Predictors of Death after Severe *Streptococcus pyogenes* Infection

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An evaluation of the relative importance of host and pathogen factors on the survival rates of patients with invasive *Streptococcus pyogenes* infection found a number of clinical and demographic factors to be associated with risk for death. Some evidence suggested a seasonal pattern to patient survival rate.

Infectious diseases caused by *Streptococcus pyogenes* are among the most acutely life threatening. Although invasive *S. pyogenes* infections are uncommon (3 per 100,000 population annually in the United States, United Kingdom, and Australia) (*1*–*3*), the case-fatality rate is high relative to many other infections (*1,3,4*). Identification of specific host and pathogen characteristics with poor survival rates in patients who have these infections could help identify potential pathogenic mechanisms for further research at a cellular level, potentially resulting in identification of novel therapeutic targets.

The Study

As part of a European study of severe *S. pyogenes* infections, the United Kingdom undertook enhanced surveillance during 2003–2004 (*2,5,6*). Case-patients were defined as persons with *S. pyogenes* isolated from a sterile site or from a nonsterile site if the patient had pneumonia, necrotizing fasciitis, puerperal sepsis, meningitis, septic arthritis, or if streptococcal toxic shock syndrome (STSS) developed (*7*). Methods are reported elsewhere (*2,8*).

To identify patient outcome, data from England and Wales were linked to death registrations obtained from the Office for National Statistics by using probabilistic methods (*9*). Deaths were identified that occurred up to 30 days after diagnosis of infection; time between diagnosis and death was measured from the date the culture-positive specimen was taken.

Data were analyzed by using STATA statistical software version 8.2 (Stata Corporation, College Station, TX, USA). A nonproportional test for equality of survivor function (Peto-Peto-Prentice) was used to assess differences between subgroups, with Cox proportional hazards regression used for multivariable analysis.

Of the 3,566 case-patients with severe *S. pyogenes* infection, 3,422 (96%) had sufficient identifiers to be linked to death registrations and were used for all further analyses. Overall, 698 (20%) case-patients died within 30 days after collection of culture-positive specimens. Risk for death was highest within 1 day after specimen collection (11% [375]), extending to 16% (559) for the first 7 days, beyond which risk for death dropped substantially.

Analysis of the certified cause of death identified an infectious underlying cause in 280 (50%) deaths occurring from any International Classification of Diseases, 10th Revision, condition classification within 7 days. *S. pyogenes* infection was specified as the cause of death in 5 of these (Table).

Age strongly influenced survival rate; the oldest patients had the poorest survival rates ($p<0.001$; Figure 1). Most deaths in patients <45 years of age (73/104 [70%]) occurred within the first 2 days, whereas deaths in older age groups were more dispersed over time. Other patient factors were independently associated with risk for death (online Appendix Table, available from http://www.cdc.gov/EID/content/15/8/1304-appT.htm). Of patients without any identified concurrent illnesses, 87/518 (17%) died within 7 days.

Case-fatality rates paralleled seasonal incidence (online Appendix Figure, available from http://www.cdc.gov/EID/content/15/8/1304-appF.htm), and were highest from December to April (17%–21%), gradually falling through the summer to their lowest point in October (6%). After adjustment for other significant factors, patients whose infection was diagnosed in October were 82% less likely to die than were those whose infection was diagnosed in January.

Patients identified with necrotizing fasciitis had the highest risk for death within 7 days (34%), >2 times higher than patients with other clinical manifestations, after adjustment for other significant factors. Patients who reported gastrointestinal symptoms were 2 times as likely as those who did not to die within the first 7 days ($p = 0.02$). Only 9/76 (12%) patients who had gastrointestinal symptoms met the case definition for STSS. Cellulitis, the most common clinical symptom, was associated with more deaths (130/438 [30%] patients) than was any other condition. Survival probability in the 30 days after a culture-positive specimen was significantly reduced among patients in

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Table. Conditions selected as cause of death within 7 days after diagnosis of severe *Streptococcus pyogenes* infection, England and Wales, 2003–2004

