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Deaths from necrotizing fasciitis in the United States, 2003–2013

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SUMMARY

Necrotizing fasciitis (NF) is a life-threatening infection requiring urgent surgical and medical therapy. Our objective was to estimate the mortality burden of NF in the United States, and to identify time trends in the incidence rate of NF-related mortality. We obtained data from the National Center for Health Statistics, which receives information from death certificates from all states, including demographic information and cause of death. The U.S. Multiple Cause of Death Files were searched from 2003 to 2013 for a listing of NF (ICD-10 code M72.6) as either the underlying or contributing cause of death. We identified a total of 9871 NF-related deaths in the United States between 2003 and 2013, corresponding to a crude mortality rate of 4·8 deaths/1 000 000 person-years, without a significant time trend. Compared to white individuals, the incidence rate of NF-associated death was greater in black, Hispanic, and American Indian individuals, and lower in Asian individuals. Streptococcal infection was most commonly identified in cases where a pathogen was reported. Diabetes mellitus and obesity were more commonly observed in NF-related deaths compared to deaths due to other causes. Racial differences in the incidence of NF-related deaths merits further investigation.

Key words: Epidemiology, mortality, necrotizing fasciitis (NF), *Staphylococcus*, *Streptococcus*.

INTRODUCTION

Necrotizing fasciitis (NF) is a life-threatening infection requiring urgent surgical and medical therapy, and the suspected diagnosis must be quickly established by surgical exploration [1]. Development of NF may follow traumatic injury, surgical intervention, or may be spontaneous with a clear antecedent injury [2]. The rapid progression of infection hinges on the expression of bacterial toxins that permits the infection to spread rapidly along fascial planes, and the appearance of the overlying skin often does not reflect the degree of destruction in deeper tissue layers [3]. Disruption of vascular flow rapidly leads to tissue necrosis, and the patient quickly develops an overwhelming sepsis syndrome which is fatal without tissue debridement and supportive care that includes effective antimicrobial therapy [4]. Although a clinical prediction rule was developed to guide decision-making [5], in subsequent work it was found to have limited sensitivity [6].

Cases of NF can been classified based on anatomical location and microbial aetiology. Bacterial pathogens that have been implicated in NF include group A *Streptococcus* (GAS), *Staphylococcus aureus, Clostridium* species, and mixed Gram-negative and anaerobic organisms [7]. Mixed infections with aerobic and anaerobic

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bacteria are classified as Type I, and mono-microbial infections with GAS or *S. aureus* are classified as Type II NF [8]. In a population-based study in the United States between 1996 and 2004, the incidence rate of invasive GAS infection was 3·5 cases/100 000 person-years (p-yr), with 7·2% of these cases presenting with NF [9].

There are little data available regarding time trends in the epidemiology of NF in the United States, despite concerns for an increasing burden of skin and soft tissue infections due to pathogens such as methicillin-resistant *S. aureus* (MRSA) [10]. Our objective was to estimate the mortality burden of NF in the United States over a 10-year period, and to identify temporal trends in the incidence of NF-related mortality during this period. In secondary analyses, we sought to characterize demographic factors and comorbid conditions associated with NF-related death during this period.

METHODS

Setting

Data were obtained from the National Center for Health Statistics, which receives information from death certificates from all 50 states, including demographic information and cause of death. The years 2003–2013 were included, given the change in cause-of-death codes from the International Classification of Diseases, 9th Revision (ICD-9) to the 10th revision (ICD-10) that occurred prior to 2003 [11]. The multiple cause of death (MCOD) data file includes both underlying and contributing causes (both diseases and injuries) that ultimately led to the individual's death.

Case definition

The U.S. Multiple Cause of Death Files were searched from 2003 to 2013 for a listing of necrotizing fasciitis (ICD10 code M72.6) as either the underlying or contributing cause of death. Analysis was not restricted to cases where NF was reported as the underlying cause of death, as the instructions for completing the death certificate refer to the underlying cause of death as 'the disease or injury which initiated the train of morbid events leading directly or indirectly to death or the circumstances of the accident or violence which produced the fatal injury' [12]. Thus, NF arising from an injury or surgical procedure may be recorded as a contributing cause of death, rather than the underlying cause of death. To explore the underlying microbiological diagnosis, each death record was examined for ICD-10 codes corresponding to streptococcal infection (ICD-10 codes A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A49.1, M00.0), staphylococcal infection (ICD-10 codes A41.0, A41.1, A41.2, A49.0, M00.2), gas gangrene (A48.0), Gram-negative organisms (A41.5), and anaerobes (A41.4).

