Describing the resistance patterns of necrotising fasciitis in Acute Care Surgery

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"*I stand as one, but I stand as ten thousand***"** Maya Angelou. It is for this reason that I appreciate the following:

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Abstract

Objective- This study aims to identify the microorganisms and antibiotic resistance patterns in necrotising fasciitis.

Methods- This is a retrospective audit over two consecutive years (June 2015 - July 2017) of all patients who had surgery for necrotising fasciitis at an ACS unit.

Results- Necrotising fasciitis accounted for 15% of all skin and soft tissue sepsis that required surgery. There were 10 male (52.6%) and nine female (47.4%) patients. The most common co-morbidity was diabetes mellitus in 10 (52.6%) patients, the compliance and control were monitored by glycosylated haemoglobin (HbA1C) in 50% of the diabetic group, with a mean of 8.98 (Range 5-12.9). Fifteen percent of cases (n=3) had a confirmed diagnosis of HIV, with a negative result in eight (42%). ICU was required in three patients two of whom were on inotropes and one patient required renal replacement therapy. Surgery was performed within 24 hours for 11 (57%) patients. The most common anatomical site for debridement was perineum in nine patients (47%). Monomicrobial infection was the most common subtype of necrotising fasciitis with methicillin sensitive staphylococcus aureus in five (26%) as the predominant microbe. Gram-negative organism Escherichia-coli was the second most common monomicrobial infection. All Gram-positive organisms were sensitive to cloxacillin and co-amoxiclavulanic acid. Two gram negatives(15%) of the 13 organisms cultured were resistant to co-amoxiclavulanic acid. The 30 day mortality was 15%.

Conclusion- Necrotising fasciitis is a rare but lethal infection. In our limited series, monomicrobial infection is the most common subtype. 15% of the community acquired organisms were resistant to the empiric antibiotic of choice co-amoxiclavulanic acid. (word count= 261)

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Literature review

A literature search for necrotising fasciitis using medical search databases such as PubMed and Google scholar was used. The primary focus was the contemporary microbiology and management. The historical relevance development of diagnostic strategies was investigated to aid in comparison to the findings in our study.

Introduction

Necrotizing soft-tissue infections (NSTIs) are life-threatening, invasive often rapidly spreading soft-tissue infections which can involve any or all layers of the skin and soft-tissue compartment. It primarily involves the relatively avascular muscle fascia and can later cause secondary necrosis of surrounding subcutaneous fat and skin. Classically the appearance of tissue has been described by the friability of the tissue and loss of tissue planes which is associated with dish-water grey exudate with or without purulent collections.[1] The pathophysiology of necrotising fasciitis (NF) involves a breach of the skin barrier protection or by haematogenous spread of the bacterium.[1] Immune suppression due to various chronic ailments e.g. diabetes mellitus has been associated with an increased predisposition for NF. The incidence of NSTI in the western countries has been described as 0.4 per 100 000 population and associated with mortality ranging from 30-80% depending on the subtype and immune status of the patient.[2] In South Africa, we do not know the incidence or mortality of necrotising fasciitis. The underlying socioeconomics of a middle to low income country results in delayed access to health care, delayed diagnosis and delay to surgery. Immune suppression from poorly controlled

diabetes or untreated HIV could impact outcomes. There is no data to support or refute these clinical impressions. There are sparse data on microbiology and antibiotic resistance to aid local antibiotic guidelines.

Background

BL Wilson in 1952 first coined the name necrotising fasciitis in his article.[3] These were a case series of overt clinical signs of NF with necrosis spreading to skin and muscle. Since then various terms have been used to describe this entity such as 'Flesh eating bacterial infection', 'Haemolytic streptococcal gangrene', 'Gas gangrene', 'Wet gangrene' and 'Fournier's gangrene' if it involves the perineum. The currently acceptable nomenclature is 'Necrotising soft tissue infection' (NSTI) which is an umbrella term that encompasses necrotising cellulitis, fasciitis and myositis. The NF variety is the most lethal due to its ability to progress rapidly and sometimes the necrotic skin and muscle are secondary to the necrotising fasciitis.

Epidemiology

NF is a rare surgical clinical entity. The historic heterogeneity of the nomenclature for NSTI's results in difficulty in calculating its true incidence. In the United Kingdom, the incidence is estimated at 0.24-0.4 per 100 000 adults.[4] Similarly in the United States of America based on a 13 year retrospective review the incidence of NF was estimated at 3 800 - 5 800 admissions per year.[5] The incidence of NSTI due to invasive group A streptococcal (GAS) infections in the United States is 0.4 per 100,000, according to active surveillance data from the Center of Disease Control (CDC).[6]

The incidence of NF in Thailand is reported as 15.5 per 100 000 and was associated with high rates of limb loss or amputation.[7] The figures for many African countries and other middle to low income countries are lacking including for South Africa. The increasing worldwide obesity and hence diabetes mellitus rates could result in an increased incidence of NF. There was a 35% cumulative increase between 2001 and 2010 with a 2.7% per year increase in a study from Texas.[8] This is the largest cohort study on NF epidemiology trends in the literature. There are small case series over a period of time suggesting a global increase in incidence.[9]

Pathophysiology

Inoculation may be direct via trauma (sometimes minor) or surgery i.e. insect bites, lacerations, surgical incisions, illicit drug use and child-birth, or could be indirect where local inflammation facilitates the haematogenous entry of exotoxins.[1,5,10]

These bacteria then release toxins which stir an inflammatory response and cause thrombosis in the venules and arterioles which leads to ischaemic necrosis of skin, subcutaneous and muscular layers.[11] The bacteria release enzymes which enable it to liquefy barriers and promote the spread of infection.[12] There is a balance of host factors (genetic factors which regulate the pro-inflammatory cytokines) and micro-organism virulence (which stimulate the severity of the inflammatory response). It is this overwhelming inflammation that leads to local tissue destruction and systemic multi-organ involvement. There is a vicious cycle of fulminant infection, toxin production, cytokine activation, micro- thrombosis and ischemia, and tissue dysfunction and death, which progresses rapidly unlike in uncomplicated non-necrotizing skin and soft tissue infections. The toxin-producing organisms like Staphylococcus aureus can lead to toxic shock

syndrome. These exotoxins cause diffuse vasodilatation, affect cardiac contractility, increase the permeability of capillaries etc. Patients have multi-organ failure due to the diffuse action of these toxins and this leads to higher mortality rates.[13]

