाएगा।

#### अध्ययन की प्रक्रिया:

अध्ययन में **NSTI** के रोगियों में ऑपरेटिव हस्तक्षेप के अल्पकालिक परिणामों का मूल्यांकन शामिल है। सर्जरी से पहले आपको पूरी देखभाल के बारे में परामर्श दिया जाएगा। सभी घटनाओं को दर्ज किया जाएगा। प्रयोगशाला / सूक्ष्मजीवविज्ञानी / हिस्टोपैथोलॉजी नमूना संसाधित किया जाएगा और सभी निष्कर्षों को दर्ज किया जाएगा। जटिलताओं, यदि कोई संभावित रूप से दर्ज की जाएगी।

#### आपके लिए संभावित जोखिम:

सर्जरी और बीमारी के कारण शामिल जोखिम के अलावा कोई अतिरिक्त जोखिम नहीं है।

आपके लिए संभावित लाभ:

आपके पास **NSTI** के लिए प्रारंभिक ऑपरेटिव हस्तक्षेप और प्रोटोकॉल के सभी लाभ होंगे।

#### नुकसान भरपाई:

कोई नहीं।

#### प्रतिपूर्ति:

इस शोध अध्ययन में भाग लेने के लिए आपको भुगतान नहीं किया जाएगा।

#### अन्य लोगों को संभावित लाभ:

अनुसंधान के परिणाम भविष्य के रोगियों को चिकित्सा ज्ञान और / या चिकित्सीय लाभ की उन्नति के रूप में समाज को लाभ प्रदान कर सकते हैं।

#### आपके पास जो विकल्प हैं:

यदि आप भाग लेने की इच्छा नहीं रखते हैं, तो भी आपको अपनी स्थिति के लिए मानक उपचार मिलेगा।

इस शोध अध्ययन के दौरान चोट या किसी मेडिकल समस्या के मामले में आपको क्या करना चाहिए?



आपकी सुरक्षा अनुसंधान की प्रमुख चिंता है। यदि आप घायल हैं या इस अध्ययन में होने के परिणामस्वरूप कोई चिकित्सा समस्या है, तो आपको सहमति फॉर्म के अंत में सूचीबद्ध लोगों में से एक से संपर्क करना चाहिए। आपको आवश्यक देखभाल / उपचार प्रदान किया जाएगा।

#### **आपसे प्राप्त जानकारी की गोपनीयता:**

आपको अपनी मेडिकल जानकारी की गोपनीयता (व्यक्तिगत विवरण, शारीरिक परीक्षाओं के परिणाम, जांच, और आपके मोबाइल डेटा) की गोपनीयता के बारे में अधिकार है। इस दस्तावेज़ पर हस्ताक्षर करने से, आप रिसर्च टीम के जांचकर्ताओं, अन्य अध्ययन कर्मियों, प्रायोजकों, संस्थागत नैतिकता समिति और किसी भी व्यक्ति या एजेंसी को अनुमति दे सकते हैं जो आवश्यक होने पर ड्रग कंट्रोलर जनरल ऑफ इंडिया जैसे कानून को अपना डेटा देख सकते हैं। इस शोध के भाग के रूप में किए गए नैदानिक परीक्षणों और चिकित्सा के परिणामों को आपके मेडिकल रिकॉर्ड में शामिल किया जा सकता है। इस अध्ययन की जानकारी, अगर वैज्ञानिक पत्रिकाओं में प्रकाशित की जाती है या वैज्ञानिक बैठकों में प्रस्तुत की जाती है, तो इससे आपकी पहचान का पता नहीं चलेगा।

#### **अध्ययन में भाग न लेने का आपका निर्णय आपको कैसे प्रभावित करेगा?**

इस शोध अध्ययन में भाग नहीं लेने का आपका निर्णय आपकी चिकित्सा देखभाल या अन्वेषक या संस्था के साथ आपके संबंधों को प्रभावित नहीं करेगा। आपका डॉक्टर अभी भी आपकी देखभाल करेगा और आप किसी भी लाभ को नहीं खोएंगे जिससे आप परेशान हैं।