NF mortality rates adjusted for age, race/ethnicity, and sex

Characteristics of individuals with NF-related deaths in the United States were summarized according to demographic characteristics. Age at death was defined based on the following age groups: <1, 1–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, ⩾85 years. Age-adjusted mortality rates and rate ratios (RRs) were calculated with 95% confidence intervals (CIs) using bridged-race population estimates of U.S. census population data, which allows for comparison of different race categories across various collection systems [13]. Goodness-of-fit was examined by testing the statistical significance of the model deviance with the χ^2 test, along with visual inspection of the plot of variance *vs.* mean.

Time trend analysis

Count data were modelled using maximum-likelihood analysis in a negative binomial regression model [14]. A negative binomial regression model was employed, rather than a Poisson model, because a violation of the assumption of equal mean and variance (overdispersion) was observed that reached statistical significance [15]. In order to test for a temporal trend in the rate of NF-associated deaths in the population, year was included as a dummy variable in the negative binomial regression model, with population as the offset.

Matched case-control analysis for associated diagnoses

To identify comorbid conditions associated with NF-related death, a previously validated approach developed by Redelings and colleagues [16] was employed. For each record of NF-related death during the study period, a random sample of deaths from the MCOD dataset during the same year was selected, and matched at a 10:1 ratio (controls:case) by age group, sex, and race/ethnicity. Groups of comorbidities were defined based on the leading ICD-10 diagnoses in all NF-related deaths. For each comorbidity, we calculated a matched odds ratio

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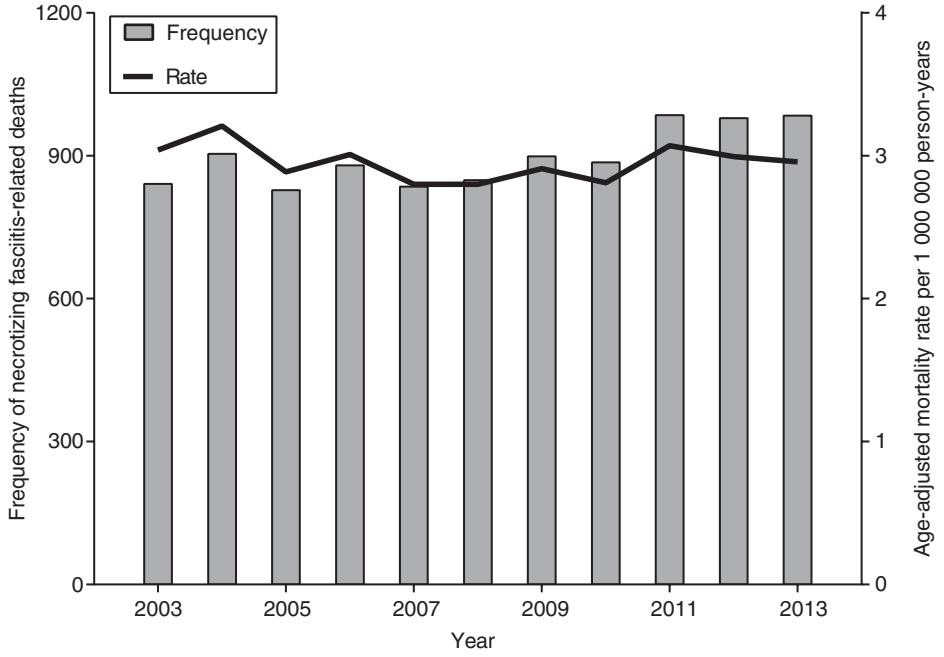

Fig. 1. Annual frequency and rate of necrotizing fasciitis-related deaths in the United States, 2003–2013.

Table 1. *Necrotizing fasciitis-related mortality rates/1 000 000 p-yr*

Characteristic	Deaths *n* (%)	Age-adjusted mortality rate/1 000 000 p-yr (95% CI)	Age-adjusted mortality rate ratios (95% CI)
Age group, yr* ($N = 9870$)			
<1	34 (0·3)	0·77 (0·51–1·03)	0·45 (0·30–0·61)
1–4	5 (0·1)	0·03 (0·00–0·05)	0·02 (0·00–0·03)
5–14	34 (0·3)	0·08 (0·05–0·10)	0·04 (0·03–0·06)
15–24	73 (0·7)	0·15 (0·12–0·19)	0·09 (0·07–0·11)
25–34	297 (3·0)	0·67 (0·59–0·74)	0·39 (0·34–0·44)
35–44	794 (8·0)	1·71 (1·59–1·83)	Reference
45–54	1876 (19·0)	3·91 (3·74–4·09)	2·29 (2·10–2·48)
55–64	2461 (24·9)	6·56 (6·30–6·81)	3·83 (3·52–4·17)
65–74	1893 (19·2)	8·22 (7·85–8·59)	4·80 (4·41–5·20)
75–84	1585 (16·1)	10·99 (10·45–11·53)	6·42 (5·87–6·97)
⩾85	818 (8·3)	14·27 (13·29–15·25)	8·34 (7·52–9·15)
Sex			
Female	4807 (48·7)	2·65 (2·57–2·73)	Reference
Male	5063 (51·3)	3·31 (3·22–3·39)	1·25 (1·20–1·30)
Race/ethnicity			
White, non-Hispanic	6548 (66·4)	2·58 (2·51–2·65)	Reference
Black, non-Hispanic	1694 (17·2)	5·07 (4·88–5·26)	1·97 (1·87–2·06)
Hispanic	1209 (12·3)	3·67 (3·54–3·80)	1·42 (1·36–1·49)
Asian, non-Hispanic	255 (2·6)	1·87 (1·68–2·05)	0·72 (0·65–0·80)
American Indian or Alaskan Native, non-Hispanic	164 (1·7)	7·37 (6·46–8·27)	2·86 (2·50–3·21)