Classification

NF can be classified according to its microbiology, anatomical area and depth of necrosis. However the preferred classification uses microbiology and was first reported by Giuliano et al in 1977.[14] He described the microbiology of NF into two distinct entities, type I polymicrobial and type II monomicrobial.[14] Based on the classification created by Giuliano et al modified the classification in 1998 with the addition of the third subtype.[15] Finally, the fourth subtype was added by the pathologist Jain et al in India in 2006 to complete the modern classification as it is known today.[16]

This expands to include two extra subtypes onto the previous classification, and is currently the preferred one to use.[4]

Modified Guiliano classification

Types of NF	Aetiology	Organisms
Type 1	Polymicrobial/synergistic often bowel flora-derived	Mixed anaerobes and aerobes
Type 2	Often monomicrobial, skin or throat derived	Usually group A □- haemolytic streptococcus (GAS) occasionally ± staphylococcus aureus
Type 3	Gram-negative often marine related organisms	Vibrio species mainly
Type 4 (fungal)	Usually trauma associated immunocompetent patients	Candida species immunocompromised patients. Zygomycetes immunocompetent patients

In this classification Type, I is polymicrobial, the major cause (70-80%) of NF in clinical practice. The bacterial mixture is anaerobic, aerobic and facultative anaerobic bacteria. It usually

has three or more bacteria involved that work synergistically. It affects the immunocompromised and is easier to recognise and has a better prognosis when compared with the other subtypes. The mortality rate of Type I necrotising fasciitis is variable and depends on the immune status of the patient. Common causes of Type I NF are perianal sepsis, intra-abdominal sepsis and post-surgery necrotising fasciitis.

Type II is monomicrobial gram-positive sepsis which is usually Group A streptococcal or staphylococcus aureus infection from skin or throat infection. It is the second most common subtype and has been associated with 20-30% of infections. Presentation may initially seem innocuous however if not treated adequately is very aggressive and may be associated with toxic shock syndrome. The mortality of Type II is more than 32% and increases if associated with myositis and with toxic shock syndrome (TSS) is 23-44%. Immune suppression is not necessary and infection can be sporadic in nature.[4,13]

Type III is usually monomicrobial with a gram-negative organism, often marine (Vibrio and Aeromonas species) but not confined to it. It has been commonly described in Asia following ingestion of contaminated seafood or wounds being infected by contaminated water. Non-marine gram-negative infection is not very common and involves the Haemophilus influenzae, Klebsiella species or Aeromonas species (freshwater). Within this category, the digestive enzymes associated with marine subtype tend to increase its mortality rate (30-40%) when compared with the other gram-negative.[4,17]

Type IV NF caused by fungal sepsis which is related to traumatic jury i.e. burn injury and polytrauma patients with prolonged hospitalization or in transplant patients on immunosuppresion. candida is mostly associated with infection

in the immunocompromised population whereas mucor or rhizopus species are related to immune competent patients. Due to immune compromise the mortality rate in this group tends toward 50%.[4,17]

The classification by Sarani et al combines microbiology with anatomical location and depth of necrosis.[18]

Classification factor	Comment
Anatomic location	Fournier's gangrene of perineum/ scrotum
Depth of infection	Necrotising adipositis (most common) fasciitis, myositis
Microbial cause	Type I: Polymicrobial (most common) Type II: Monomicrobial Staphylococcus, Streptococcus, Clostridia Species Type III: Vibrio Vulnificus

Risk factors

The most common predisposing medical condition in patients with NF is diabetes mellitus with its impaired cutaneous wound healing and increased susceptibility to infection. These patients tend to have higher risks of amputation when compared to non-diabetics for limb NF.[19] However, other conditions which may predispose to a decreased immune status also contribute to susceptibility i.e. HIV infection, end-stage kidney disease, post-transplantation on immune suppressive drugs, other cancer types and liver cirrhosis.[20,21]

The other known risk factors contributing to the development of NF are intravenous drug use, peripheral vascular disease and increased age, particularly above 50 years have been related to high morbidity.[2,4,22] Neglected pressure sores or peri-anal sepsis

increases the risk of development of NF. Delay not only worsens the clinical presentation but negatively affects the clinical outcome if a large area is debrided.

In a Taiwanese hospital, Cheng et al noted that there are clinical parameters that are associated with higher mortality in diabetic and non-diabetic alike; these are related to admission hypotension and dyspnoea. Other features include the thrombocytopenia, hyperkalaemia and a positive blood culture. Diabetics though were more likely to have an amputation related to the treatment of NF.[19]

Although HIV related immunosuppression is a risk factor for perineal or anorectal infections and NF, it does not seem to have a worse prognosis. In literature describing the presentation of Fournier's gangrene in sub-Saharan countries, Meki et al found that the HIV infection was not statistically significant risk factor for mortality. Rather they also concluded that the body surface area that required debridement was far more significant.[23,24]

Even though the rates of new HIV infection have increased in the USA and South Africa alike; the access to antiretroviral medication has ensured that HIV can be treated like any chronic comorbidity. There is evidence that CD4 count below 200 cells/mm^3 and a viral load above 30 000 copies/ml have been associated with an increase with infectious complications and mortality.[25] The decrease in CD4 lymphocytes results in decreased wound strength.[26]

When Sandler et al investigated the outcomes of HIV/AIDS patients who have emergency surgery they concluded that in the emergency setting unless the patient had an AIDS defining disease the presence of HIV infection did not significantly affect the mortality or morbidity. However, if the patient did not have

viral suppression then poorer outcomes were to be expected in those patients.[25] These poor outcomes were the common post-surgical complications i.e. pneumonia, thromboembolism, wound complications, urogenital sepsis and myocardial infarctions. The proportion of morbidity and mortality was significantly higher in patients who had AIDS compared to well controlled HIV and non-infected patients.

