Idiopathic Necrotizing Fasciitis:
Clinical Presentation, Microbiology,
Risk Factors and Determinants of Mortality

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Abstract

Early recognition and treatment of necrotizing fasciitis (NF) is essential for survival. Idiopathic NF occurs in the absence of a known causative factor or portal of entry for bacteria, so it may not be considered immediately when patients are admitted. This study aimed to identify specific features of idiopathic NF that are important for early recognition and to assess factors associated with mortality. The records of 185 patients with surgically confirmed necrotizing fasciitis between January 1998 and June 2006 were retrospectively reviewed. The infection was classified as either idiopathic or secondary NF, and the clinical presentation, etiology, predisposing factors, microbiology, and outcome of the two groups were compared. Idiopathic NF occurred in 115 of 185 patients (62.2%). Patients with idiopathic NF were more like than those with secondary NF to have diabetes mellitus or chronic renal insufficiency, and they were less likely to have fever or skin bullae. Significant predictors of death in patients with idiopathic NF were shock on admission, impaired renal function, and elevated aspartate aminotransferase. Mortality did not differ significantly between idiopathic and secondary NF. Idiopathic NF should be considered as a cause of unexplained soft tissue pain and tenderness, even in the absence of typical signs of this infection. ( J Intern Med Taiwan 2008; 19: 337-345 )

Key Words: Idiopathic necrotizing fasciitis, Microbiology, Risk factors, Mortality
Introduction

The term necrotizing fasciitis (NF) was first coined by Wilson in 1952 to describe a life-threatening bacterial infection characterized by systemic toxicity; rapidly progressive inflammation; and necrosis of the subcutaneous tissue, superficial fascia, and superficial portion of the deep fascia, followed by necrosis of the overlying skin. NF is an uncommon but devastating disease. Despite recent progress in antibiotic therapy, surgery, and supportive care, case fatality rates remain high, ranging from 25% to 100% in reported series. The course of the disease is often fulminant, and the prognosis hinges on accurate diagnosis and immediate treatment.

Cases in which the precipitating event is known are classified as secondary NF. Bacterial invasion may result from blunt trauma with contusion, abrasions, penetrating injury (e.g., laceration, intravenous drug abuse, and surgical procedures), childbirth, or burns, i.e., anything that causes a break in the epidermidis. Idiopathic NF, however, occurs in the absence of a known or identifiable etiologic factor, which may make the diagnosis more challenging.

Only a few published articles have focused on the clinical characteristics of idiopathic NF, with most being reports of only small case series. One group has reported a series 60 cases of idiopathic NF, but many of these patients had perineal infection rather than NF of the limbs. Some authors suggest that differentiating idiopathic from secondary NF is unimportant since the treatment is the same. We are concerned, however, about the potential diagnostic challenge posed by idiopathic NF. We therefore designed this retrospective study to describe the clinical presentation and microbiology of idiopathic NF, comparing them with those of secondary NF. We also looked at risk factors for death in patients with idiopathic NF.

Methods

The medical records of all patients treated at our institution between January 1999 and June 2006 for NF were retrospectively reviewed. The records were identified by a computer search of the Medical Records Department database for all patients diagnosed with NF (International Classification of Diseases, Ninth Revision). A total of 185 such patients were identified. In all cases, the diagnosis of NF had been confirmed by finding necrotic subcutaneous tissue and fascia at surgery, along with ease in separating the superficial fascia from underlying tissues. Permanent histopathology tissue specimens, when available, were examined to confirm the diagnosis. Patients with foot gangrene due to diabetes mellitus or peripheral vascular disease requiring amputation were excluded from the study.

Data extracted from the records included age and gender; site of infection; symptoms and physical findings on admission; admitting diagnosis; presumed portal of entry of infection; number and type of comorbidities; time between symptom onset and presenting for medical care; vital signs; laboratory findings on admission; and radiologic findings before surgery. Culture results from tissue samples obtained from the first operative debridement were analyzed. The time from admission to operation, the number of debridements, length of hospitalization, and in-hospital mortality were also documented.

