Review

Early diagnosis of necrotizing fasciitis

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Background: **Necrotizing fasciitis is a rapidly progressing skin infection characterized by necrosis of the fascia and subcutaneous tissue, accompanied by severe systemic toxicity. The objective of this systematic review was to identify clinical features and investigations that will aid early diagnosis.**

Methods: **A systematic literature search of PubMed was undertaken using the keywords 'necrotising fasciitis', 'necrotising skin infection', 'diagnosis' and 'outcome'. Case series of 50 or more subjects with information on symptoms and signs at initial presentation, investigations and clinical outcome were included.**

Results: **Nine case series were selected, with a total of 1463 patients. Diabetes mellitus was a co-morbidity in 44·5 per cent of patients. Contact with marine life or ingestion of seafood in patients with liver disease were risk factors in some parts of Asia. The top three early presenting clinical features were: swelling (80·8 per cent), pain (79·0 per cent) and erythema (70·7 per cent). These being non-specific features, initial misdiagnosis was common and occurred in almost three-quarters of patients. Clinical features that helped early diagnosis were: pain out of proportion to the physical findings; failure to improve despite broad-spectrum antibiotics; presence of bullae in the skin; and gas in the soft tissue on plain X-ray (although this occurred in only 24·8 per cent of patients).**

Conclusion: **A high index of suspicion of necrotizing fasciitis is needed in a patient presenting with cutaneous infection causing swelling, pain and erythema, with co-morbidity of diabetes or liver disease. The presence of bullae, or gas on plain X-ray can be diagnostic. Early surgical exploration is the best approach in the uncertain case.**

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Introduction

Necrotizing fasciitis (NF) is a rapidly progressing infection of the skin and soft tissues that has been known since the days of Hippocrates[1]. It causes extensive necrosis of the fascia and subcutaneous tissue leading to severe systemic toxicity. Early diagnosis and surgical intervention can reduce mortality and amputation rates. Its rarity and the paucity of early pathognomonic signs make NF a major diagnostic challenge.

A systematic review was conducted with the objective of determining clinical features and investigations that could aid in early diagnosis.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology[2].

Search strategy

A systematic literature search from January 1980 until May 2013 was undertaken in PubMed. Keywords used were 'necrotising fasciitis', 'necrotising soft tissue infection', 'diagnosis' and 'outcome' combined with the Boolean AND, OR operators. Both free-text and medical subject heading (MeSH) searches for keywords were employed. Results were limited to studies undertaken in humans and published in English. Inclusion criteria were: case series with information on initial presenting symptoms, and signs, investigations and outcome (amputation and mortality); and case series with at least 50 patients.

Data extraction and assessment of methodological quality

Data extraction and assessment of methodological quality were undertaken by two reviewers independently.