Predictors of poor outcome

There are many factors reported by Kalaivani et al that are associated with a poor outcome. These are advanced age (particularly above 50 years), raised creatinine at the time of admission and delay of debridement by 24 hours.[20] In this series, the authors also noted a higher morbidity when a larger surface area is debrided. Lastly, it was noted that even though diabetic related infection is the most common co-morbidity, its presence is not a significant predictor of mortality.

Clinical presentation

The spectrum of clinical picture is wide, depending on the progression of necrosis. Initially, it can present like cellulitis (erythema, soft tissue swelling) and can be a diagnostic dilemma. Necrotising fasciitis tends to be tenser and extremely painful. This pain can be masked if patients have received anti-inflammatory medication. A clinical picture suggestive of 'cellulitis' with signs of systemic toxicity should alert the clinician to a potential diagnosis of NF. As necrosis progresses this might be more obvious with haemorrhagic bullae, anaesthesia, skin necrosis. These are late signs. Crepitus in the tissue is present with organisms that produce

hydrogen or nitrogen. Clostridium perfringens is the most commonly associated bacteria with crepitus. Signs of systemic toxicity include tachycardia, tachypnoea, arrhythmias, shock, metabolic acidosis, hypoxia and multi organ failure. Diagnosis usually requires a high index of suspicion. With established necrosis, the wound can produce greyish- black fluid which smells putrid.[1,4,11,14]

Diagnostic adjuncts

Late presentation of NF is usually an obvious diagnosis. The diagnostic dilemma question arises when the symptoms are early, this is when radiological assistance is necessary and can hasten surgical intervention. There are four imaging modalities each with advantages and disadvantages that allow for their use in the emergency setting. Plain x-rays which are readily available, show swelling of the soft tissue and the presence of gas in the subcutaneous which indicates gas forming organisms. The localisation of a foreign body as a source of infection can be confirmed on plain x-rays. However, it is unable to estimate the extent of tissue involvement.[27]

The use of ultrasound is operator dependant even though it is readily available, it may underestimate the extent of disease.[27] The typical features seen are an increase in the distortion of fascial layers, hypervascularity, or increased thickness of the subcutaneous tissue.[27] With the presence of soft tissue gas this may indicate abscess collection or necrosis.

Contrasted computed tomography (CT) features that are diagnostic of NF fascial air tracking, muscle oedema, fluid collections in fascial spaces that more than expected with oedema, subcutaneous oedema, lymphadenopathy and regional vasculature thrombosis.[28–30] The common side effects associated with this type of radiology is contrast associated

allergy and renal failure especially in diabetic or chronic renal failure patients. [27,31]

Magnetic resonance imaging (MRI) is the best modality for diagnosing soft tissue infections. Gadolinium based contrast medium is used therefore an anaphylactic reaction can be prompted however this is infrequent when compared to CT. Signs suggestive of NF are there is increased signaling on fluid sensitive sequences extending along deep thickened fascial planes. Fat suppressed T2 weighted images show varying inflammatory changes. Due to hypoperfusion the extent of disease evidenced by contrast enhancement may be underestimated. Gas in the deep fascial planes is not seen consistently on MRI as on CT. Nevertheless, the signal voids seen on gradient echo sequence is pathognomonic of NF.[27]

There can be doubt in the very early diagnosis of NF and a quick bedside test of making an incision on the affected area down to the fascia to confirm necrosis or even send a specimen for a frozen section.[32] This modality could be of some assistance where radiology is not readily available.

Risk indicators

The **L**aboratory **R**isk **I**ndicator for **Ne**crotising **F**asciitis(LRINEC) was developed by Wong et al, to aid in distinguishing the more lethal yet early NF from severe soft tissue infection. It uses biochemical parameters of C-reactive protein (CRP), white cell count, glucose, creatinine, haemoglobin and sodium, which are scored to a total of 13 points to calculate a probability score. These are used to categorise patients into a low, medium or high probability of their presentation being necrotising fasciitis.[33]

This study was a retrospective observational analysis of patients who presented with NF. The primary outcome was to differentiate early NF from complicated soft tissue infection.[33] Many investigators have tried to utilise the scoring system to acquire similar results to the initial LRINEC score, however, this has not proven to be possible. The negative - (94%) and positive predictor values (92%) have not been reproducible for LRINEC scores more than six in other studies though. CRP has been thought to be a routine investigation in working up patients. Unfortunately, many retrospective studies have not been able to completely adhere to the score because of its data inconsistencies.[34,35] Knowing that malignancy is a risk factor for developing NF, Foo et al showed that in haematological malignancy LRINEC was not a reliable score, 75% of patients who clinically were treated for NF had a score below six.[34,36] They postulate that this subset of patients has a low white cell count, thrombocytopenia and anaemia all of which are necessary for the calculation.

Even though it has not been fully validated, it continues to be presented in the management algorithms of NF as a useful adjunct to increase suspicion in severe or complex soft tissue infections.[34] Prospective studies specific to the utility of the LRINEC score are needed to validate its use in clinical practice or if the score needs to be amended to include some clinical parameters too. While the LRINEC score has been utilized to diagnose early NF, Menyar et al has shown that patients presenting with an LRINEC score above six are associated with an increase in septic shock, prolonged ICU admission and mortality[37]. Similarly, Su et al concurs that higher LRINEC scores are associated with sicker patients who are at higher risk for mortality and limb loss.[38]

Unlike the LRINEC score, the Fournier's' gangrene severity score (FGSI) introduced by Laor et al in 1995 includes clinical

parameters to determine the prognosis and survival.[39,40] These are clinically temperature, heart rate and respiratory rate alongside biochemical markers i.e. sodium, potassium, haematocrit, white cell count and bicarbonate. A score above nine indicates a 75% probability of death and thus those with a score below nine are associated with a 78% probability of survival. Currently, the studies that have been used to validate the use of FGSI have been retrospective and of those, the largest is reported by Corcoran et al who reported on their 10 year experience.[41] They did however agree that the limitation of their study was its retrospective nature and concluded that there needs to be a prospective evaluation to improve the quality of evidence for the use of the FGSI score.