#### **क्या आप शुरू करने से पहले अध्ययन में भाग लेना बंद करने का निर्णय ले सकते हैं?**

इस शोध में भागीदारी विशुद्ध रूप से स्वैच्छिक है और आपको इससे हटने का अधिकार है बिना किसी कारण के अध्ययन के दौरान किसी भी समय यह अध्ययन।

#### **क्या जांचकर्ता आपको अध्ययन से दूर कर सकता है?**

यदि आप जांचकर्ताओं या अनुसंधान टीम के निर्देशों का पालन नहीं करते हैं या यदि अन्वेषक को लगता है कि आगे की भागीदारी से आपको नुकसान हो सकता है, तो आप अपनी सहमति के बिना अध्ययन से बाहर हो सकते हैं।

#### **नई जानकारी का अधिकार**

यदि अनुसंधान दल को इस शोध अध्ययन के दौरान कोई नई जानकारी मिलती है जो अध्ययन में भाग लेने को जारी रखने के आपके निर्णय को प्रभावित कर सकती है, या कुछ संदेह पैदा कर सकती है, तो आपको उस जानकारी के बारे में बताया जाएगा।

संपर्क करें

**अधिक जानकारी / प्रश्नों के लिए, आप निम्नलिखित पते पर संपर्क कर सकते हैं:**

डॉ. पीयूष शर्मा

पोस्ट ग्रेजुएट छात्र (शैक्षणिक),

सामान्य सर्जरी विभाग,

एम्स, जोधपुर

मोबाइल नंबर -8294699389

## PATIENT PROFORMA

**TITLE:** “CLINICAL PROFILE AND OUTCOME OF CASES WITH NECROTISING SOFT TISSUE INFECTION: A PROSPECTIVE OBSERVATIONAL STUDY”

**GENERAL INFORMATION:**

1. Signed Consent Form	Yes	No
2. Completed Form	Yes	No

NAME	ID	
AGE/SEX	ADDRESS	
DOA	CONTACT	
DOS		
DOD		
	YES/NO	PARTICULAR
Presentation:		
Site affected: <ul style="list-style-type: none"> <li>● R upper limb</li> <li>● R lower limb</li> <li>● L upper limb</li> <li>● L lower limb</li> <li>● Scrotum</li> <li>● Abdominal wall</li> <li>● Gluteal/Sacral</li> <li>● Head &amp; neck</li> <li>● Thorax</li> </ul>		
Severe skin signs <ul style="list-style-type: none"> <li>● Crepitations</li> <li>● Livedo</li> <li>● Necrosis</li> </ul>		

Systemic symptoms <ul style="list-style-type: none"> <li>● AKI</li> <li>● Severe sepsis</li> <li>● Septic shock</li> </ul>		
Comorbidities <ul style="list-style-type: none"> <li>● Diabetes mellitus</li> <li>● Hypertension</li> <li>● Obesity</li> <li>● CKD</li> <li>● Severe peripheral vascular disease</li> <li>● COPD</li> <li>● Chronic corticosteroids or immunosuppressive drug use</li> <li>● Malignancy</li> </ul>		
Precipitating events <ul style="list-style-type: none"> <li>● Trauma</li> <li>● IM/IV injections</li> <li>● Insect bite</li> <li>● Snake bite</li> <li>● Animal bite</li> <li>● Toxin exposure</li> <li>● Chronic wounds</li> <li>● Preexisting dermatosis and skin infections</li> <li>● Post- operative</li> <li>● Idiopathic</li> <li>● Unknown</li> </ul>		
Laboratory findings <ul style="list-style-type: none"> <li>● Haemoglobin</li> <li>● White blood cell count</li> <li>● Increased creatine</li> <li>● C-reactive protein level &gt;75 mg/L</li> <li>● Serum albumin</li> <li>● Serum electrolytes</li> <li>● RBS</li> <li>● APACHE II Score</li> <li>● LRINEC Score</li> <li>● SIARI Score</li> </ul>		

