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Deaths from Necrotizing Fasciitis in the United States, 2003–2013

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SUMMARY

Necrotizing fasciitis is a life-threatening infection requiring urgent surgical and medical therapy. Our objective was to estimate the mortality burden of necrotizing fasciitis in the United States, and to identify time trends in the incidence rate of necrotizing fasciitis-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 through 2013 for a listing of NF (ICD10 code M72.6) as either the underlying or contributing cause of death. We identified a total of 9,871 necrotizing fasciitis-related deaths in the U.S. between 2003 and 2013 (Figure 1), corresponding to a crude mortality rate of 4.8 deaths per 1,000,000 person-years, without a significant time trend. Compared to white individuals, the incidence rate of necrotizing fasciitis-associated death was greater among black, Hispanic, and American Indian individuals, and lower among Asian individuals. Streptococcal infection was most commonly identified in cases where a pathogen was reported. Diabetes mellitus and obesity were more commonly observed among necrotizing fasciitis-related deaths compared with deaths due to other causes. Racial differences in the incidence of necrotizing fasciitis-related deaths merits further investigation.

Keywords

Necrotizing fasciitis; epidemiology; mortality; Streptococcus; Staphylococcus

INTRODUCTION

Necrotizing fasciitis 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 necrotizing fasciitis 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

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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 necrotizing fasciitis can been classified based on anatomic location and the microbial etiology. Bacterial pathogens that have been implicated in necrotizing fasciitis include group A Streptococcus (GAS), *Staphylococcus aureus*, *Clostridium* species, and mixed gram-negative and anaerobic organisms [7]. Mixed infections with aerobic and anaerobic bacteria are classified as Type I, and mono-microbial infections with GAS or *S. aureus* are classified as Type II necrotizing fasciitis [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, with 7.2% of these cases presenting with necrotizing fasciitis [9].

There are little data available regarding time trends in the epidemiology of necrotizing fasciitis 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 necrotizing fasciitis in the United States over a 10-year period, and to identify temporal trends in the incidence of necrotizing fasciitis-related mortality during this period. In secondary analyses, we sought to characterize demographic factors and co-morbid conditions associated with necrotizing fasciitis-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. Years 2003 through 2013 were included, given the change in cause of death codes from the International Classification of Disease 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 through 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 necrotizing fasciitis 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, necrotizing fasciitis 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).

Necrotizing Fasciitis Mortality Rates Adjusted for Age, Race/ethnicity, and Sex

Characteristics of individuals with necrotizing fasciitis-related deaths in the U.S. were summarized according to demographic characteristics. Age at death was defined based on the following age groups: < 1 year, 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 [15]. Goodness-of-fit was examined by testing the statistical significance of the model deviance with the chi-squared test, along with visual inspection of the plot of variance-versus-mean.

Time Trend Analysis

Count data were modeled using maximum likelihood analysis in a negative binomial regression model [13]. 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 [14]. In order to test for a temporal trend in the rate of necrotizing fasciitis-associated deaths in the population, year was included as a dummy variable in the negative binomial regression model, with the population as the offset.

Matched Case-Control Analysis for Associated Diagnoses

To identify co-morbid conditions associated with necrotizing fasciitis-related death, a previously validated approach developed by Redelings and colleagues [16] was employed. For each record of necrotizing fasciitis-related death during the study period, a random sample of deaths from the multiple cause of death dataset during the same year was selected, and matched at a 10:1 ratio (controls:case) by age category, sex, and race/ethnicity. Groups of co-morbidities were defined based on the leading ICD-10 diagnoses among all necrotizing fasciitis-related deaths. For each co-morbidity, we calculated a matched odds ratio (MOR) and the associated 95% CI. All analyses were performed in Stata v13.0 (Statacorp, TX).

RESULTS

A total of 9,871 necrotizing fasciitis-related deaths in the U.S. between 2003 and 2013 (Figure 1) were identified, corresponding to a summary mortality rate of 4.8 deaths per 1,000,000 person-years. Necrotizing fasciitis was reported as the underlying cause in 4,185 deaths (42%), and a contributing cause of death in 5,686 deaths (58%). An autopsy was reported in 885 of 9,871 deaths (9%), and autopsy status was unknown in an additional 1,034 deaths (11%). In a negative binomial regression model, there was not a significant

time trend in the incidence rate of necrotizing fasciitis-associated deaths during the study period (p=0.47).