A prediction of death score has been created by Anaya et al using the following variables: Minor - HR more than 110; temperature less than 36°C; serum creatinine 132∝mol/L and Major - WCC >40, age >50years and Hct >50%. The total points for the score were 12, with the probability of mortality being 6% if less than two points and 88% if there were more than six points.[42] This is a retrospective analysis from which patients can be stratified to ones who need more intensive care (ICU) and those who may not require intensive intervention. Prospective studies to validate mortality prediction are still needed.

Antimicrobial treatment

The antibiotic guidelines vary from country to country. Empiric therapy needs to have broad coverage to include gram-positive, gram-negative and anaerobic organisms. Both the British and American antibiotic guidelines recommend the use of anti-methicillin-resistant staphylococcus (MRSA) (daptomycin or vancomycin) and broad-spectrum gram-negative cover (piperacillin-tazobactam, extended-spectrum cephalosporins or

carbapenems) and anaerobic coverage (metronidazole or clindamycin). Antifungal cover (fluconazole) should be added if there is microbiological confirmation of fungal sepsis.[17] Gentamycin is added to the prescription chart in the British guidelines whenever the source of sepsis is intra-abdominal, pelvic or perineum. This is based on local resistance patterns. A multi-institutional study performed in the USA by Kao et al showed that in the cultured specimens the majority gram-positive organisms were MRSA (35%) compared to sensitive staphylococcus (16%) or streptococcus only in 15%. Also noted in that series was the low number of gram-negative (10%), anaerobes (5%) and fungi (4%) cultured.[43] In a retrospective review done by Das et al in New Zealand showed that gram-positive organisms were more common in patients diagnosed with NF over a 6-year period.[44] Of the gram-positive organisms, the streptococcus species (41%) were the most common followed by staphylococcus species (31%). The methicillin-resistant staphylococcus (MRSA) accounted for 3.1% of NF cases, gram-negative bacilli accounted for less than 10% and anaerobes were less than five percent.

Perineal NF is commonly caused by commensal organisms of the rectum, vagina and urethra. Bjurlin et al showed in a retrospective series that the majority (83%) of their cultured specimens were polymicrobial. In descending frequency Bacteroides, E-coli, Streptococcal and methicillin sensitive Staphylococcus were cultured. However, monomicrobial sepsis showed a dominance of staphylococcus infection (28%) with MRSA accounting for 14% of the total infections.[45] This group also noted that candida infections (7%) particularly in diabetic patients are increasing as well as community acquired MRSA.[45]

Group A streptococcal infection of the soft tissue is sensitive to beta lactam antibiotic and evidence shows that when given to mice in combination with lincosamide (clindamycin) the microbial numbers are decreased significantly despite a delay in initiation of

therapy.[46] Stevens et al explain that the penicillin's mechanism of action is based on binding the penicillin binding proteins (PBP) which are expressed on the wall of the organism. The number of these PBP are varied based on the growth phases and are significantly reduced during the stationary phase which decreases the efficacy of beta lactam organism. Therefore, the addition of lincosamide can suppress toxin synthesis, decrease the PBP's which decrease the integrity of the organism wall and has a longer post antibiotic effect.[13,46]

In South Africa empiric therapy includes co-amoxiclavulanic acid until clinical resolution of symptoms following surgical debridement. However, if it is not available then ampicillin, gentamycin and metronidazole should be given. In case of refractory of penicillin allergy the antibiotic cover should include clindamycin and ciprofloxacillin.[47] Unlike the first world countries the methicillin resistant staphylococcus is not covered in the empiric therapy of NF due to its infrequency in community acquired sepsis.

Specimen collection

De-escalation of antibiotic therapy is determined by obtaining adequate specimens that can be evaluated for microbiology. Ensuring the microbiologist receives adequate specimens aid in the clinical management of the patients. Therefore, it is imperative that the surgeon samples correctly. When fluid/aspirate is collected the volume must be adequate and not mixed with any other media. The site needs to be sterile (aseptic technique) and the ideal site is the deep portion of an infected area so as not to confuse the tissue with contamination of samples. Tissue size is to be approximately 3-4mm^3 for delivery of similar strips of tissue for various media.[48] Collection of swabs

of the tissue are not adequate samples as they do not have appropriate volumes required for inoculation into the different media. Similarly, the swab strands trap the fluid and do not allow for proper microbiology identification.

Surgery and timing

The cornerstone of NF management is surgical debridement. The fascial necrosis and sepsis are poorly perfused and hence antibiotic penetration alone is not adequate. The necrotic tissue allows bacterial growth and perpetuates the vicious cycle of spreading sepsis. The purpose of debridement is to remove necrotic tissue, collect adequate tissue specimen for culture and sensitivity and allow adequate assessment of surface area or depth of sepsis with deep compartment involvement that might require limb ablation.[1] All necrotic and inflamed tissue should be removed to include the fascial layer. Tunnelled debridement should be avoided. Although the skin and subcutaneous tissue above necrotic fascia might still look viable, it is only a matter of time before it also becomes necrotic as the perforator vessels are involved in sepsis and thrombosis. This also doesn't allow to fully ensure a healthy margin is reached as the direct vision of fascia is impaired. The "finger test" where the finger can easily able to traverse tissue planes can be used as a guide on how far the debridement should go. A margin of bleeding healthy tissue should be left behind.[4,11] The surface area that is debrided should not be considered while there is still unhealthy tissue involved as it has already been shown to associated with poor outcomes if there is inadequate debridement.