Patients with a known etiology for their NF when admitted, including any injury or trauma causing a break in the epidermidis, or those who had undergone surgery prior to admission, were classified as having secondary NF. All others were classified as having idiopathic NF. These two groups were compared in terms of the variables listed above. In addition, patients who survived idiopathic NF were compared with those who had died from the infection.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS Company, Chicago, IL). Continuous variables were analyzed using Student’s t test. Comparisons of proportions were made using Pearson’s chi square.
statistic to identify univariate differences among variables. Fisher's exact test for 2 x 2 tables was used in the small-sample case. Variables showing marginal association with a P value of <0.15 on univariate analysis were further examined by regression analysis. All analyses were two tailed. A p value of ≤ 0.05 was considered to be statistically significant.

### Results

#### Patient characteristics

There were 56 women and 129 men in the study group, with a median age of 60 years (range: 19-89 years). Idiopathic NF occurred in 115 patients (62.2%), and secondary NF in 70 patients (Table 1).
### Table 3. Logistic Regression Analysis of Factors Distinguishing Patients with Idiopathic From Secondary Necrotizing Fasciitis

<table>
<thead>
<tr>
<th>Independent predictors of idiopathic infection</th>
<th>Odds Ratio (95% CI*)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.149 (2.169-4.098)</td>
<td>0.017</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1.458 (3.106-6.579)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fever</td>
<td>0.260 (0.490-0.925)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

* CI: confidence interval.

### Table 4. Physical Findings in 185 Patients with Necrotizing Fasciitis

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Total NFn = 185 (%)</th>
<th>Idiopathic NFn = 115 (%)</th>
<th>Secondary NFn = 70 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>63 (34.1)</td>
<td>41 (35.7)</td>
<td>22 (31.4)</td>
</tr>
<tr>
<td>β-hemolytic streptococci</td>
<td>40 (21.6)</td>
<td>22 (19.1)</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>21 (11.4)</td>
<td>14 (12.2)</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>17 (9.2)</td>
<td>9 (7.8)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td><em>Corynebacterium spp.</em></td>
<td>6 (3.2)</td>
<td>3 (2.6)</td>
<td>3 (4.3)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Gram-negative bacteria</th>
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<th>Secondary NFn = 70 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella spp.</td>
<td>27 (14.6)</td>
<td>20 (17.4)</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>28 (15.1)</td>
<td>17 (14.8)</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>13 (7.0)</td>
<td>10 (8.7)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td><em>Pseudomonas spp.</em></td>
<td>14 (7.6)</td>
<td>8 (7.0)</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>16 (8.6)</td>
<td>7 (6.1)</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>9 (4.9)</td>
<td>6 (5.2)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Aeromonas spp.</td>
<td>8 (4.3)</td>
<td>5 (4.3)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>5 (2.7)</td>
<td>4 (3.5)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>5 (2.7)</td>
<td>3 (2.6)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>3 (1.6)</td>
<td>3 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td>5 (2.7)</td>
<td>2 (1.7)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>3 (1.6)</td>
<td>1 (0.9)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Eikenella corrodens</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Chryseobacterium spp.</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

| Anaerobes                                     |                      |                          |                        |
| Bacteroides spp.                              | 11 (5.9)             | 9 (7.8)                  | 2 (2.9)                |
| Prevotella spp.                                | 9 (4.9)              | 3 (2.6)                  | 6 (8.6)                |
| Stenotrophomonas maltophilia                  | 5 (2.7)              | 2 (1.7)                  | 3 (4.3)                |
| Peptostreptococcus spp.                       | 3 (1.6)              | 2 (1.7)                  | 1 (1.4)                |
| Clostridium spp.                              | 3 (1.6)              | 2 (1.7)                  | 1 (1.4)                |
| Propyromonas spp.                             | 2 (1.1)              | 1 (0.9)                  | 1 (1.4)                |
| Propionibacteria                              | 1 (0.5)              | 1 (0.9)                  | 0 (0.0)                |
| Fusobacterium varium                          | 2 (1.1)              | 0 (0.0)                  | 2 (2.9)                |
| Veillonella spp.                               | 1 (0.5)              | 0 (0.0)                  | 1 (0.1)                |
| Unidentified anaerobes                         | 2 (1.1)              | 2 (1.7)                  | 0 (0.0)                |