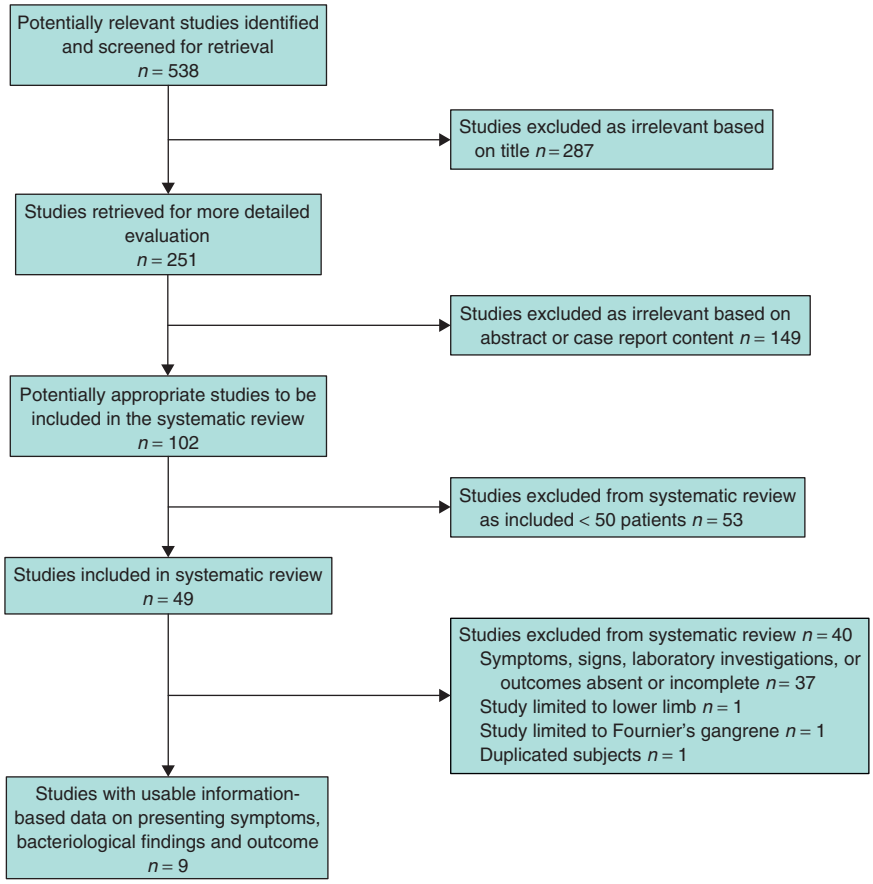


Fig. 1 PRISMA flow chart showing selection of articles for review

Disagreements were resolved by consensus. Baseline data collected were: year of publication, diagnosis of NF, number of patients examined, mean age, sex ratio, co-morbidities, and site of NF. Specific outcome data collected were: incidence of signs and symptoms at presentation, investigations (laboratory, radiological and microbiological), bacteriological profile (incidence of monomicrobial and polymicrobial disease, distribution of bacterial types) and outcome (amputation and mortality).

The classification of NF into types I–IV, as described by Morgan[3], was used as a reference. The laboratory risk indicator for NF (LRINEC) score described by Wong and colleagues[4] was also employed.

Results

Nine studies[5–13] with a total of 1463 patients were included in this systematic review (*Fig. 1*). One[10] was a prospective study and eight[5–9,11–13] were retrospective. All but one were single-institution studies; the study by Dworkin and co-workers[7] was a case series from four urban centres. All the studies provided level II evidence, according to the Oxford Centre for Evidence-based Medicine criteria (http://www.cebm.net/?o=1025).

Aetiology and co-morbidities

Eight of the nine studies had trauma as the most common identifiable aetiology. Up to one-third (31·4 per cent) of the cases were due to identified trauma (minor or major, 26·1 per cent) and surgical wounds (4·3 per cent). Consumption of raw or undercooked seafood, or injury by fish fins was the aetiology in studies by Park and colleagues[13], Hsiao and co-workers[11] and Huang *et al.*[12]. In this subgroup, marine bacteria, namely *Vibrio* spp., *Aeromonas* spp. and *Shewanella* spp., were commonly involved.

Diabetes mellitus was the most common co-morbidity in eight of nine studies, involving a mean of 44·5 (range 15·2–71) per cent of patients (*Table 1*). There was a strong positive correlation between diabetes and subsequent limb amputation ($R = 0{\cdot}88$), but not with death. Diabetes was associated with type 1 NF, which is polymicrobial and

Table 1 Characteristics of case series

	Elliott *et al.*[5]	Frazee *et al.*[6]	Dworkin *et al.*[7]	Nisbet *et al.*[8]	Wong *et al.*[9]	Singh *et al.*[10]	Hsiao *et al.*[11]	Huang *et al.*[12]	Park *et al.*[13]	Total
Country	USA	USA	USA	New Zealand	Singapore	India	Taiwan	Taiwan	South Korea	6
Institutions	1	1	4	1	1	1	1	1	1	12
No. of patients	198	122	80	82	89	75	128	472	217	1463
Date of study	1985–1993	1990–2001	1999–2002	2000–2006	1997–2002	1990–1995	2002–2005	2003–2009	1998–2006	1985–2009
Publication date	1996	2008	2009	2011	2003	2002	2008	2011	2009	1996–2011
Demographics										
Mean age (years)	51·5	44·1	46	55	56	40	61	59·6	58·6	55·0
Men (%)	57·1	63·9	49	56	60	72	67·2	66·7	75·6	64·8
Co-morbidities (%)										
Diabetes	56·4	22·1	55	35	71	29	58·6	52·1	15·2	44·5
Obesity	31·8	–	–	20	–	–	–	–	–	28·3
Peripheral vascular disease	16·4	–	–	–	23	–	3·1	–	–	13·6
Liver disease/alcoholism	3·6	–	–	–	3	3	3·9	9·5	53·5	15·1
Location of wound (%)										
Extremity	26·3	73·7	63	70	80	76	88·3	87·5	76·0	73·1
Trunk	–	16·4	18	12	20	35	3·9	6·4	19·0	13·0
Perineum	39·9	18·9	19	16	0	28	3·9	4·2	4·0	12·6
Head and neck	1·5	–	4	1	0	3	3·9	1·9	0·0	1·7
Multiple areas	–	16·4	–	–	–	37	–	–	44·0	34·6
Outcomes										
Misdiagnosis (%)	80·0	41·0	72	96	85	–	61·7	–	–	71·4
Early operation (< 24 h) (%)	–	–	–	60	–	–	47·7	59·3	58·0	57·4
Deaths (%)	19·2	16·4	15	30	21	27	18·8	12·1	45·6	21·5
Amputations (%)	27·8	4·1	22	9	23	7	17·2	14·0	–	15·9
Mean no. of debridements	3·8	–	1·6	2	2·7	–	2·6	–	4·2	3·2