Literature confirms that complete adequate debridement is imperative to decrease morbidity and mortality.[32,49] Ideally early debridement (less than 12 hours) is associated with lower mortality and morbidity. Notably, delay (more than 24

hours) may result from severe hypotension and the need for resuscitation. The septic shock process could is the reason for their overall poor outcome.[50] Kobayashi et al showed in a retrospective study of early debridement that patients who underwent delayed debridement have an increased risk of multiple relook debridements and acute renal injury. Thus, the World Society of Emergency Surgery (WSES) consensus meeting in 2018 recommends that early debridement for NF should be sought.[11] Following initial debridement, the wound ought to be inspected daily until confirmation of no sepsis and treated surgically when required.[1]

Closure of soft tissue defect should be done soon after an infection has been excluded, a simple split skin graft on a granulated bed suffices. Granulation tissue can be encouraged by the use of negative pressure dressing. However, more complex tissue closures are to be planned for if there is extensive body surface involvement.[51]

Ancillary therapy

Hyperbaric oxygen (HBOT) continues to be recommended as an adjunct to therapy for NF. The delivery of 100% oxygen directly to the wound bed allows for a high tissue concentration. This improves leukocyte function, inhibition of anaerobic growth, inhibition of toxin formation and enhancement of antibiotic therapy.[11,51] Protocols on the administration of the oxygen vary. Cocanour et al recommend 2.3 atmospheres given 2-3 sessions daily each lasting 30-90 minutes until healing occurs.[51] A high incidence of seizures due to oxygen toxicity is a potential side effect, thus patients should be monitored closely. Another side effect is baro-pressure particularly in the middle ear which should be managed prophylactically via decompression. Though potentially useful its use in standardized protocols remains

controversial, studies are ongoing related to the various uses of HBOT.

Intravenous immunoglobulin G (IVIG) has been mentioned as an adjunct in the management for NF. The rationale for use is its ability to neutralize extracellular toxins that mediate pathogenesis. Primarily investigated in group A streptococcal infection which is very severe and is known to be caused by toxin producing bacteria. A double blind randomized trial was terminated early due to slow patient recruitment which was meant to investigate the efficacy in GAS infection.[52] The interim results suggest though that there was decreased renal failure and neutrality of super-antigens in the group treated with IVIG. Recently another double-blind placebo-controlled trial compared placebo to IVIG according to self-reporting patients on functionality. IVIG or normal saline was given over three days for the patients admitted in ICU along with clindamycin (which also lowers virulence of bacterial antigens). No significant difference was noted in post admission performance or ICU related complications.[53] Therefore, the use of IVIG still has not been proven to add benefit in the NF, and thus not included in most treatment algorithms.

Reltecimod (AB103) is a biologic agent which is now being investigated for use in the aftermath of an infection. It works by being a CD28 mimetic and inhibits the binding of the superantigen to the T helper cell receptor. Since this experimental drug has shown efficacy in animal models it was tested for safety in human subjects and showed that there were no lethal adverse effects. Secondly, the higher dose administration of the drug was related to lower organ failure post day seven in ICU compared to placebo. Further investigation is necessary to then prove efficacy as related to NF at the higher dose that was given in the pilot study.[54]

NF is a lethal disease with a high morbidity and mortality rate. Being able to recognize the risk factors allows for the index of suspicion to increase thus management is initiated earlier. Notably when the microbiology is known the antibiotic stewardship is more accurate especially in resource limited health systems.

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Publication ready manuscript

Title: Describing the resistance patterns of necrotising fasciitis in Acute Care Surgery

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Abstract

Objective-- This study aims to identify the microorganisms and antibiotic resistance patterns in necrotising fasciitis.

Methods This is a retrospective audit over two consecutive years(June 2015 - July 2017) of all patients who had surgery for necrotising fasciitis at the ACS unit in Cape Town.

Results Necrotising fasciitis accounted for 15% of all skin and soft tissue sepsis that required surgery. There were ten male (52.6%) and nine female (47.4%) patients. The most common co - morbidity was diabetes mellitus in 10 (52.6%) patients, the compliance and control were monitored by glycosylated haemoglobin (HbA1C) in 50% of the diabetic group, with a mean of 8.98 (Range 5-12.9). Fifteen percent of cases (n=3) had a confirmed diagnosis of HIV, with a negative result in 8(42%). ICU was required in three patients two of whom were on inotropes and one patient required renal replacement therapy. Surgery was performed within 24 hours for 11 (57%) patients. The most common anatomical site for debridement was perineum in nine patients (47%). Monomicrobial infection was the most common subtype of necrotising fasciitis with methicillin sensitive staphylococcus aureus in 5 (26%) as the predominant microbe. Gram-negative organism Escherichia coli was the second most common monomicrobial infection. All Gram-positive organisms were sensitive to cloxacillin and co-amoxiclavulanic acid. Two gram negatives (15%) of the 13 organisms cultures were resistant to co-amoxiclavulanic acid. The 30 day mortality was 15 %.

Conclusion In our limited series monomicrobial infection is the most common subtype. 15% of the community acquired organisms were resistant to the empiric antibiotic of choice co-amoxiclavulanic acid.

Article text

Introduction and background

Necrotizing soft-tissue infections (NSTIs) are life-threatening, invasive often rapidly spreading soft-tissue infections which can involve any or all layers of the skin and soft-tissue compartment. It primarily involves the relatively avascular muscle fascia and can later cause secondary necrosis of surrounding subcutaneous fat and skin. Classically the appearance of tissue has been described by the friability of the tissue and loss of tissue planes which is associated with dish-water grey exudate with or without purulent collections.[1] The incidence of NSTI in the western countries has been described as 0.4 per 100 000 population and associated with mortality ranging from 30-80% depending on the subtype and immune status of the patient.[2] The pathophysiology of NF involves a breach of the skin barrier protection or by haematogenous spread of the bacterium.[1] Immune suppression due to various chronic ailments e.g. diabetes mellitus has been associated with an increased predisposition for NF. In South Africa, we do not know the incidence or mortality of necrotising fasciitis. The underlying socioeconomics of a middle to low income country results in delayed access to health care, delayed diagnosis and delay to surgery. Immune suppression from poorly controlled diabetes or untreated HIV could impact outcomes. There is no data to support or refute these clinical impressions. There are sparse data on microbiology and antibiotic resistance to aid local antibiotic guidelines.

The purpose of this study is to identify what is the microbiology and resistance patterns of necrotizing soft tissue infection the Acute care surgery unit in Cape Town Groote Schuur hospital is treating.