| Fungus                                         |                      |                          |                        |
| Candida species                                | 7 (3.8)              | 4 (3.5)                  | 3 (4.3)                |
| Others                                         | 2 (1.1)              | 2 (1.7)                  | 0 (0.0)                |

| Total                                         | 335                  | 205                      | 130                    |
The two groups did not differ significantly in terms of age or gender.

Diabetes was the most common underlying disease in idiopathic NF (64 of 115 patients, 55.7%), followed by chronic renal disease (47, 40.9%), both of which were significantly more common in this group than the secondary NF group (Table 1). Other less common (<10%) possible predisposing factors in both groups included upper gastrointestinal bleeding, chronic obstructive lung disease, coronary artery disease, chronic use of non-steroidal anti-inflammatory drugs, cerebral vascular accident, arthritis requiring chronic steroid therapy, psychological problems, malignancy, and drug abuse. Only 15 patients (13.0%) in the idiopathic NF and 15 patients (21.4%) in the secondary NF were previously completely healthy.

Clinical presentation

Fever was present in slightly less than half of patients with idiopathic NF compared with nearly two thirds of those with secondary NF (54/115, 47.0% vs. 44/70, 62.9%, p=0.036). Local heat and erythema were present in nearly all patients on presentation, while bullous lesions were significantly more common in patients with secondary NF (Table 2). There were no significant differences between the two groups in the incidence of severe complications or sites of infection.

All patients underwent surgical drainage and debridement within a median of 48 hours after admission (range: <1-24 days for the idiopathic group, <1-19 days for the secondary group). The duration of symptoms from onset to hospitalization was median of 8.5 days (range: 1-125 days) in the idiopathic group and 7.5 days (range: 1-123 days) in the secondary group. Both groups had a median of 2 operations (range: 1-8 in the idiopathic group, 1-10 in the secondary group). Twenty percent of patients in each group died (23 with idiopathic NF and 14 with secondary NF).

Laboratory findings

The two groups did not differ significantly in terms of leukocytosis (>10,000/mL) or leukopenia (<4,000/mL), a left shift in the differential count, thrombocytopenia (<100,000/mm³), prolonged prothrombin time, metabolic acidosis, abnormal liver or renal function, hypoalbuminemia, or splenomegaly.

By logistic regression analysis, independent risk factors for idiopathic NF were DM or chronic renal insufficiency, and these patients were significantly less likely to have fever than those in the secondary group (Table 3).

Microbiology

A mean of 1.81 pathogens were isolated per patient (range: 0-11) (Table 4), with a mean of 1.78 isolates per patient (range: 0-6) in the idiopathic group and 1.86 (range: 0-11) in the secondary group.

The distribution of pathogens was similar in both groups with no statistically significant differences. Infections were monomicrobial in 52 patients (45.2%) in the idiopathic group, and cultures were sterile in 8 (11.4%). Comparable figures for the secondary group were 30 (42.9%) monomicrobial infections and sterile cultures in 8 (11.4%). (Table 4)

Mortality Determinants in Idiopathic NF

In the idiopathic group, a number of factors were associated with mortality on univariate analysis, including the presence of bullae, minimal local heat, altered consciousness, shock on admission, respiratory failure requiring ventilator support, renal function impairment, coagulopathy (prothrombin time prolonged more than 3 seconds or partial thromboplastin time >1.5 times of control), elevated aspartate aminotransferase, metabolic acidosis, and positive blood cultures. However, on regression analysis, only three variables were significantly associated with mortality: shock on admission (odds ratio 6.839, 95%CI 2.158-21.670, p=0.0011), renal function impairment, (odds ratio 4.032, 95%CI 1.193-13.699, p=0.0249), and elevated aspartate aminotransferase (odds ratio 3.840, 95%CI 1.192-12.377, p=0.0242).

