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ORIGINAL PAPER

Necrotizing fasciitis, causative agents and management: a five-year retrospective study in two tertiary care hospitals in Central Malaysia

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Abstract

Purpose Necrotizing fasciitis (NF) is a rapidly progressive inflammatory infection of the fascia, with secondary necrosis of the subcutaneous tissues. The severity of the disease depends on the virulence of the organism and host immunity. There is a paucity of reports on the prevalence of NF causing pathogens and management.

Methods Retrospective data of patients treated for NF were collected from two tertiary care hospitals in Central Malaysia between January 2014 and December 2018.

Results A total of 469 NF patients were identified. More than half of the NF patients were males (n = 278; 59.28%). The highest number of cases was found among age groups between 30 and 79, with mean age of 56.17. The majority of the NF cases (n = 402; 85.72%) were monomicrobial. *Streptococcus* spp. (n = 89; 18.98%), *Pseudomonas aeruginosa* (n = 63; 13.44%) and *Staphylococcus* spp. (n = 61; 13.01%) were identified as the top three microorganisms isolated. Among the 469 NF cases, 173 (36.8%) were amputated or dead while 296 (63.1%) recovered. *Proteus* spp. (n = 19; 12.93%), *Klebsiella pneumoniae* (n = 18; 12.24%) and *Escherichia coli* (n = 14; 9.52%) were associated with all types of amputations. The most common antibiotic prescribed was unasyn (n = 284; 60.56%), followed by clindamycin (n = 56; 11.94%) and ceftazidime (n = 41; 8.74%). A total of 239 (61.8%) recovered while 148 (38.2%) were either amputated or dead when managed with the unasyn, clindamycin or ceftazidime.

Conclusion This study represents the largest NF cases series in Malaysia highlighting the causative agents and management.

Keywords Necrotizing fasciitis · Malaysia · *Streptococcus* spp. · *Pseudomonas aeruginosa* · *Staphylococcus* spp. · Unasyn

Introduction

Necrotising fasciitis (NF) is a type of soft tissue infection caused by flesh-eating bacteria. The bacteria enter through the skin following any major or minor trauma compromising skin integrity such as needle puncture, insect bites, burns, laceration, surgical trauma or from the haematogenous spread [1, 2]. NF infection is usually characterised by widespread

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necrosis of the skin, subcutaneous tissue and superficial fascia [3]. It encompasses a broad clinical spectrum of disease from cellulitis, carbuncles, abscess to Fournier's gangrene [3]. Management of NF infection is often complicated and start with broad spectrum antibiotic, drainage, surgical debridement, narrow-spectrum antibiotic, continuous clinic monitoring and post-operative wound management [4].

NF consist of four types: type I, II, III and IV [5, 6]. Type I is a polymicrobial infection (aerobic and anaerobic) affecting mainly the elderly, and those with underlying illnesses. Type II involves monomicrobial infection involving mostly Gram-positive organisms; group A streptococcus and occasionally by methicillin-resistant *Staphylococcus aureus* (MRSA), it affects all age groups without underlying diseases [7]. Type III are also monomicrobial caused by Gram negatives such as *Aeromonas hydrophilia*, *Vibrio vulnificus*, *Escherichia coli* and *Bacteroides* spp. and Gram-positive Clostridial species. Type IV are fungal associated and are rare. Type I and II are known to cause the vast majority of NF [8].

Necrotizing fasciitis affects 0.3 to 5% of every 100,000 people [9, 10] including 0.022 to 0.843 per 100,000 children [11]. A recent study from Thailand reported 15.5 NF cases per 100,000 population [12]. Delayed or inadequate preliminary therapy showed a mortality rate of 38% compared to 4.2% in patients receiving early and aggressive treatments [13]. Delayed treatment is also associated with extensive loss of soft tissue leading to limb loss, renal failure, septic shock and increased risk of mortality [14, 15].