An underlying microbiologic diagnosis was provided in 546 of 9,871 deaths (6%). Among these 546 deaths, streptococcal infection was identified in 260 deaths (48%), staphylococcal infection in 119 deaths (22%), gram-negative infection in 114 deaths (21%), gas gangrene in 28 deaths (5%), anaerobic infection in 15 deaths (3%), and a mixed infection was identified in 10 deaths (2%). Thus, type II (mono-microbial) necrotizing fasciitis due to either *Staphylococcus* or *Streptococcus* was identified in 379 of 546 deaths (69%) where a microbiologic diagnosis was included in the cause of death information.

Characteristics of individuals with necrotizing fasciitis-related death during this period are shown in Table 1. Advancing age was associated with an increasing rate of necrotizing fasciitis-related mortality, as compared with a reference group of 35 to 44-year old individuals, but no difference in mortality rates was observed among younger age categories. After adjusting for age, the rate of necrotizing fasciitis-related mortality among men was 1.25 times greater than the rate among women (95% CI 1.20 to 1.30). The age-adjusted mortality rate among black individuals was nearly two times the rate among white individuals (1.97, 95% CI 1.87 to 2.06), and the rate among Native Americans was nearly three times the rate among white individuals (2.86, 95% CI 2.50 to 3.21). In contrast, necrotizing fasciitis-related mortality among Asian individuals was 28% lower than white individuals (age-adjusted mortality rate 0.72, 95% CI 0.65, 0.80).

We aggregated ICD10 codes by block to describe the most common conditions included in the death certificates for necrotizing fasciitis-related deaths (Table 2). Diabetes mellitus was the most common co-morbid condition, identified in 21% of all deaths. Renal disease, ischemic heart disease, and substance use were also frequently reported as co-morbid conditions. In a matched case-control study of co-morbid conditions, diabetes mellitus, renal failure, and obesity were significantly associated with necrotizing fasciitis-related death, compared with death due to other causes (Table 3). In contrast, heart disease and substance use were less commonly observed among necrotizing fasciitis-related deaths, compared to other causes.

DISCUSSION

In the United States from 2003 to 2013, the overall mortality rate for necrotizing fasciitis-related death was 4.8 per 1,000,000 person-years. Contrary to our hypothesis, there was not a significant time trend in the number of cases of fatal necrotizing fasciitis during the study period. Streptococcal infection was most commonly identified in cases where a pathogen was reported, although most cases did not have a microbiologic diagnosis established in the death certificate.

There are limited prior data that estimate the disease burden of necrotizing fasciitis in the U.S.. In a study of medical claims records for cellulitis diagnoses, the incidence of necrotizing fasciitis in adults was estimated to be 40 cases per 1,000,000 person-years [17]. The incidence of necrotizing fasciitis among inpatient admissions in Texas varied between

59 cases per 1,000,000 person-years from 2001 to 2002 and 76 cases per 1,000,000 person-years 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 necrotizing fasciitis per 1,000,000 person-years 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 necrotizing fasciitis were more common among older individuals, and the greatest number of cases observed among individuals age 55 to 64. The association of advancing age with necrotizing fasciitis mortality increased for each age category 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 necrotizing fasciitis-associated mortality rate among individuals in the youngest age groups, and in fact observed declining mortality rates for every age category below the reference group.

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

In a matched case-control study, co-morbid conditions associated with necrotizing fasciitis-related deaths in the United States were identified, based on sampling of deaths certificate data from the entire population. Diabetes mellitus, obesity, and renal failure were significantly associated with necrotizing fasciitis-related death. In a hospital-based retrospective study of 299 patients with necrotizing fasciitis in New Zealand, diabetes and obesity were also found to be frequent co-morbid conditions, identified in 32% and 23% of patients, respectively [25]. It is notable that a protective effect of diabetes mellitus among patients with necrotizing fasciitis has been reported previously in analyses of hospital discharge data [18, 26], which our approach was unable to address. Although outbreaks of necrotizing fasciitis have been reported in association with black-tar heroin use [27], there was no association between necrotizing fasciitis-related death and ICD10 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 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 co-morbid factors such as diabetes mellitus, or the degree of organ failure. Strengths of the study include the completeness of death certificate reporting in the United States, and prior work with ICD coding to capture incident cases of necrotizing fasciitis in settings such as the National Surgical Quality Improvement Program [29].