tends to run a more indolent course than types II and III, which are monomicrobial.

The presence of liver cirrhosis had a strong positive correlation with mortality ($R = 0{\cdot}86$). In the study by Park and colleagues[13], liver cirrhosis was the most common co-morbidity (50·7 per cent). Huang and co-workers[12] reported a ninefold increase in mortality for patients with *versus* those without cirrhosis. *Vibrio* spp. and other marine bacteria were rarely encountered in six of the nine studies, but were common in the series[11–13] from South Korea and Taiwan.

The study by Nisbet *et al.*[8] of 82 patients suggested that congestive heart failure and gout were independent predictors of death. Nisbet and colleagues[8] and Wong and co-workers[9] also noted that concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) might have suppressed fever and delayed the diagnosis of NF.

Clinical features

Table 2 shows the symptoms and signs, imaging results, laboratory findings and microbiology of the case series. Across the nine studies, swelling (80·8 per cent) was the commonest presenting symptom, followed by pain (79·0 per cent) and erythema (70·7 per cent). More advanced findings were bullae (25·6 per cent), skin necrosis (24·1 per cent) and crepitus (20·3 per cent) (*Fig. 2*). The presence of bullae was reported in eight of nine studies, and there was moderate positive correlation with amputation ($R = 0{\cdot}68$) and mortality ($R = 0{\cdot}65$). At presentation, fever was present in only 40·0 per cent of the patients. Septic shock with hypotension was a late sign. It had an incidence of 21·1 per cent and was reported in eight of nine studies. There was a strong positive correlation with mortality ($R = 0{\cdot}78$).

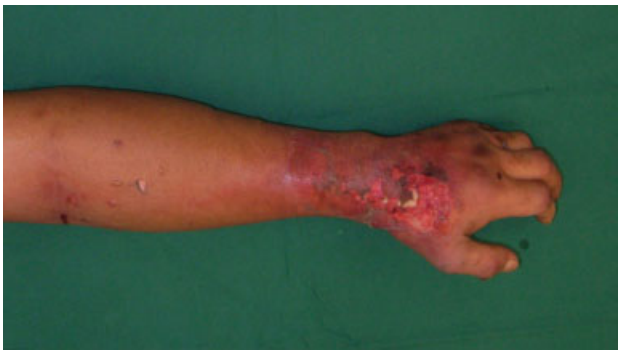
Investigations

None of the studies collated the LRINEC score[4] at admission and only isolated parameters were reviewed. Numerous parameters were shown to relate significantly to the severity of NF and subsequent death[11,12]: white cell count over 15 000/μl or less than 4000/μl, more than 10 per cent neutrophils, platelet count below 100 000/μl, abnormal coagulation (activated partial thromboplastin