Piperacillin-tazobactam is one of the preferred antibiotic for the polymicrobial infection alternatively, cefotaxime and metronidazole, or ampicillin and sulbactam (unasyn) with clindamycin are recommended [16]. The addition of glycopeptide like vancomycin is recommended when causative agent cultured is MRSA or if the patient had recent hospital admission or antibiotic exposure [4]. If the infections are due to *A. hydrophilia* or *V. vulnificus*, combination of doxycycline with ceftriaxone or cefotaxime or ciprofloxacin is recommended [17].

There appears to be a paucity in reports regarding the actual causative organisms and details of the disease regionally. The study aimed at outlining the distribution and prevalence of causative organisms, management and evaluation of the associated organisms with different types of amputations. These data are vital in guiding clinical practice protocols, clinical practice guidelines and overall successful treatment of NF.

Materials and methods

The study was approved by the Medical Research and ethics committee, Ministry of Health Malaysia (NMRR-19-1871-47903). Retrospective data of patients treated for NF were collected from two tertiary care hospitals in Central Malaysia (Hospital Seremban and Hospital Ampang) from January 2014 to December 2018. A review of each patient's clinical record for NF diagnosis were performed, data on patient demographics, clinical presentation, aetiological agents, type of NF, site of infection and clinical management (antibiotic regime) was retrieved. Only patients who were clinically and microbiologically defined as NF were included in the study. Data was analysed using statistical package for social sciences (SPSS) software version 25. Descriptive characteristics were obtained as mean, frequency and percentages.

Results

Sociodemographic characteristics of respondents

Table 1 shows the sociodemographic characteristics of respondents. A total of 469 patients were identified with NF from the five year retrospective data obtained from the two hospitals. The results show that majority (59.28%) were males. The median age of the respondents was 56.17 (± 11.99), age group 50–59 showed the highest number of cases. Majority were Malays (66.7%), followed by Indians (21.7%).

Patients and aetiological agents for NF

Table 2 shows the distribution of microorganism associated with NF cases. The results indicate that 402 (85.72%) out of 469 NF

Table 1 Prevalence of NF in relation to sociodemographic characteristics of respondents

Variable	Total (n = 469)	
	Frequency	Percentage
Gender		
Male	278	59.28
Female	191	40.72
Age (mean ± SD)	56.17 ± 11.99	
< 29	3	0.64
30–39	42	8.96
40–49	88	18.76
50–59	150	31.98
60–69	119	25.37
70–79	58	12.37
80–89	7	1.49
90–99	2	0.43
Race		
Malay	313	66.74
Indian	102	21.75
Chinese	48	10.23
Others (Orang Asli and Indonesian)	6	1.28

Table 2 Distribution of microorganism and antibiotics used in the studied population

	Total (n = 469)	
	Frequency	Percentage
Microorganism		
Gram positive	n = 180	38.4%
Streptococcus spp.	89	18.98
Pseudomonas aeruginosa	63	13.43
Staphylococcus spp.	61	13.01
Enterococcus spp.	30	6.40
Gram negative	n = 149	31.78%
Pseudomonas aeruginosa	63	13.44
Klebsiella pneumoniae	44	9.38
Proteus spp.	42	8.96
Others	73	15.55
No growth	60	12.79
Mixed growth	7	1.49

patients were infected by monomicrobial organism, seven (1.49%) had polymicrobial infection and 60 (12.79%) were culture negative. As illustrated in Table 2, Gram-positive pathogens were detected in 180 (38.4%) NF patients, while 149 (31.78%) showed infection by Gram-negative organisms. *Streptococcus* species was found to be the most common among the Gram-positive (n = 89) and *Pseudomonas aeruginosa* (n = 63) as the frequently encountered Gram-negative.

Amputation was required in 147/469 (31.34%) NF cases at different levels (Table 3). *K. pneumoniae* and *Proteus* spp. followed by *P. aeruginosa* and *Streptococcus* spp. were the most predominant pathogens associated with amputation. As observed in the Table 4, *Proteus* spp. could be noted as the leading cause of all types of amputations.