Methodology

A retrospective review was performed of operative reports and theatre records to identify patients who had surgery for soft tissue infection in the Acute Care Surgery (ACS) unit at Groote Schuur Hospital for 24 months from 1 June 2015 to 31 July 2017. The inclusion criteria were patients above the age of 18 years presenting to the ACS unit who required surgery for necrotising fasciitis. The anatomical sites were the torso, abdomen, perineum and lower extremities. Excluded patients were paediatric patients (below 18 years), debridement that was performed at a referring institution, anatomical sites that are referred to other speciality and hence surgery not performed by ACS i.e. otolaryngology and orthopaedic surgery and all non-necrotising soft tissue sepsis.

Data were retrieved from clinical notes, operation reports and National Health Laboratory Services (NHLS) database. Data collected included demographics (gender, age), time of admission and surgery, presence of diabetes and human immune deficiency virus (HIV), biochemical markers of compliance with a recent HbA1C, HIV viral load and CD4 count and use of antiretroviral therapy. Admission vital signs (blood pressure, pulse rate and temperature) was recorded. We checked and collected the NHLS database for the following tests: presentation white cell count, renal function, blood culture during that admission, and tissue cultures sent during surgery. Organ failure and mortality during the same admission was recorded.

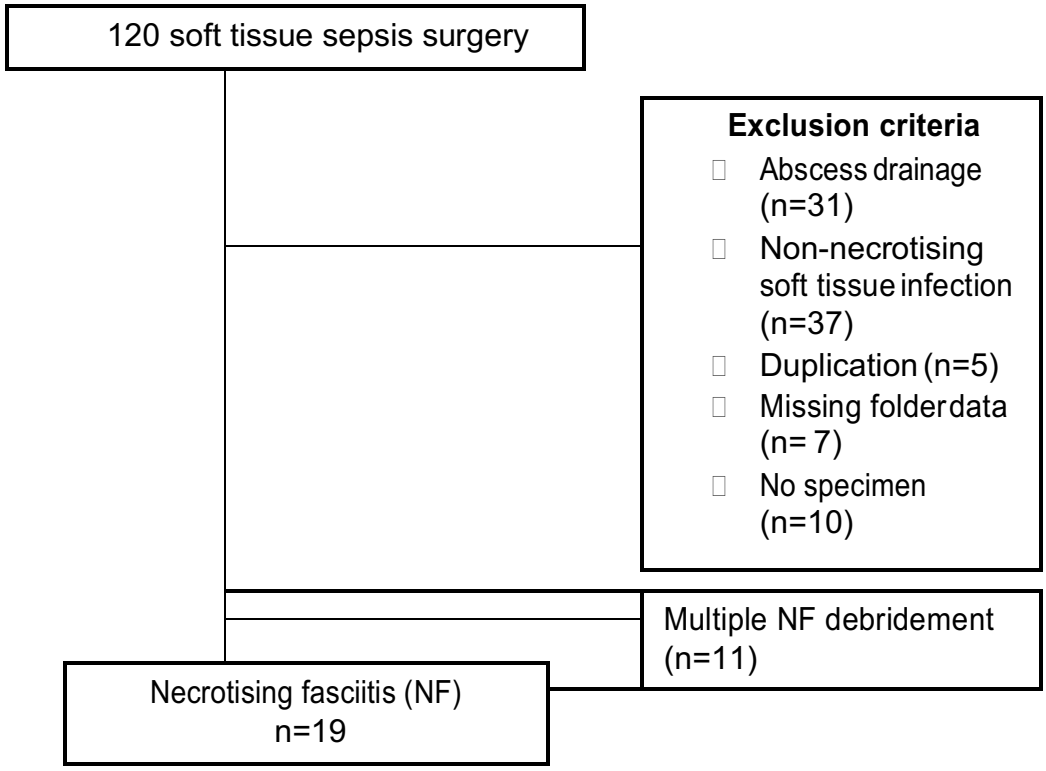
Data was captured on an Excel spreadsheet on a password protected computer that was only available to the investigators. Data will be analysed using Mathematica version 11.3, Wolfram Research, Urbana, Illinois, USA. The descriptive statistics were computed using the Microsoft Excel software (2017). Mortality is calculated at discharge and confirmed on Clinicom, which is a hospital database of all the patients reviewed in the public health care system.

The protocol was approved by the ethics committee at the University of Cape town (HREC ref 569/2018).

The NF classification referred to is based on microbiology. The commonly used antibiotics are co-amoxiclavulanic acid, clindamycin and ciprofloxacin for community acquired NF. HIV testing is not mandatory for all patients unless requested by the patient or if there is clinical suspicion. Glycosylated haemoglobin (HbA1C) was also not routinely checked and was dependant on clinician decision. Diabetic foot sepsis and necrosis were excluded from this study inadvertently as it is seen as a different disease process with multifactorial aetiology for sepsis and perfusion.

Results

There were 120 operations performed for soft tissue sepsis from June 2015 to July 2017, at ACS Groote Schuur hospital. Simple abscess drainage was performed on 31 cases and 37 patients had a debridement for non- necrotising soft tissue sepsis. These patients were excluded from our study. A further 17 cases had to be excluded as enough data could not be retrieved from patient notes. The number of duplication due to various reasons was 5.



Flow chart of patients

Of all soft tissue sepsis surgery performed in that time frame (n=120), 15.8% (n=19) had surgical confirmation of necrotising fasciitis with microbiology samples available for analysis in this study. There were nine females (47.4%) and ten males (52.6%). The mean age of the patients was 41 (SD 15.76). Ten (52.6%) patients were known with diabetes and three of those were insulin dependent. HbA1C was checked in 50% of the diabetic group and none of the non-diabetic group. The mean HbA1C was 8.98 (range 5-12.9)

HIV ELISA was performed on ten patients, two were positive and eight negative. One patient was diagnosed previously and on anti-retroviral therapy. Seven patients were never tested for HIV.