In summary, we estimate the U.S. mortality burden of necrotizing fasciitis to be 4.8 deaths per 1,000,000 person-years, with a stable annual incidence rate during the period 2003–2013. Age, sex, and race were independently associated with the rate of necrotizing fasciitis-related deaths during the study period. The observed racial differences in the mortality rate of necrotizing fasciitis merits further investigation.

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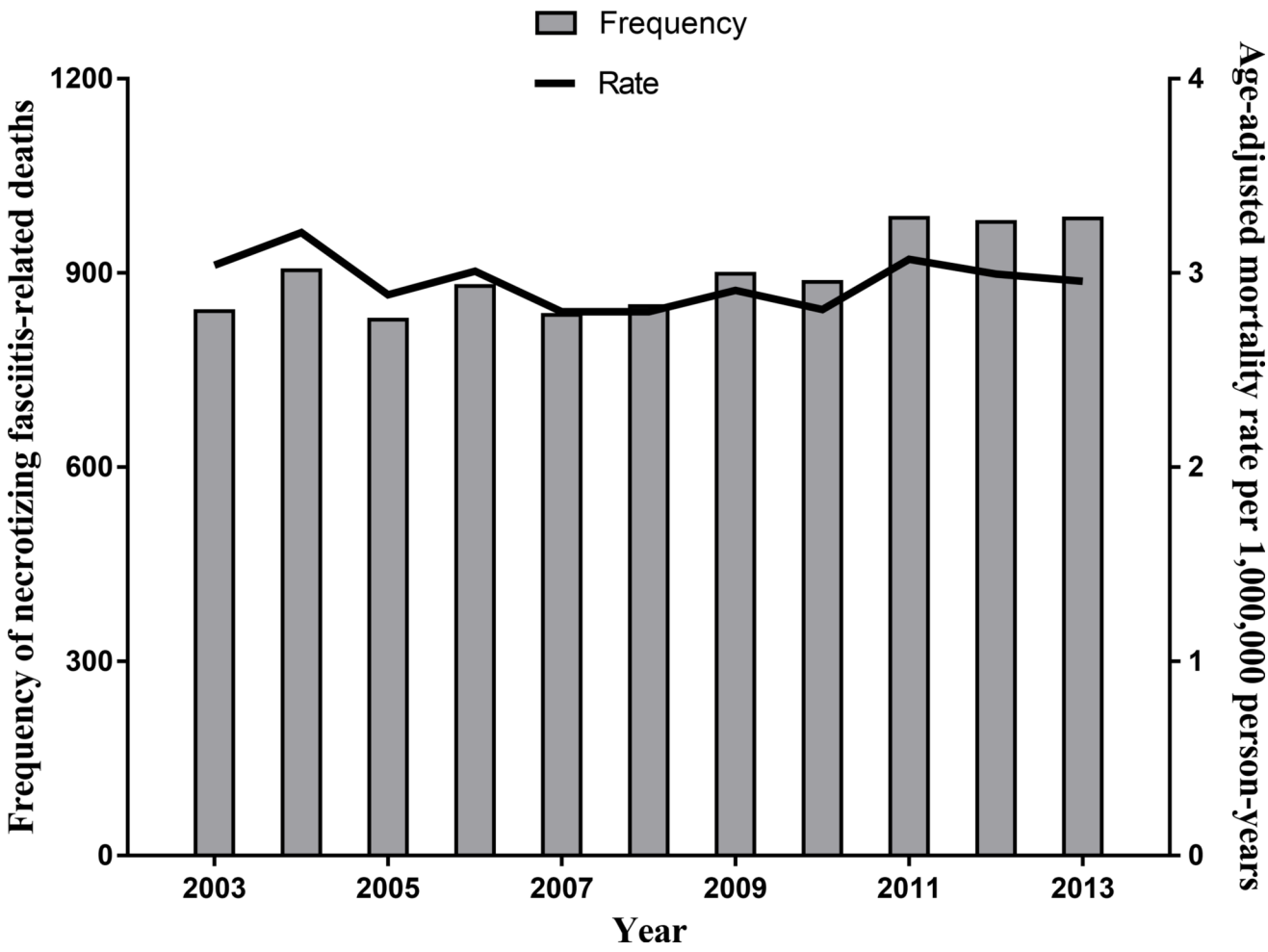