Association of causative organism and antibiotics with outcome

A tripartite relation between causative agent, antibiotic regimen and outcome was investigated to determine the suitable antibiotic for recovery. The subjects were divided into two categories such as recovered (no death or no amputation) and not-recovered (death or amputation). In total, 173 (36.8%) were amputated or dead while 296(63.1%) recovered. As shown in Table 4, it is found that ceftazidime followed by unasyn and clindamycin showed most recovery. Unasyn was prescribed for most cases and it showed good recovery for both Gram-positive and Gram-negative organisms (Table 5).

Discussion

Necrotizing fasciitis is currently reported globally and is known to be caused by many species of microorganisms (types I to IV above). In the two studied hospitals in Malaysia, it was found that NF are most frequently caused

Table 3 Microorganism in relation to the amputation types

Microorganism	Amputation n = 147 (%)	AKA n = 39 (%)	BKA n = 74 (%)	Lower limb n =31 (%)	Transhumeral n = 3 (%)
Proteus spp.	19 (12.93)	2 (5.13)	14 (18.92)	2 (6.45)	1 (33.33)
Klebsiella pneumoniae	18 (12.24)	7 (17.95)	4 (5.41)	7 (22.58)	0
Pseudomonas aeruginosa	15 (10.20)	3 (7.69)	10 (13.51)	2 (6.45)	0
Streptococcus spp.	14 (9.52)	3 (7.69)	7 (9.46)	4 (12.90)	0
Escherichia coli	14 (9.52)	1 (2.56)	4 (5.41)	7 (22.58)	2 (66.67)
Enterococcus spp.	12 (8.16)	3 (7.69)	4 (5.41)	5 (16.13)	0
Bacteroids spp.	6 (4.08)	3 (7.69)	2 (2.70)	1 (3.23)	0
Staphylococcus spp.	5 (3.40)	2 (5.13)	3 (4.05)	0	0
Acinetobacter spp.	5 (3.40)	3 (7.69)	2 (2.70)	0	0
Citrobacter spp.	5 (3.40)	2 (5.13)	3 (4.05)	0	0
Morganella morganii	5 (3.40)	1 (2.56)	3 (4.05)	1 (3.23)	0
Corynebacterium spp.	1 (0.68)	0	1 (1.35)	0	0
Providencia stuartii	1 (0.68)	0	0	1 (3.23)	0
Shigella spp.	1 (0.68)	0	1 (1.35)	0	0
No growth	24 (16.33%)	9 (23.08%)	14 (18.92)	1 (3.23)	0
Mixed growth	2 (1.37%)	0	2 (2.70)	0	0

AKA above knee amputation, *BKA* below knee amputation

Table 4 Antibiotics and recovery

Antibiotics	No recovery Amputation/ death (n = 173)	Recovery No amputation and no death (n = 296)	Total treated with respective antibiotic
Unasyn	111(39.1%)	173 (60.9%)	284
Clindamycin	22(39.3%)	34(60.7%)	56
Ceftazidime	15(31.9%)	32(68.1%)	47
Others	25(30.5%)	57(69.5%)	82

by a single pathogen as observed by other researches [12]. During the recent years, polymicrobial NF are less common when compared to several decades back [18]; however, a recent Scandinavian study reported 50% of the NF infections were polymicrobial [19]. The present retrospective study shows that *Streptococcus* spp. (18.98%), *P. aeruginosa* (13.43%) and *Staphylococcus* spp. (13.01%) as the three most prevalent pathogens that were implicated in NF. The organisms were also found to be the most predominant pathogens associated with NF around the world [20]. *Streptococcus* spp.