The mean heart rate on admission was 99 beats per minute with 42% (8) being tachycardic (HR>100) and mean systolic blood pressure was 126mmHg. Two patients presented in septic shock requiring ICU admission and inotrope support. The mean white cell count (WCC) was 22.3 cells/mL^3. Acute kidney injury was found in five (26.3%) patients with one requiring renal replacement therapy while in intensive care. There were three ICU admissions.

TABLE 1: DEMOGRAPHICS AND CLINICAL PARAMETERS

		N	%	
GENDER	Male	10	52.6	
	Female	9	47.4	
RISK FACTORS	Diabetes	10	52.6	
	HIV	3	15.7	
		Mean	**SD**	**Range**
AGE	Age *(Years)*	41.84	15.76	20-72
VITAL SIGNS	Heart rate *(Beats / minute)*	99.05	18.96	67-140
	Systolic Blood pressure *(mmHg)*	126	27.96	70-180
	Temperature *(Degree Celsius)*	37.4	0.78	36.4-39
	White cell count *(Cells/mL^3)*	22.38	10.44	4-49
	Creatinine *(mmol/L)*	148	164.25	38-669
SURGERY TIME	Time to surgery *(Hours)*	11.74	12.63	1-48

Surgery was performed within 24 hours in 11 (57.89%) of which seven was within six hours. Three patients (15.78%) waited longer than 24 hours although the mean time to surgery was 11.74. For five patients the data could not be retrieved regarding waiting time to theatre.

The anatomical area debrided was the perineum with nine patients (47.36%), then lower limb six (31.57%), and four torso (three anterior abdominal wall and one retroperitoneal). Re-debridement was deemed necessary on clinical grounds

indicated and performed for six patients with a further two requiring more than one relook. No patients had flaps or skin-graft and all healed with secondary intention. There were no amputations performed.

Intra-operative specimen sent were as follows: nine tissue cultures and three pus swabs. The microscopy showed mixed flora in seven samples, however, more than one organism was identified only in three samples. There were five gram-positive organisms, three staphylococcus aureus, one Streptococcus anginosus (STRAN) and one Streptococcus constellatus subsp pharynges (STRCP). Three cultures identified a single bacterium. These were two pseudomonas (Putida and Aeruginosa) and one Enterobacter aerogenes. Three patients had a mixed growth of two or more gram-negative and anaerobic organisms (Escherichia coli, Providentia stuartii, Proteus mirabilis, Citrobacter freundii and Enterococcus faecium). None of the blood cultures taken on admission yielded any organism growth.

The three Staphylococcus aureus organisms were all sensitive to cloxacillin, one was resistant to penicillin and one was resistant to penicillin, macrolides and clindamycin. The STRAN was a sensitive organism and STRCP was only resistant to macrolides. All three pseudomonas were sensitive to ciprofloxacin and cephalosporins. Two of the pseudomonas were resistant to trimethoprim. The two Escherichia coli were both resistant to ampicillin/amoxicillin but sensitive to co-amoxiclavulanic acid, cephalosporins and aminoglycosides. The enterobacter aerogenes was resistant to co-amoxyclavulanic acid, ampicillin, cefoxitin but sensitive to ciprofloxacin, cefepime and aminoglycosides. The enterobacter faecium was also a moderately resistant organism with resistance to ampicillin and aminoglycosides. The proteus mirabilis was a sensitive

organisms. The citrobacter freundii was a moderately resistant organism with resistance to ampicillin, co-amoxyclavulanic acid and cephalosporins. It was sensitive to carbapenems, ciprofloxacin, aminoglycosides and trimethoprim. Of the 13 organisms cultured two (15.3) were resistant to the empiric antibiotic of choice co-amoxiclavulanic acid. All gram-positives were sensitive to cloxacillin and co-amoxiclavulanic acid. Two gram- negatives were resistant to co-amoxiclavulanic acid and all were sensitive to ciprofloxacillin.

TABLE 2: MICROBIOLOGY AND RESISTANCE

	Organism	Resistant antibiotics
GRAM POSITIVE		
1	Staphylococcus Aureus	*Bactrim*
2	Staphylococcus Aureus	*Ampicillin*
3	Staphylococcus Aureus	*Ampicillin*
		Erythromycin
		Azythromycin
		Clindamycin
		Bactrim
4	Streptococcus Constalatus SP	*Erythromycin*
		Azythromycin
5	Streptococcus Anginosus	
GRAM NEGATIVE		
6	Psuedomonas Putida	*Bactrim*
		Tigecycline
7	Enterobacter Aerogenes	*Co-Amoxyclavulanic acid*
		Ampicillin
		Cefoxitin
		Colistin
8	Psuedomonas Aeruginosa	
9	Psuedomonas Aeruginosa	*Bactrim*
10	Citrobacter Freundii	*Ampiciilin*
		Co-Amoxyclavulanic acid
		Cephalosporins
11	Enterococcus Faecium	*Ampiciilin*
		Gentamycin
		Streptomycin
12	Escherichia Coli	*Ampiciilin*
		Bactrim
13	Proteus Mirabilis	*Colistin*
		Tigecycline

In hospital mortality rate was 15.7%. All three ICU admissions died. The aetiology of NF in the mortality group was appendicitis with retroperitoneal sepsis, Fournier's gangrene and abdominal wall sepsis. Two of these patients were diabetic and one was HIV positive.

Discussion

The ACS unit serves a diverse community of middle to low income population in an urban and some under-developed communities. Community acquired resistance is not as prevalent as in first world countries like the USA where up to 26% of community staphylococcus sepsis is MRSA[3]. This is a small case series of NF, being retrospective data retrieval was poor. The total number of cases was significantly less than what we perceived our clinical load was. The diabetic foot necrosis and progressive sepsis were not included in this study. That contributed towards the decreased total number of cases and amputations performed. The ACS unit was also in its inception years and patient management had not been standardised. And yet there were a few learning points from this case series.

The incidence of NF is increasing globally. This has been attributed to worldwide obesity and hence increasing numbers of patients with diabetes mellitus. There was a 35% cumulative increase between 2001 and 2010 with a 2.7%per year increase in a study from Texas.[4] This is the largest cohort study on NF epidemiology trends in the literature. There are small case series over a period of time suggesting a global increase in incidence.[5] The incidence figures for many African and other middle to low income countries are lacking including South Africa. This study was not aimed or powered to work out the incidence in our community. However, we can estimate that the South African incidence of NF is on the rise together with the rise of obesity and diabetes.