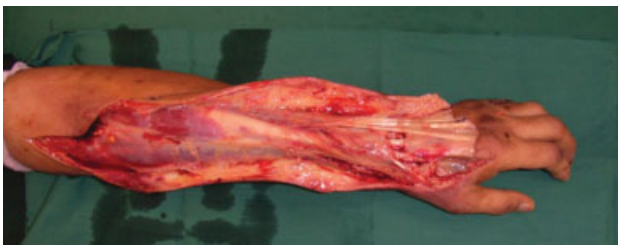
Table 2 Clinical features

	Elliott *et al.*[5]	Frazee *et al.*[6]	Dworkin *et al.*[7]	Nisbet *et al.*[8]	Wong *et al.*[9]	Singh *et al.*[10]	Hsiao *et al.*[11]	Huang *et al.*[12]	Park *et al.*[13]	Total
No. of patients	198	122	80	82	89	75	128	472	217	1463
Signs and symptoms (%)										
Erythema	66·3	80·3	71	–	100	72	52·3	61·0	88·9	70·7
Warmth	–	–	–	–	97	–	–	34·1	–	44·0
Pain or tenderness	72·9	54·1	100	89	98	91	54·7	74·3	100·0	79·0
Swelling	75·0	–	74	87	–	99	71·1	83·7	79·7	80·8
Bullae	23·7	11·5	31	22	45	15	–	13·3	57·1	25·6
Crepitus	36·5	6·6	14	–	14	15	–	–	–	20·3
Skin necrosis	31·1	23·8	19	–	14	–	–	–	–	24·1
Fever > 37·5°C	31·6	44·3	56	44	53	37	43·0	40·1	31·8	40·0
Hypotension	11·1	21·3	20	–	18	9	25·0	12·1	53·0	21·1
Gas on X–ray (%)	57·4 (85 of 148)	42 (29 of 69)	14	–	17	16	–	4·9	–	24·8
Laboratory data reported	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes (5 of 9)
Microbiology (%)										
Positive wound culture	69·2	82·0*	75	–	82	87	77·3	90·9	42·7	76·5
No growth of wound culture	31·8	18·0*	25	–	18	13	22·7	9·1	57·3	23·7
Polymicrobial	84·6	45·3	44	32	54	79	23·4	33·7	2·8	40·5
Monomicrobial	15·4	36·7	31	68	28	19	53·4	57·2	76·0	46·5
Blood culture	–	–	–	18	–	–	28·9	25·7	66·1	35·2

*Value reflects combined wound and blood cultures.



a Necrotizing fasciitis of left arm



b After debridement

Fig. 2 a Necrotizing fasciitis of the left arm demonstrating ruptured bullae with clear fluid, fixed discoloration and skin gangrene. **b** Thorough debridement of the involved fascia showing underlying tendons and muscle bellies; note the extent of the debridement

time over 60 s, international normalized ratio more than 1·5), serum creatinine concentration over 2·0 mg/dl, raised liver enzyme levels, C-reactive protein concentration exceeding 13 mg/dl and creatinine kinase level over 700 units/l.

The presence of gas in the soft tissue on plain X-ray was reported in six of nine studies, but had a relatively low mean rate of 24·8 per cent.

Microbiology

The overall rate of positive wound cultures was 76·5 per cent and the positive blood culture rate was 35·2 per cent. Of the nine studies, five had a higher rate of polymicrobial infection, whereas four reported more monomicrobial infections. The polymicrobial infection reports came from the USA (3 studies), India (1) and Singapore (1). The monomicrobial infection reports came from New Zealand (1), Taiwan (2) and South Korea (1 study).

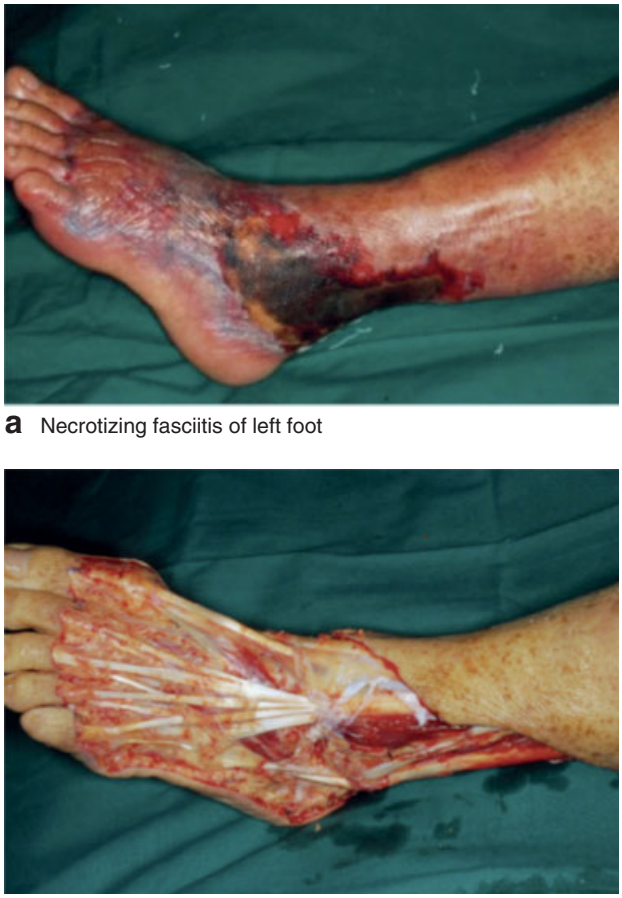
Organisms common in polymicrobial infections were: *Staphylococcus* spp., *Streptococcal* spp., *Bacteroides* and *Escherichia coli*[5–7,9,10]. Among monomicrobial infections, *Streptococcus pyogenes* was found in the study by Nisbet and colleagues[8]; *Staphylococcus aureus* was reported by Huang *et al.*[12]. Marine bacteria (*Vibrio* spp., *Aeromonas* spp. and *Shewanella* spp.) were causal organisms in the studies from Korea[13] and Taiwan[11,12]. Both of these countries have extensive coastal areas. *Vibrio* spp. and other bacteria such as *Aeromonas* spp. are commonly found in marine organisms living in warm coastal waters, where temperatures range from 9°C to 21°C[9].