Table 5 Causative organism, antibiotics used and recovery

Organism	Antibiotics	Amputation/ death (n = 173)	No amputation and no death (n = 296)	Total treated with respective antibiotic
Streptococcus spp.	Unasyn	16 (27.1%)	43 (72.9%)	59
	Clindamycin	1 (8.4%)	11 (91.6%)	12
	Ceftazidime	0 (0%)	8 (100%)	8
	Others	1 (10%)	9 (90%)	10
Pseudomonas aeruginosa	Unasyn	6 (24%)	19 (66%)	25
	Clindamycin	0 (0%)	2 (100%)	2
	Ceftazidime	7 (28%)	18 (72%)	25
	Others	3 (27.3%)	8 (72.7%)	11
Staphylococcus spp.	Unasyn	6 (18.2%)	27 (81.8%)	33
	Clindamycin	2 (25%)	6 (75%)	8
	Ceftazidime	2 (50%)	2 (50%)	4
	Others	2 (12.5%)	14 (87.5%)	16
Klebsiella pneumoniae	Unasyn	18 (46.2%)	21 (53.8%)	39
	Clindamycin	1 (50%)	1 (50%)	2
	Ceftazidime	1 (50%)	1 (50%)	2
	Others	0 (0%)	1 (100%)	1
Proteus spp.	Unasyn	13 (46.4%)	15 (53.6%	28
	Clindamycin	1 (50%)	1 (50%)	2
	Ceftazidime	3 (60%)	2 (40%)	5
	Others	4 (57.1%)	3 (42.9%)	7
Enterococcus spp.	Unasyn	9 (39.1%)	14 (60.9%)	23
	Clindamycin	0 (0%)	0 (0%)	0
	Ceftazidime	0 (0%)	0 (0%)	0
	Others	4 (57.1%)	3 (42.9%)	7
Other microbes	Unasyn	31 (65.9%)	16 (34.1%)	47
	Clindamycin	6 (54.5%)	5 (45.5%)	11
	Ceftazidime	2 (66.6%)	1 (33.4%)	3
	Others	5 (41.6%)	7 (58.4%)	12
No growth	Unasyn	11 (40.7%)	16 (59.3%)	27
	Clindamycin	9 (52.9%)	8 (47.1%)	17
	Ceftazidime	0 (0%)	0 (0%)	0
	Others	6 (37.5%)	10 (62.5%)	16
Mixed growth	Unasyn	1 (33.3%)	2 (66.6%)	3
	Clindamycin	2 (100%)	0 (0%)	2
	Ceftazidime	0 (0%)	0 (0%)	0
	Others	0 (0%)	2 (100%)	2
Total		173	296	469

was recorded to be the most prevalent pathogen-associated with NF worldwide, but for the other organisms, there are variations in accordance with the study area [12, 21–23]. In this study, *P. aeruginosa* was found to be the most prevalent Gram-negative causing NF, while other Asian countries such as Thailand and Taiwan reported *E. coli* to be the most prevalent NF causing microbe [12, 24].

Regarding the common pathogens associated with amputation, Gram negatives such as *Proteus* spp. (19/147; 12.93%), *K. pneumonia* (18/147; 12.24%), *P. aeruginosa* (15/147; 10.20%) and *E. coli* (14/147; 9.52%) were found to be more prevalent followed by Gram-positive *Streptococcus* spp. (14/147; 9.52%) and *Enterococcus* spp. (12/147; 8.16%). However, in some other studies, *Streptococcus* spp. or type II, *S. aureus*, *P. aeruginosa* and *E. coli* were more frequently associated with amputation [12, 22, 23]. Although type I and II NF are common, it was found that type III (mono microbial Gram negatives) are the major category associated with amputations. Also, amputations in patients with culture-negative NF were found in the study. Culture-negative cases commonly seen in NF may be due to inadequate sample obtained from non-significant sites, complication of diabetic foot ulcer especially peripheral vasoconstriction, and in many cases, antibiotics given prior to sample collection.