Condition classification (International Classification of Diseases, 10th Revision, code), N = 557*	Underlying cause, no. (%)	All mentions,† no. (%)
Infectious and parasitic diseases (A00–B99)	67 (12)	303 (54)
Neoplasms (C00–D48)	52 (9)	80 (14)
Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism (D50–D89)	0 (0)	9 (2)
Endocrine system (E00–E90)	12 (2)	50 (9)
Mental and behavioral disorders (F00–F99)	19 (3)	32 (6)
Diseases of the nervous system (G00–G99)	7 (1)	12 (2)
Diseases of the eye and adnexa (H00–H59)	4 (1)	5 (1)
Diseases of the ear and mastoid process (H60–H95)	2 (<1)	2 (<1)
Diseases of the circulatory system (I00–I99)	108 (19)	297 (53)
Diseases of the respiratory system (J00–J99)	99 (18)	223 (40)
Diseases of the digestive system (K00–K93)	32 (6)	66 (12)
Diseases of the skin and subcutaneous tissue (L00–L99)	67 (12)	102 (18)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	39 (7)	69 (12)
Diseases of the genitourinary system (N00–N99)	17 (3)	65 (12)
Complications of pregnancy, childbirth, and the puerperium (O00–O99)	1 (<1)	1 (<1)
Certain conditions originating in the perinatal period (P00–P96)	1 (<1)	3 (1)
Congenital abnormalities (Q00–Q99)	2 (<1)	7 (1)
Symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified (R00–R99)	7 (1)	49 (9)
Injury, poisoning, and certain other consequences of external causes (S00–T98)	0 (0)	49 (9)
External causes of mortality (V01–Y98)	21 (4)	61 (11)

*Percentages based on 557 deaths (cause of death was not available for 2 patients).
†Conditions noted on the death certificate as the underlying or contributory cause of death.

whom STSS developed (p<0.001; Figure 2); 47/178 (26%) of these patients died within a day of specimen collection.

Risk for death varied according to the *emm*/M-type responsible for the infection. The highest risk was associated with *emm*/M3 (33%) or *emm*/M1 (28%), with *emm*/M3 being borderline significant after adjustment for other significant factors.

Conclusions

This analysis highlighted the scale and rapidity of deaths in patients with severe *S. pyogenes* infection, reemphasizing the importance of early recognition of invasive disease and prompt initiation of antimicrobial drug and supportive therapy. A number of factors conferred a heightened risk for death, which other studies also have found: increasing age, diagnosis of necrotizing fasciitis or pneumonia, and underlying malignancy (*1,10,11*). Although necrotizing fasciitis carried the highest risk for all-cause mortality, it is a relatively rare condition, accounting for only 10% of all deaths, compared with the more common and typically less severe cellulitis (30% of deaths). Some evidence indicated that *emm*/M3 was more commonly associated with death than were other *emm*/M-types, also found elsewhere (*1,11*). Development of STSS was a strong predictor of poor outcome, although whether this syndrome is independently related to death is unclear, given that several of its constituent markers effectively denote the progressive failure of organ systems. For this reason, STSS was not included in the multivariable analysis. Notably, patients with gastrointestinal symptoms had a poorer outcome than others; presumably this is a sign of overwhelming sepsis possibly linked to toxin production. Although relatively uncommon (3% of case-patients), gastrointestinal symptoms clearly are of diagnostic importance and should be included in the severity assessment of patients with other signs and symptoms of *S. pyogenes* infection.

An intriguing and novel finding from this analysis is that risk for death mirrors seasonal changes in incidence (highest in the winter/spring months and falling substantially to a nadir in October). An unadjusted-for confounder could explain this pattern, such as a preceding viral infection, but no candidates with a suitable seasonal pattern