Figure 1.
Annual frequency and rate of necrotizing fasciitis related deaths in the U.S., 2003–2013.

Table 1

Necrotizing fasciitis-related mortality rates per 1,000,000 person-years

Characteristic	Number of deaths (%)	Age-adjusted mortality rate per 1,000,000 person-years (95% CI)	Age-adjusted mortality rate ratios (95% CI)
Age categories * (N=9,870)			
< 1 year old	34 (0.3)	0.77 (0.51, 1.03)	0.45 (0.30, 0.61)
1–4 years old	5 (0.1)	0.03 (0.00, 0.05)	0.02 (0.00, 0.03)
5–14 years old	34 (0.3)	0.08 (0.05, 0.10)	0.04 (0.03, 0.06)
15–24 years old	73 (0.7)	0.15 (0.12, 0.19)	0.09 (0.07, 0.11)
25–34 years old	297 (3.0)	0.67 (0.59, 0.74)	0.39 (0.34, 0.44)
35–44 years old	794 (8.0)	1.71 (1.59, 1.83)	Reference
45–54 years old	1,876 (19.0)	3.91 (3.74, 4.09)	2.29 (2.10, 2.48)
55–64 years old	2,461 (24.9)	6.56 (6.30, 6.81)	3.83 (3.52, 4.17)
65–74 years old	1,893 (19.2)	8.22 (7.85, 8.59)	4.80 (4.41, 5.20)
75–84 years old	1,585 (16.1)	10.99 (10.45, 11.53)	6.42 (5.87, 6.97)
>84 years old	818 (8.3)	14.27 (13.29, 15.25)	8.34 (7.52, 9.15)
Sex			
Female	4,807 (48.7)	2.65 (2.57, 2.73)	Reference
Male	5,063 (51.3)	3.31 (3.22, 3.39)	1.25 (1.20, 1.30)
Race/ethnicity			
White, non-Hispanic	6,548 (66.4)	2.58 (2.51, 2.65)	Reference
Black, non-Hispanic	1,694 (17.2)	5.07 (4.88, 5.26)	1.97 (1.87, 2.06)
Hispanic	1,209 (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)

* Age-specific mortality rates are reported

Table 2

Most common co-morbid diagnoses among individuals with necrotizing fasciitis-related deaths in the United States, 2003–2013 (N=9,817)

Co-morbid Condition	ICD10 Block Codes	Number of deaths (%)
Diabetes mellitus	E10–E14	2,109 (21)
Other forms of heart disease	I30–I52	1,972 (20)
Renal failure	N17–N19	1,592 (16)
Other diseases of the respiratory system	J95–J99	1,002 (10)
Mental and behavioral disorders due to psychoactive substance use	F10–F19	934 (10)
Ischemic 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, hematopoietic and related tissue	C81–C96	282 (3)

Table 3

Medical conditions associated with necrotizing fasciitis deaths in the United States, 2003–2013.

Condition	ICD-10 Codes	Necrotizing fasciitis-related deaths (%) N=9,871	Matched controls* (%) N=98,710	Matched OR (95% CI)
Diabetes mellitus	E10–E14	2,109 (21%)	10.316 (10%)	2.37 (2.25, 2.50)
Heart disease	I00–I99	3,301 (33%)	49,007 (50%)	0.49 (0.47, 0.51)
Renal failure	N17–N19	1,695 (17%)	8,223 (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%)	5,872 (6%)	1.06 (0.97, 1.15)
Obesity	E65–E68	519 (5%)	1,928 (2%)	2.83 (2.56, 3.13)

*Each case of necrotizing fasciitis-related death was matched to 10 controls by age, sex, and race/ethnicity