It was observed that there is higher amputation rate (147/469; 31.34%) among the studied NF cases compared to 6.01% (35/582) in Taiwan, 8.42% (127/1507) in Thailand, 13.75% (11/80) in the USA and 22% in Scandinavia [12, 19, 23, 25]. The most predominant bacteria in AKA was found to be *K. pneumoniae* while *Proteus* spp. has higher prevalence in BKA. It is well established that NF is a rapidly progressing deadly disease; the prognosis and amputation rates reduction will work only with surgical debridement and prompt treatment with antibiotics. Since both Gram positives and Gram negatives can cause NF, whether it is monomicrobial or polymicrobial, broad-spectrum antibiotic coverage should be administered. Tissue cultures should be taken intra-operatively, so that its sensitivity will guide subsequent antibiotic management. Precise antimicrobial should be used on the basis of sensitivity results to reduce resistance. The retrospective data analysis of NF patients in the study indicates that the empiric antimicrobials are Unasyn (ampicillin and sulbactam), clindamycin and ceftazidime. The combination of ampicillin and sulbactam in Unasyn makes it the drug of choice due to its wide spectrum of coverage. Clindamycin has relatively broad activity, but specifically suppresses the bacterial toxin synthesis, has a longer post antibiotic effect, increases the phagocytic activity of Group A β-streptococcus and also was shown to suppress the lipopolysaccharide-induced tumour necrosis factor-α production by monocytes [26–29]. Third-generation cephalosporin (ceftazidime) is indicated in cases where *P. aeruginosa* is suspected [4, 30]. In the present study, we found unasyn, clindamycin and ceftzidime as the effective antibiotics for recovery. A total of 239 (61.8%) recovered while 148 (38.2%) were either amputated or dead when managed with the above three antibiotics (Table 4). A study in Scandinavia recommends the use of carbapenem and clindamycin [19], while that of The Netherlands recommends penicillin or 2nd/3rd generation cephalosporin, clindamycin and gentamicin [31]. A case report of Fournier scrotal gangrene from Taiwan showed the successful treatment of the polymicrobial infection (*Streptococcus agalactiae*, *Staphylococcus haemolyticus*, *Escherichia coli*, *peptostreptococc*i and *Prevotella corporis*) with metronidazole and ceftriaxone [32]. Other suggested antibiotics include piperacillin-tazobactam, linezolid, daptomycin, and tigecycline if the tissue was previously colonized with resistant strains [33–35]. Suspected *Vibrio* spp. are to be subjected to treatment with doxycycline in combination with a third-generation cephalosporin [36]. The current empirical antibiotics cover majority of the organisms that causes NF in the studied hospitals. Although broad-spectrum antibiotics are the best treatment options for NF, cordial cooperation between orthopaedic surgeons, the clinical microbiologists as well as infectious disease physician is vital.

The present study has certain limitations including lack of data concerning antibiogram and the inability to determine the drug resistant species among the studied bacteria due to incomplete medical records. Another limitation is that only lower limbs are considered ignoring the parameters concerning the upper limb. The retrospective study is considered as novel in Malaysia due to the fact that it is the first of its kind on the microbiological profile and the management strategies of NF patients.

Conclusions

In conclusion, *Streptococcus* spp., *P. aeruginosa* and *Staphylococcus* spp. are the most common causative microorganisms of NF. Among the amputations investigated, BKA was the most common. *Proteus* spp. and *K. pneumoniae* are ranked the most prevalent pathogens associated with all types of amputations. Among the antibiotics currently prescribed for NF, unasyn, clindamycin and ceftazidime were proved to be more effective. Antibiotic resistance, though may be encountered, has not been assessed as a result of reliable data concerning antibiogram. Therefore, a multi-centre study from different levels of the healthcare system is recommended with more considerations on larger sample size, antibiotic resistance and reasons for increased amputations.

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TEK, MAHAH, ZS, SSSS; data curation, LPY; writing—original draft preparation, SM, RN, VKN and SR; writing—review and editing, SM, RR, VKN and SR.; visualization, SR and VKN; supervision, SR; project administration. All authors have read and agreed to the published version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate This is a retrospective study; hence, no consent was obtained from subjects; however, the study was conducted after approval from the ethics committee.

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