CI, Confidence interval.
* Age-specific mortality rates are reported

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(mOR) and the associated 95% CI. All analyses were performed in Stata v. 13.0 (StataCorp., USA).

RESULTS

A total of 9871 NF-related deaths in the United States between 2003 and 2013 (Fig. 1) were identified, corresponding to a summary mortality rate of 4·8 deaths/1 000 000 p-yr. NF was reported as the underlying cause in 4185 (42%) deaths, and a contributing cause of death in 5686 (58%) deaths. An autopsy was reported in 885 (9%) of 9871 deaths, and autopsy status was unknown in an additional 1034 (11%) deaths. In a negative binomial regression model, there was not a significant time trend in the incidence rate of NF-associated deaths during the study period ($P = 0{\cdot}47$).

An underlying microbiological diagnosis was provided in 546 (6%) of 9871 deaths. Of these 546 deaths, streptococcal infection was identified in 260 (48%) deaths, staphylococcal infection in 119 (22%) deaths, Gram-negative infection in 114 (21%) deaths, gas gangrene in 28 (5%) deaths, anaerobic infection in 15 (3%) deaths, and a mixed infection was identified in 10 (2%) deaths. Thus, type II (mono-microbial) NF due to either *Staphylococcus* or *Streptococcus* was identified in 379 (69%) of 546 deaths where a microbiological diagnosis was included in the cause-of-death information.

Characteristics of individuals with NF-related death during this period are shown in Table 1. Advancing age was associated with an increasing rate of NF-related mortality, compared with a reference group of individuals aged 35–44 years, but no difference in mortality rates was observed in younger age groups. After adjusting for age, the rate of NF-related mortality in men was 1·25 times greater than the rate in women (95% CI 1·20–1·30). The age-adjusted mortality rate in black individuals was nearly double the rate in white individuals (1·97, 95% CI 1·87–2·06), and the rate in Native Americans was nearly three times the rate in white individuals (2·86, 95% CI 2·50–3·21). In contrast, NF-related mortality in Asian individuals was 28% lower than white individuals (age-adjusted mortality rate 0·72, 95% CI 0·65–0·80).

We aggregated ICD-10 codes by block to describe the most common conditions included in the death certificates for NF-related deaths (Table 2). Diabetes mellitus was the most common comorbid condition, identified in 21% of all deaths. Renal disease, ischaemic heart disease, and substance use were also frequently reported as comorbid conditions. In a matched case-control study of comorbid conditions, diabetes mellitus, renal failure, and obesity were significantly associated with NF-related death, compared with death due to other causes (Table 3). In contrast, heart disease and substance use were less commonly observed in NF-related deaths, compared to other causes.

Table 2. *Most common comorbid diagnoses in individuals with necrotizing fasciitis-related deaths in the United States, 2003–2013 (N = 9817)*

Comorbid condition	ICD-10 block codes	Deaths *n* (%)
Diabetes mellitus	E10–E14	2109 (21)
Other forms of heart disease	I30–I52	1972 (20)
Renal failure	N17–N19	1592 (16)
Other diseases of the respiratory system	J95–J99	1002 (10)
Mental and behavioural disorders due to psychoactive substance use	F10–F19	934 (10)
Ischaemic heart diseases	I20–I25	753 (8)
Hypertensive diseases	I10–I15	717 (7)
Diseases of liver	K70–K77	617 (6)
Obesity and other hyperalimentation	E65–E68	519 (5)
Chronic lower respiratory diseases	J40–J47	338 (3)
Influenza and pneumonia	J09–J18	323 (3)
Metabolic disorders	E70–E90	304 (3)
Malignant neoplasms of digestive organs	C15–C26	294 (3)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	C81–C96	282 (3)

DISCUSSION

In the United States from 2003 to 2013, the overall mortality rate for NF-related death was 4·8/1 000 000 p-yr. Contrary to our hypothesis, there was not a significant time trend in the number of cases of fatal NF during the study period. Streptococcal infection was most commonly identified in cases where a pathogen was reported, although most cases did not have a microbiological diagnosis established in the death certificate.