Outcomes

In a series of 198 patients, Elliot and colleagues[5] showed that survivors had a shorter delay between admission and first debridement (1·2 *versus* 3·1 days). Similarly, Wong and co-workers[9] showed that a delay before surgery of more than 24 h correlated with an increased mortality rate in a series of 89 patients (relative risk 9·4; $P < 0·05$). A Kaplan–Meier curve of this series showed a decrease in cumulative survival as the time between admission and operation increased. The cumulative survival rate was 93·2 (95 per cent confidence interval 86·6 to 99·8) per cent when the delay was 24 h, declining to 75·2 (62·0 to 88·4) per cent at 48 h. The importance of early aggressive surgical intervention has also been noted by others[14–18]. The number of debridement procedures was reported in six of nine studies, with a mean of 3·2 per patient (*Fig. 3*).

Misdiagnosis of NF as cellulitis or abscess was common. Six of the nine studies reported the rate of misdiagnosis, which was a mean of 71·4 per cent across the reports, ranging from 41·0 to 96 per cent.

The mortality rate was reported in all studies, with a mean of 21·5 (12·1–45·6) per cent. Infection by *Vibrio* spp. in the Korean study[13] accounted for the highest mortality rate among the reviewed series. The series with the lowest mortality rate was that by Huang *et al.*[12]. The amputation rate was reported in eight studies, with a mean incidence of 15·9 (range 4·1–27·8) per cent.



a Necrotizing fasciitis of left foot

b After debridement

Fig. 3 Skin necrosis in necrotizing fasciitis of the left foot **a** at presentation and **b** after complete thorough excisional debridement

Discussion

NF was misdiagnosed in the initial stage of disease in almost three-quarters of patients in this systematic review. There are well defined pointers towards earlier diagnosis, and it is clear that prompt diagnosis and intervention reduces mortality and amputation rates.

Patients with NF usually present with the triad of pain, swelling and erythema[5,7,9,11–13]. It is often misdiagnosed as cellulitis or abscess. The most consistent feature of early NF is that the pain is out of proportion to the swelling or erythema[7,9–11]. Four other features are diagnostic clues to differentiate NF from simple soft tissue infection: the tenderness extends beyond the apparent involved area owing to enzymes and toxins spreading along the fascia below the skin; margins of involvement are indistinct; lymphangitis is rarely seen in NF because the infection is in the deep fascia and not in the skin[19]; and NF is rapidly progressive despite the use of antibiotics[19]. Regular review of the patient's condition with a visual pain score and marking of the extent of infection on the skin can be helpful in equivocal cases.

The development of clear blisters (bullae) in the skin marks the intermediary stage between early (non-specific cutaneous features) and late NF with skin necrosis (*Table 3*)[20]. In this systematic review, the presence of bullae had moderate positive correlation with amputation and mortality rates, suggesting that this was a turning point in the disease.

Patients who present the greatest diagnostic challenge are those with skin infection and severe pain but no fever. The masking effect of NSAIDs, steroids and antibiotics should be recognized. Absence of pyrexia should not be used to rule out NF; in the present systematic review, only 40·0 per cent of patients were febrile.