Microbiological flora <ul style="list-style-type: none"> <li>● Polymicrobial</li> <li>● Monomicrobial</li> <li>● Tubercular</li> <li>● Fungal</li> <li>● Sterile</li> </ul>		
Radiological Investigation: <ul style="list-style-type: none"> <li>● X-ray</li> <li>● USG</li> <li>● Doppler</li> <li>● CT Angiography</li> </ul>		
Treatment <ul style="list-style-type: none"> <li>● Debridement</li> <li>● Amputation</li> <li>● No. of Debridements</li> <li>● No. of amputations</li> <li>● Timing of surgical intervention <ul style="list-style-type: none"> <li>○ Within 12hrs</li> <li>○ 12-24 hrs</li> <li>○ 24-48 hrs</li> <li>○ Beyond 48 hrs</li> </ul> </li> </ul>		
Hospital stay ICU admission (No. of days) Ventilator support		
Outcome <ul style="list-style-type: none"> <li>● Healing by secondary intervention</li> <li>● Skin grafting</li> <li>● Amputation</li> <li>● Death</li> </ul>		



Identification NO.	AGE	SEX	Microbiological isolates	Cefoxitin	Cefepime	Ceftriaxone	Piperacillin-Tazobactam	Ciprofloxacin	Levofloxacin	Gentamicin	Cotrimoxazole	Colistin	Aztreonam	Amikacin	Tetracycline	Tigecycline	Meropenem	Cefosulbactam	Imipenem	Ertapenem	Minoocycline	Netilmicin	Clindamycin	Penicillin G	Linezolid	Moxifloxacin	Vancomycin	Cefuroxime	Erythromycin	Teicoplanin	Ampicillin	Ceftazidime	Cefotaxime	Daptomycin	Anaphotericin B	Caspofungin	Fluconazole	Voriconazole	Micafungin		
	70	1	E. coli	-	1	0	0	-	0	1	-	1	1	1	0	-	1	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Klebsiella pneumoniae	-	1	1	1	-	1	-	1	-	-	1	-	1	-	-	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Streptococcus pyogenes	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	1	-	0	1	1	-	-	-	-	-	-	-	-	-	-
2	50	1	E. coli	0	0	0	1	1	-	-	1	1	0	1	1	-	1	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Pseudomonas	-	0	-	1	0	0	0	-	1	0	0	-	0	-	0	-	0	-	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-
3	41	1	Acinetobacter baumannii	-	0	0	0	-	0	1	-	0	1	-	1	-	1	0	-	-	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Proteus mirabilis	1	-	-	1	1	-	1	1	-	-	1	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	38	1	E. coli	1	0	0	1	0	-	0	-	1	0	1	-	1	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	71	1	Acinetobacter baumannii	0	0	0	1	0	-	0	0	1	-	0	-	0	-	0	0	-	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Klebsiella pneumoniae	0	0	0	0	-	-	-	-	0	1	-	-	-	1	-	0	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	53	0	E. coli	1	1	0	1	-	0	-	-	1	1	-	1	-	1	1	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Klebsiella pneumoniae	1	0	0	1	-	-	-	0	1	1	0	1	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Proteus mirabilis	-	-	-	1	-	1	1	-	-	-	1	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	63	1	E. coli	0	0	0	1	-	-	1	-	0	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Proteus mirabilis	1	-	-	1	1	-	1	-	-	1	-	-	1	1	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Pseudomonas	0	1	0	1	-	0	0	0	1	0	1	-	-	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	56	1	Klebsiella pneumoniae	0	0	0	0	-	0	0	-	1	1	-	0	-	0	-	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Enterobacter	0	1	1	1	-	1	1	-	1	1	1	-	0	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			MRSA	-	-	-	-	0	0	1	0	-	-	-	-	1	-	-	-	-	-	-	0	0	1	-	1	-	0	1	-	-	-	-	1	-	-	-	-	-	-
9	52	1	Serratia marcescens	-	1	1	1	-	1	-	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