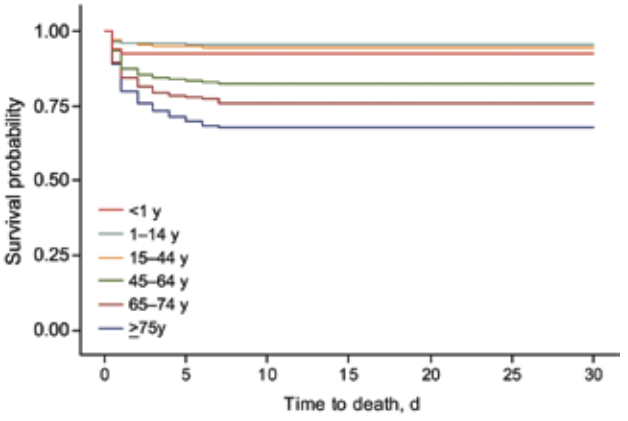

Figure 1. Kaplan-Meier analysis of time to death after diagnosis of severe *Streptococcus pyogenes* infection, by age, England and Wales, 2003–2004.

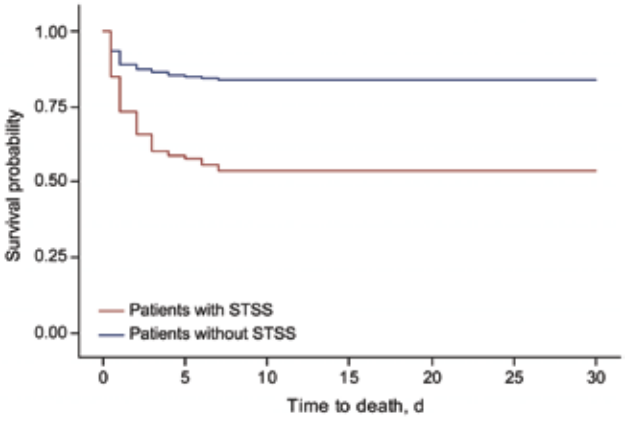

Figure 2. Kaplan-Meier analysis of time to death after diagnosis of severe *Streptococcus pyogenes* infection, by development of streptococcal toxic shock syndrome (STSS), England and Wales, 2003–2004.

are apparent. Although *emm*/M-type was included in the model, differences could exist in the circulation of specific subtypes with particular virulence profiles throughout the year, again not accounted for in this analysis. Seasonal differences in case-fatality rates may yield some important clues about the drivers behind the seasonal incidence pattern of *S. pyogenes* infections. An explanation centered wholly around transmission dynamics seems less favored because it would not explain the changing risk for death. An immunologically focused explanation would fit better because it could explain both the changing incidence rate and the changing case-fatality rate. The length of daylight in a given day can affect the production of vitamin D and melatonin. Both vitamin D and melatonin are known to impact immune function (*12–14*). Although neither appear to be consistent with an autumnal boost to host immunity, if the beneficial effect of vitamin D production during the summer has a cumulative maximal impact in the autumn (*15*), then this theory could offer an explanation.

Because *S. pyogenes* is a largely sporadic infection occurring diffusely throughout the population, opportunities for control of severe infections remain limited. The 26 serotypes included in a multivalent vaccine currently under phase II clinical trials represent 67% of all isolates collected in this study, and 80% of all deaths occurring within 7 days after diagnosis (*16*). The impact of any vaccine will clearly depend on many factors, with the possibility of serotype replacement undermining any such efforts. The challenge to provide a lasting control measure for these devastating infections will continue long into the future.

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Appendix Table. Death within 7 days after diagnosis of severe *Streptococcus pyogenes* infection, by variable, England and Wales, 2003–2004