There are limited prior data that estimate the disease burden of NF in the United States. In a study of medical claims records for cellulitis diagnoses, the incidence of NF in adults was estimated to be 40 cases/1 000 000 p-yr [17]. The incidence of NF in

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Table 3. *Medical conditions associated with necrotizing fasciitis (NF) deaths in the United States, 2003–2013*

Condition	ICD-10 Codes	NF-related deaths ($N = 9871$) *n* (%)	Matched controls* ($N = 98\,710$) *n* (%)	Matched OR (95% CI)
Diabetes mellitus	E10–E14	2109 (21)	10 316 (10)	2·37 (2·25–2·50)
Heart disease	I00–I99	3301 (33)	49 007 (50)	0·49 (0·47–0·51)
Renal failure	N17–N19	1695 (17)	8223 (8)	2·31 (2·18–2·45)
Substance use	F10–F19	934 (9)	12 076 (12)	0·74 (0·69–0·80)
Liver disease	K70–K77	617 (6)	5872 (6)	1·06 (0·97–1·15)
Obesity	E65–E68	519 (5)	1928 (2)	2·83 (2·56–3·13)

CI, Confidence interval.
* Each case of NF-related death was matched to 10 controls by age, sex, and race/ethnicity.

inpatient admissions in Texas varied between 59 cases/1 000 000 p-yr from 2001 to 2002 and 76 cases/1 000 000 p-yr from 2009 to 2010, with an overall in-hospital mortality rate of 9·3% [18]. A larger study of necrotizing soft tissue infections using the Nationwide Inpatient Sample found that the number of hospital discharges for necrotizing soft tissue infections peaked in 2004, with an overall decline between 1998 and 2010 [19], although this approach may underestimate deaths that occur following discharge from the hospital [20]. Our estimate of 4·8 cases of fatal NF/1 000 000 p-yr is similar in scale to the population incidence rate that has recently been reported from New Zealand [21].

During the study period, we observed that fatal cases of NF were more common in older individuals, with the greatest number of cases observed in individuals aged 55–64 years. The association of advancing age with NF mortality increased for each age group beyond the reference group of 35- to 44-year-olds. In contrast with a previous report from Cook County, Illinois [22], we did not observe an increasing NF-associated mortality rate in individuals in the youngest age groups, and in fact observed declining mortality rates for every age group below the reference group.

In an adjusted analysis using population census data, we observed a greater incidence rate in black, Hispanic, and American Indian individuals compared to white individuals, and a lower incidence rate in Asian individuals. The observed relationship between race/ethnicity and NF-related mortality is likely multifactorial in aetiology. In a population-level study of sepsis syndrome in the United States, racial differences in outcomes were partly explained by differences in organ impairment [23]. The mortality rate was not adjusted for the presence of specific comorbidities, income level, or insurance status, which may further contribute to the observed mortality differences. Finally, disparities in access to healthcare, leading to delays in the recognition and appropriate management of NF, provide an additional explanation for the finding of increased mortality rates in Hispanic, black, and American Indian individuals compared to white individuals [24].

In a matched case-control study, comorbid conditions associated with NF-related deaths in the United States were identified, based on sampling of death certificate data from the entire population. Diabetes mellitus, obesity, and renal failure were significantly associated with NF-related death. In a hospital-based retrospective study of 299 patients with NF in New Zealand, diabetes and obesity were also found to be frequent comorbid conditions, identified in 32% and 23% of patients, respectively [25]. It is notable that a protective effect of diabetes mellitus in patients with NF has been reported previously in analyses of hospital discharge data [18, 26], which our approach was unable to address. Although outbreaks of NF have been reported in association with black-tar heroin use [27], there was no association between NF-related death and ICD-10 codes for substance use.

This study has several important limitations. Errors in the population estimates from the census data will be reflected in the calculated mortality rates. The completeness of a death certificate depends on the information available to the clinician at the time of death, and the appropriate recognition of all relevant contributing causes of death [28]. Additionally, relevant factors such as income level and health insurance status are not included on the death certificate, and there is limited information regarding the severity of comorbid factors such as diabetes mellitus, or the degree of organ failure. Strengths of the study include the

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completeness of death certificate reporting in the United States, and prior work with ICD coding to capture incident cases of NF in settings such as the National Surgical Quality Improvement Program [29].

In summary, we estimate the US mortality burden of NF to be 4·8 deaths/1 000 000 p-yr, with a stable annual incidence rate during the period 2003–2013. Age, sex, and race were independently associated with the rate of NF-related deaths during the study period. The observed racial differences in the mortality rate of NF merits further investigation.

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DECLARATION OF INTEREST

None.

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