10	60	1	E. coli	0	0	0	0	-	0	0	0	1	0	0	1	-	1	0	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	85	1	Acinetobacter baumannii	-	0	0	0	0	-	-	-	0	1	0	0	1	0	0	0	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Enterobacter	-	-	-	-	0	0	0	-	-	-	-	0	0	-	-	-	-	-	-	-	-	0	-	-	-	-	0	0	-	-	-	-	-	-	-	-	-	-
			MRSA	0	-	-	-	0	0	1	1	-	-	-	-	1	-	-	-	-	-	-	0	0	1	-	1	-	0	1	-	-	-	-	-	-	-	-	-	-	-
12	18	0	Acinetobacter baumannii	-	0	0	0	-	-	-	0	-	-	0	-	-	0	-	-	-	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	45	1	E. coli	0	0	0	1	-	0	-	-	1	-	-	0	-	1	0	0	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Klebsiella pneumoniae	-	1	1	1	-	1	1	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Enterobacter	-	0	-	0	0	1	-	-	0	1	-	1	0	0	0	0	-	1	-	-	0	1	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-
14	65	1	Streptococcus pyogenes	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	1	-	0	1	-	-	-	-	-	-	-	-	-	-	-
15	66	1	Acinetobacter baumannii	-	0	0	0	-	0	-	0	1	0	0	0	-	0	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Streptococcus pyogenes	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-
16	76	0	Sterile	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
17	60	0	E. coli	1	1	0	1	0	-	1	-	1	1	1	-	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18	18	0	Acinetobacter baumannii	0	0	-	-	-	0	-	-	0	1	-	0	-	0	0	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19	58	1	Streptococcus pyogenes	-	-	1	-	-	1	-	0	-	-	-	-	-	-	-	-	-	-	-	1	1	1	-	1	-	0	-	-	-	-	-	-	-	-	-	-	-	-
20	26	1	Klebsiella pneumoniae	0	0	0	0	-	0	0	0	1	-	0	-	1	0	-	0	-	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Pseudomonas	-	1	-	1	-	-	1	-	1	1	1	-	-	1	-	1	-	-	1	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
			Proteus mirabilis	1	0	-	-	-	1	1	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21	22	0	E. coli	0	0	0	0	-	0	0	1	1	-	0	0	-	1	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22	23	0	MRSA	0	-	-	-	-	0	1	1	1	-	1	-	-	-	-	-	-	-	-	0	0	1	-	1	-	1	1	-	-	-	-	-	-	-	-	-	-	-
23	75	1	Mucormycosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24	75	1	Streptococcus pyogenes	-	-	0	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	0	-	1	-	-	1	-	-	-	-	-	-	-
25	73	1	Proteus vulgaris	-	-	-	1	1	1	1	1	-	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26	59	0	E. coli	1	0	0	1	-	-	1	1	1	0	1	-	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Acinetobacter baumannii	-	0	0	0	0	1	0	0	1	-	0	-	1	0	0	0	0	-	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Pseudomonas	-	0	0	0	0	0	-	0	1	-	1	-	1	0	-	1	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27	37	1	MRSA	0	-	-	-	0	0	1	1	-	-	-	-	1	-	-	-	-	-	-	1	0	1	0	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-
28	56	0	E. coli	0	0	0	1	-	-	0	0	0	1	0	0	-	1	0	0	0	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-	-
29	83	1	Sterile	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
30	67	1	Klebsiella pneumoniae	0	0	0	0	-	0	0	0	1	0	0	-	-	0	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31	49	1	E. coli	0	0	0	1	-	0	1	0	1	0	1	-	1	1	0	1	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32	53	0	Acinetobacter baumannii	-	0	0	0	0	0	-	-	0	1	-	0	-	0	0	0	0	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33	56	1	Klebsiella pneumoniae																																						