The best way to diagnose NF seems to be the 'finger test'. This involves infiltrating the suspect area with local anaesthetic and making a 2-cm incision down to the deep fascia. If the index finger dissects the subcutaneous tissue

Table 3 Evolution of physical signs of necrotizing fasciitis from early to late disease[20]

Stage 1 (early)	Stage 2 (intermediate)	Stage 3 (late)
Warm to palpation	Blister or bullae formation (serous fluid)	Haemorrhagic bullae
Erythema	Skin fluctuance	Skin anaesthesia
Tenderness to palpitation (extending beyond apparent areas of skin involvement)	Skin induration	Crepitus
Swelling		Skin necrosis with dusky discoloration progressing to frank gangrene

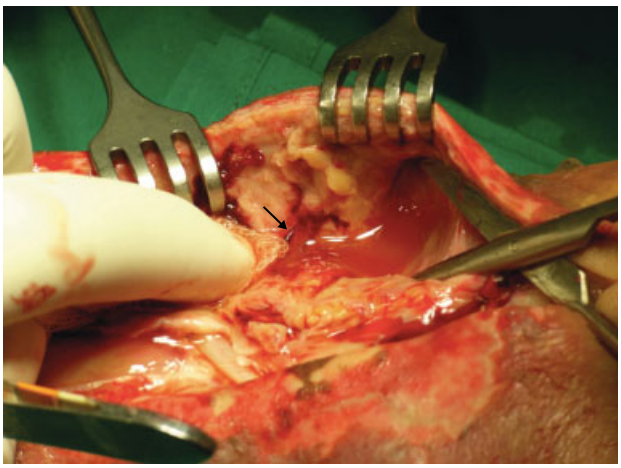


Fig. 4 Dishwater pus pathognomonic of necrotizing fasciitis. Arrow shows thrombosed cutaneous perforating vein

off the deep fascia easily along the tissue plane, the test is positive. Other positive macroscopic findings are: grey necrotic tissue; fascial oedema; thrombosed vessels; thin, watery, foul-smelling fluid, described as dishwater pus (*Fig. 4*); and non-contracting muscles[21]. Urgent definitive surgical debridement should follow.

A number of co-morbidities are associated with NF. Clinicians should have a higher index of suspicion when patients with diabetes or liver cirrhosis present with cutaneous infection. In certain parts of Asia, ingestion of raw seafood or injury from marine animals in susceptible individuals should suggest the possibility of NF from marine organisms.

Isolated abnormal blood parameters, reflecting the deranged physiology, have been noted by several authors. However, these are of limited use owing to the lack of sensitivity and specificity of individual tests. The LRINEC[4] scoring system provides the clinician with a risk stratification for predicting NF. Although it has been verified by some authors, it has limitations in *Vibrio* spp. infections[22,23] and cervical NF[24]. Clinical suspicion is still superior to laboratory testing or the LRINEC score.

Previous studies have emphasized the synergistic effects of polymicrobial bacteria in the pathogenesis of NF[14,25,26]. However, there are increasing reports of NF caused by monomicrobial infection, especially in Asia[8,11–13]. Information on bacteriology from wound and blood cultures remains important for fine-tuning the antibiotic selection over empirical treatment.

This review has limitations. With the exception of the study by Singh and colleagues[10], the series were retrospective. As such, several limitations were encountered commonly: missing data; not all variables of interest were recorded; variable criteria for the diagnosis of NF were used; and biased data recording, for example negative microbiology results may not be captured.

A prospective, multicentre registry enrolling all patients presenting with soft tissue infections to the emergency department, as suggested by Frazee and colleagues[6], could be a valuable future development and enhance the understanding of NF in its early stages. This might include standard recording of presenting symptoms with clinical photography, thorough blood investigations, imaging and bacteriological studies, and standard diagnostic criteria.

In a patient presenting with swelling and pain from cutaneous infection that is out of proportion to the physical findings there should be a high index of suspicion of NF. The presence of diabetes strengthens the possibility. Contact with marine life and ingestion of seafood are risk factors in some communities. In the equivocal case, regular clinical reviews and failure to improve despite broad-spectrum antibiotics will guide the decision for early surgical exploration. There should be a low threshold for limited exploration under local anaesthetic with use of the finger test to aid early diagnosis.

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