Variable	No. (%) who died	Hazard ratio (95% confidence interval)*	p value
Patient characteristics			
Age, y (n = 3,422)			
<1	118 (8)	0.21 (0.07–0.60)	<0.01
1–14	292 (4)	0.21 (0.11–0.43)	<0.01
15–44	1,226 (6)	0.32 (0.21–0.50)	<0.01
45–64	525 (18)	0.46 (0.32–0.66)	<0.01
65–74	416 (24)	0.68 (0.46–0.99)	0.04
≥75	845 (32)	Reference	
Sex (n = 3,419)			
Male	1,849 (15)	Reference	
Female	1,570 (18)	0.89 (0.69–1.16)	0.39
Predisposing risk factors (n = 2,124)			
Admitted from an institution†	142 (35)	1.57 (1.06–2.31)	0.02
Alcoholism	79 (27)	1.94 (1.10–3.41)	0.02
Diabetes	145 (27)	1.01 (0.64–1.59)	0.97
Healthcare-associated infection	185 (18)	0.88 (0.55–1.39)	0.58
Injecting drug use	436 (4)	0.68 (0.33–1.38)	0.29
Malignancy	153 (31)	1.54 (1.04–2.27)	0.03
Nonsteroidal antiinflammatory drug use	42 (28)	1.37 (0.72–2.60)	0.34
Recent childbirth	81 (2)	0.51 (0.07–3.85)	0.52
Skin lesion	650 (20)	1.23 (0.91–1.67)	0.18
Steroid use	69 (28)	1.39 (0.78–2.49)	0.26
Varicella	41 (2)	0.37 (0.05–2.73)	0.33
Month of diagnosis (n = 3,422)			
January	367 (19)	Reference	
February	311 (17)	1.01 (0.61–1.67)	0.98
March	411 (18)	0.92 (0.57–1.49)	0.74
April	403 (18)	0.80 (0.49–1.31)	0.38
May	304 (17)	1.07 (0.62–1.85)	0.80
June	257 (13)	0.93 (0.48–1.78)	0.82
July	282 (17)	0.88 (0.51–1.51)	0.63
August	205 (14)	0.82 (0.41–1.66)	0.59
September	186 (12)	0.69 (0.32–1.52)	0.36
October	209 (6)	0.18 (0.04–0.75)	0.02
November	226 (15)	1.18 (0.66–2.09)	0.57
December	261 (21)	1.14 (0.65–2.00)	0.64
Clinical features (n = 2,407)			
Nonfocal bacteremia	519 (21)	1.28 (0.87–1.89)	0.21
Cellulitis	811 (16)	0.73 (0.52–1.04)	0.08
Erysipelas	20 (25)	2.36 (0.82–6.77)	0.11
Meningitis	28 (21)	2.27 (0.78–6.61)	0.13
Necrotizing fasciitis	125 (34)	2.22 (1.42–3.47)	<0.01
Pneumonia	438 (31)	1.73 (1.18–2.55)	0.01
Puerperal sepsis‡	55 (2)		
Septic arthritis	204 (7)	0.50 (0.20–0.97)	0.04
Streptococcal toxic shock syndrome*	178 (46)		
Gastrointestinal symptoms	71 (28)	2.00 (1.10–3.63)	0.02
emm/M-type (n = 2,345)§			
emm/R28	136 (17)	Reference	
emm/M1	414 (28)	1.14 (0.66–1.97)	0.65
emm/M3	305 (33)	1.70 (0.97–1.98)	0.06
emm/M4	91 (11)	0.42 (0.14–1.27)	0.12
emm/M5	86 (23)	1.36 (0.65–2.83)	0.42
emm/M6	45 (20)	1.03 (0.40–2.65)	0.95
emm/M12	113 (16)	1.21 (0.58–2.50)	0.61
emm/M18	50 (16)	1.01 (0.39–2.63)	0.98
emm/M22	38 (11)	0.48 (0.11–2.12)	0.33

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emm/M33	31 (6)	0.55 (0.12–2.48)	0.44
emm/M43	48 (8)	0.88 (0.25–3.16)	0.85
emm/M81‡	40 (8)		
emm/M82	51 (10)	0.42 (0.09–1.95)	0.27
emm/M83	133 (7)	0.44 (0.14–1.37)	0.16
emm/M87	229 (17)	0.75 (0.39–1.44)	0.39
emm/M89	192 (17)	0.54 (0.27–1.08)	0.08
Other	343 (11)	0.55 (0.28–1.09)	0.09

*Adjusted for all variables in the table except streptococcal toxic shock syndrome.
†Data available for 1,767 case-patients.
‡Dropped from the model owing to complete prediction of failure because of small number of case-patients.
§*emm*/M-types identified from ≥30 case-patients.

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