In the idiopathic NF group, 45.7% of those who survived had been correctly diagnosed on admission.
versus 26.1% of those who died, a non-significant
difference (p=0.089). The lack of significance is per-
haps due to the relatively small number (23) of pa-
tients who died. Among survivors, the mean interval
from admission to first surgery and from symptom
onset to first surgery were 3.7 and 11.1 days, respec-
tively. Comparable intervals for those who died was
2.8 and 12.1 days, respectively. Again, the differences
were not statistically significant (p=0.791 and
p=0.397).

Discussion

In this retrospective study, we describe 185 pa-
tients seen over an 8-year period with surgically con-
firmed NF. Idiopathic NF was diagnosed in 115 pa-
tients, a proportion of 62.2%, higher than that of id-
iopathic disease in other published series, which has
ranged from 16% to 61% \(^5,11-14\). The major difference
we found between idiopathic and secondary NF in
our patients were that diabetes and chronic renal dis-
ease were significantly more common underlying
features in idiopathic infections, whereas fever and
bullae were more likely to be found in secondary in-
fections, although bullae were not independently as-
associated on regression analysis. Laboratory and cul-
ture results did not differ significantly between the
two groups.

Impaired immunity has been implicated in the
pathogenesis of NF \(^15\), a suggestion that is particu-
larly appealing in trying to explain idiopathic NF, where
there is no obvious explanation for the infection. Our
finding that only 13% of patients in the idiopathic
group and 21.4% in the secondary group had no pre-
vious known history of disease supports this con-
tention. The higher proportion of patients with dia-
betes or chronic renal disease in the idiopathic group
would be consistent with the idea that certain types
of immunodeficiency predispose to NF in the absence
of obvious entry sites for pathogens. This is only spec-
culative, of course, as we did not specifically evaluate
immune function in these patients.

The previously reported proportion of fever in
patients with NF ranges from 52% to 70% \(^3,7,10\). It was
surprising to find that less than half (47%) of the pa-
tients in our series with idiopathic NF experienced
high fevers compared with 62.9% of those with sec-
ondary NF. Patients with idiopathic infections were
also less likely to have bullae than those in the sec-
ondary group. The reason for this discrepancy in
presentation is unclear, but it does suggest that idi-
opathic infections may be more insidious in their on-
set. Certainly in patients in whom there might be a
suspicion of NF the absence of, fever or bullous skin
lesions should not immediately exclude the diagno-
sis.

NF is frequently polymicrobial, with a wide
range of pathogens implicated in the infection
\(^6,7,18-20\). In our study, slightly less than half of both idiopath-
ic and secondary infections were polymicrobial. This
is an intriguing result. It is easy to understand how
contamination of wounds with multiple organisms
might lead to secondary NF, but idiopathic NF has
been thought most likely to occur as a result of
hematogenous bacterial spread or from bacterial in-
vasion through small unrecognized breaks in the epi-
dermis, events that would more likely be monomi-
crobial \(^21-23\). However one might explain the patho-
genesis of idiopathic NF, it is clear from our series
that broad spectrum antibiotic coverage is important
even in patients with idiopathic infections until cul-
ture and sensitivity results are available to guide treat-
ment.

In reported series of monobacterial idiopathic
NF, streptococci have been the most frequent
pathogens \(^24,25\). In our series, isolates of Staphylococ-
cus aureus (34.1%) was very slightly more common
than of streptococci (33%). Of the latter, \(\beta\)-hemolyt-
ic streptococci were the most frequent, being cultured
in 19.1% of idiopathic NF cases.

Certain predisposing conditions reportedly are
correlated with certain bacteria: trauma with
Clostridium spp; diabetes with Bacteroides spp, S.
aureus, and Enterobacteriaceae; and immunosuppression with Pseudomonas spp and Enterobacteriaceae. Based on the greater frequency of diabetes among patients with idiopathic NF in our series, we might have expected more case of bacteroides, S. aureus, or Enterobacteriaceae infections in that group. However, the incidence of clostridial, staphylococcal, enterobacter, and bacteroides isolates did not differ significantly between our two study groups.