This series has reiterated that septic markers like temperature, heart rate and WCC are not always raised despite patients having frank necrosis. The risk prediction scores have failed to

be diagnostic for NF due to these variables not responding uniformly. NF remains a clinical diagnosis and requires a high index of suspicion.

This disease process affected young diabetics most in our study (50% diabetic, mean age 41). This was similar to the systematic review by Marchesi which looked at 15 studies and found diabetes to be a risk factor in 60% of patients.[6] Only half the diabetics had their glycaemic control checked with HbA1C with a mean above 8. Every contact with health care is an opportunity to check compliance, optimise medication and intervene should there be any warning signs. Since the time of data collection, the ACS in house diabetic protocol has changed and currently, we check HbA1Cs on all diabetics unless already done within 3 months of admission. Our endocrinologists work closely and advise on optimisation. The dieticians and diabetic nurse will be involved as needed to aid the patient.

The prevalence of HIV in South Africa is 20.4% and 12 % of the adults in Western Cape are infected with HIV.[7] HIV was not a major risk factor associated with NF (15.7%) despite the increased prevalence of HIV in our communities. This also is in line with other surgical complications literature on HIV positive patients. In the emergency surgery setting, well controlled HIV infection does not increase morbidity and mortality.[8,9] It is also surprising that with such high prevalence in the country, this hospital admission was not used as an opportunity to counsel the patient for an HIV test on all. The current practice in ACS has also changed. All admitted patients are counselled and if willing, a test is performed. HIV has become a chronic illness and many life-threatening complications of AIDS can be prevented by treatment.

Monomicrobial gram-positive NF was the most common like in other series, however, the causative organism here is staphylococcus aureus instead of streptococcal species[10]. The second prominent organism was Escherichia coli infection in isolation or polymicrobial infection. This infection was commonly seen in patients who have perianal sepsis.

Community acquired methicillin resistant staphylococcus aureus was not present in any of our patients. This supports the empiric antibiotic protocol of omitting vancomycin. Currently, the institutional recommendations of covering gram-negative and gram-positive organisms and including the anaerobes are validated by our findings of the typical microbes found in NF.[11] The gram-negative organisms, however, showed some resistance to co- amoxiclavulanic acid. Two of the 13 organisms found in the first debridement specimen (15.3%) were resistant to co- amoxiclavulanic acids which are the empiric antibiotic of choice. This being a small case series is difficult to interpret to change management guidelines and policies. We need to do an adequately powered study to validate these results and thus use this as a pilot study.

The extremities were seen to be frequently affected in international literature.[12,13,10] However, in this series the perineum was more prominent. Due to the exclusion of diabetic foot sepsis and NF associated with that, this series is not a true reflection of all NF cases operated on.

Forty percent(n=4) of the samples that were taken from the perineal location did not yield any results as some were rejected by the microbiology laboratory. These could be as a result of specimen incorrectly labelled, inadequate samples, or inappropriate preservation of tissue handed in for processing. All surgeons and registrars should be educated about the correct

sampling techniques and should be encouraged to send tissue for MCS for all patients with NSTIs.

Timing of the debridement was primarily within 48 hours and when the index of suspicion was increased the debridement occurred within six hours of being seen. Though there is no “golden hour “on the timing of debridement in literature, the standard practice is to aim for debridement within 12 hours [14]. The delayed group did not contribute to patients who had poor outcomes in this series. Regardless NF is lethal and expedited surgery within 12 hours of admission should be the aim, source control is paramount.

The mortality in our small case series was 15% (n=3), lower than reported in the literature. Of the three patients who succumbed to death, only one patient was infected with HIV and antiretroviral naïve. The other two were diabetic patients. All three deaths were on patients with organ failure requiring support and they had torso NF (appendicitis, abdominal wall and Fournier’s gangrene) These are predictors of poor outcome and the limited finding of this study supports that.

Conclusion

This is a small case series but has highlighted a few aspects of NF and patient management. It's the basics we need to do right. For e.g. early diagnosis, expedited source control while obtaining adequate samples at debridement as it could alter treatment in 15% and moving forward with better optimisation of chronic diseases. Patients with established organ failure are at high risk of mortality. An adequately powered prospective analysis of NF resistance patterns is necessary for our practice as this pilot study suggests that our empiric antibiotic of choice might not cover all community acquired organisms.

Limitations

The management for the chronic comorbidity is physician dependent and thus not all the variables are equal, recording of past medical history. A protocol has since been devised to equate for some of the same variables i.e. diabetics on medication need to be followed for compliance to medication evidenced by HBA1C. The incidence of HIV in surgical emergencies is not known if the test is not readily done or recorded as part of co morbidities. Now in keeping with the WHO guidelines, when a patient is newly diagnosed regardless of the CD4, antiretrovirals are initiated. That suggests that the records need to reflect the viral load and compliance with antiretroviral therapy.

Future investigation

The incidence of obesity in our population but has not previously been accounted for when describing debridement of soft tissue infections. In the era of antiretroviral therapy, HIV is becoming more of a well-controlled comorbid disease. The evidence is needed relating to incidence and outcomes related to emergency surgery in resource-limited society.

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Academic approval documents

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OMB

Dear Dr Kloppers

PROJECT TITLE: DESCRIBING THE RESISTANCE PATTERNS FOR NECROTIZING FASCIITIS IN ACUTE CARE SURGERY (MMED Candidate - Dr T Mabogoane)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 September 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Tumiso Mabogoane will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

UNIVERSITY OF CAPE TOWN

Department of Surgery
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1 Jun 2018

Dr T Maobogoane

Department of Surgery
University of Cape Town

Dear Dr Maobogoane

RE: Project 2018/045

PROJECT TITLE: Necrotising Fasciitis: Does The Antibiotic Shotgun Work Or Should We Aim Higher?

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

Yours sincerely

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."