While some authors believe that early diagnosis and treatment are factors important for survival, our patients in whom NF was suspected on admission did no better than those in whom the diagnosis was made later. The outcome thus did not appear to hinge on immediate diagnosis. In other words, not only early diagnosis but also appropriate yet timely treatment, whether medical or surgical, is the factor important for survival. The latter may be even more important than the former. Hence, it has been suggested that the key to successful treatment includes close observation on progression of the disease, especially when pain is disproportionate to the area of involvement; good cooperation between the physician and the patient; appropriate use of effective antibiotics; and early consultation for surgery when NF is suspected.

We found no significant difference for mortality between idiopathic and secondary NF in this study. This was somewhat surprising, as we had assumed that the diagnosis of idiopathic infections might be difficult and thus delay appropriate treatment. It may be that more direct, rapid bacterial invasion occurs in secondary disease, predisposing such patients to more fulminant infection. On the other hand, a substantial number of patients with secondary NF in our series also have various comorbidities that might impair their immune response to some extent.

Many past studies of idiopathic NF, while mentioning prognostic factors, have had too few cases for accurate statistical analysis. Our regression analysis identified shock on admission, impaired renal function, and elevated aspartate aminotransferase as factors independently associated with mortality in idiopathic infections.

A potential limitation of our study is that patients were classified as having idiopathic or secondary NF simply on the basis of a chart review. If the history and examination were incomplete or incorrectly recorded, patients with apparent idiopathic NF might in fact have had a secondary infection. This is a common problem in retrospective chart reviews and could theoretically skew the results of the statistical analysis. A further limitation is the fact that the records reviewed were chosen because NF was listed as a diagnosis. Because autopsies are infrequently performed in our culture, we cannot exclude the possibility that some patients died of NF that was never recognized clinically.

**Conclusion**

NF, whether idiopathic or secondary, is an extremely serious infection but one which can be successfully treated. Although we found no difference in mortality between the two groups in our study, we remain concerned as clinicians about the possible failure to diagnose idiopathic NF promptly, particularly since we found that fever and skin findings were not as marked in those patients compared with the ones who had secondary NF. This potentially devastating infection should be suspected in any patient with unexplained soft tissue pain and tenderness, especially in those with underlying diabetes or chronic renal disease. NF should figure in the differential diagnosis of suspected septic shock. Treating presumed sepsis with antibiotics is routine, but the surgery usually required for NF cannot be done in a timely manner if the diagnosis is not even considered.

**References**

原發性壞死性筋膜炎：臨床表徵，微生物學，危險因子及死亡決定因素

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摘 要

壞死性筋膜炎的早期診斷與治療，是存活與否的基本關鍵。原發性壞死性筋膜炎，因
為沒有明顯已知的致病因素，亦找不到致病菌入侵的入口，使得其診斷更具挑戰性。本研
究在於找出原發性壞死性筋膜炎中有利於早期診斷的臨床特徵，及與死亡相關的決定因
子。我們收集自87年7月至95年6月間，共185個經外科手術確定診斷的壞死性筋膜炎案
例，予以回溯性研究。將這些案例分為原發性及次發性兩組，分析比較兩組的臨床表徵、
致病因素及其罹病因素、致病病原體及臨床預後。結果收集的185個壞死性筋膜炎案例中
有115個(62.2%)為原發性。相對於次發性壞死性筋膜炎而言，原發性壞死性筋膜炎的特徵
為：併發有糖尿病或慢性腎功能不足者，較少發燒，較少有水疱形成。與死亡相關的因子
為：入院時有休克，腎功能不足，黃疸酸草酸轉化酶升高者。兩組死亡率並無差異。所
以，對於不可解釋的軟組織疼痛或壓痛，即使沒有典型的症狀，仍應考慮原發性壞死性筋
膜炎的可能。