Serious Infections in People with Scleroderma: A National U.S. Study

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Abstract
Objective: To study incidence, time-trends and outcomes of serious infections in scleroderma.

Methods: We used the 1998-2016 U.S. National Inpatient Sample data. We examined the epidemiology, time-trends and outcomes of five serious infections (opportunistic infections (OI), skin and soft tissue infections (SSTI), urinary tract infection (UTI), pneumonia, and sepsis/bacteremia) in hospitalized people with scleroderma. We performed multivariable-adjusted logistic regression analyses to analyze independent association of factors with healthcare utilization (hospital charges, length of hospital stay, discharge to non-home setting), and in-hospital mortality. Results: There were 49,904,955 hospitalizations with serious infections in people without scleroderma and 61,615 in those with scleroderma. During 1998-2016, the most common serious infections in scleroderma were pneumonia (45%), sepsis (32%), SSTI (19%), UTI (3%) and OI (3%). In 2013-14, sepsis surpassed pneumonia as the most common serious infection; by 2015-16, sepsis was 1.8-times more common than pneumonia. Over the study period, hospital charges increased, while length of hospital stay and in-hospital mortality decreased, overall and for each serious infection. Multivariable-adjusted analyses showed that sepsis, age ≥80 years and Deyo-Charlson score ≥2 were associated with significantly higher odds of healthcare utilization and in-hospital mortality; and Medicare or Medicaid insurance payer, Northeast location, urban teaching or non-teaching hospital, and medium or large hospital bed size with significantly higher odds of healthcare utilization. Conclusions: Outcomes in people with scleroderma hospitalized with serious infections have improved over time, except higher hospital charges. Identification of factors associated with higher healthcare utilization and in-hospital mortality allows for developing interventions to improve outcomes.

Background
Systemic sclerosis, also called scleroderma, is a multisystem autoimmune disease, associated with high morbidity and mortality [1] and frequent hospitalizations [2]. In an analysis of national U.S. data from 2002–2003, the most common reasons for scleroderma hospitalizations were diseases of the circulatory, gastrointestinal, musculoskeletal followed respiratory system [3]. Respiratory infection (8%) was the third leading cause of mortality (principal diagnoses) in hospitalized scleroderma...
patients and ranked higher than heart failure [3]. In a study of 116 patients with scleroderma examined over 14 years with a median follow-up of 2-years, of the 31 people who died, 13 (11%) died of infections [4]. In a systematic review of infections in connective tissue diseases, most studies were limited to lupus, and only one study included people with scleroderma [5]. Therefore, while infection has a significant contribution to mortality in people with scleroderma [3, 4], few studies have examined the epidemiology of hospitalized infections and their outcomes in scleroderma [5]. Therefore, our study objective was to examine the epidemiology, time-trends, healthcare utilization and mortality of serious infection hospitalizations in scleroderma in a national U.S. cohort.

Methods

Data Source and Study Cohort Selection

Our study cohort included five, common serious infection hospitalizations in people with scleroderma in the U.S. NIS 1998-2016 sample. The NIS is a 20% stratified sample of discharge records from all participating community hospitals from all participating states [6]. The NIS is the largest publicly available, de-identified all-payer inpatient health care database in the U.S. It has been used for epidemiological studies of hospitalization, mortality and costs, since it represents all hospitalizations in the U.S. The Institutional Review Board at the University of Alabama at Birmingham (UAB) approved this study.

We identified five types of serious infections based on the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes in the primary diagnosis position for hospitalization: (1) opportunistic infections (OI; 010.xx –018.xx, 031.xx, 078.5, 075.xx, 053.xx, 112.4, 112.5, 112.81, 112.83, 130.xx, 136.3, 117.5, 027.0, 039.xx, 117.3, 114.xx, 115.xx, 116.0); (2) skin and soft tissue infections (SSTI; 040.0, 569.61, 681.xx, 682.xx, 785.4, 728.86, and 035.xx); (3) urinary tract infection (UTI; 590.xx); (4) pneumonia (003.22, 481.0, 513.0, 480.xx, 482.xx, 483.xx, 485.xx, 486.xx); and (5) sepsis/bacteremia (038.xx and 790.7), as previously [7, 8]. These diagnostic codes have been shown to be valid in administrative datasets, with positive predictive values of 70% to 100% in people with rheumatoid arthritis [9]. We also used the ICD-10-CM codes for infections for the 2015-2016 data due to a coding system change to ICD-10-CM in 2015 in the U.S. (Appendix 1).
Composite infection was defined as any of the serious infection occurring as primary diagnosis for hospitalization. Scleroderma was identified based on the presence of an International Classification of Diseases, ninth or tenth revision, clinical modification (ICD-9-CM or ICD-10-CM) code for scleroderma (710.1 or M34) in a non-primary position during the index hospitalization. A previous study showed sensitivity of 81% and specificity of 95% using a diagnostic code approach for scleroderma [10].

**Covariates and Outcomes**

We adjusted each regression model for covariates/confounders, including age, sex, race, serious infection type (OI, SSTI, UTI, pneumonia, sepsis [reference]), median household income, the insurance payer, hospital characteristics (region, location/teaching status, bed size) and Deyo-Charlson comorbidity index, a validated measure of medical comorbidity that includes 17 comorbidities, with higher score indicating more comorbidity load.

We examined healthcare utilization and in-hospital mortality, details are as follows: (1) health care utilization: total hospital charges above the median for each calendar year; the length of hospital stay above the median of 3 days; and discharge to non-home settings (rehabilitation or an inpatient facility); and (2) in-hospital mortality.

**Statistical Analyses**

We followed the survey analysis procedures that account for the weights, clusters and strata as defined in NIS, including the modified weights with the change in sampling in 2012. We compared the summary statistics using chi-square or student’s t-test, as appropriate. Rates were calculated per 100,000 NIS claims. We analyzed time-trends in rate of each serious infection using Cochran Armitage test. We performed multivariable-adjusted logistic regression analyses for each study outcome, adjusting for all covariates listed in the section above. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. We used SAS 9.3 (Cary, N.C.) for all analyses. We considered a p-value <0.05 to be statistically significant, which corresponds to a 95% CI that excludes unity.

**Results**

**Characteristics and outcomes of people with vs. without scleroderma admitted with**
serious Infection

There were 49,904,955 hospitalizations with serious infections in people without scleroderma and 61,615 in those with scleroderma. The average age of patients with scleroderma with a serious infection was 61.4 years (median of 61.7 years; Appendix 2), similar to all scleroderma hospitalizations.

Compared to patients admitted with serious infection without scleroderma, people with scleroderma were younger (median age, 65 vs. 62 years), and were more likely to be female (52% vs. 84%), or have Deyo-Charlson score of 2 or more (42% vs. 64%; Appendix 2).

Compared to patients hospitalized with serious infection without scleroderma, people with scleroderma had higher median hospital charges ($16,832 vs. $22,105), longer median hospital stay (3.7 vs. 4.4 days); were more likely to have hospital stay >3 days (59% vs. 66%), hospital charges above the median (75% vs. 79%), or to be discharged home (74% vs. 83%); and had higher mortality (6.2% vs. 9%) (Appendix 2).

Serious Infection Type in Scleroderma: Characteristics and Outcomes

Over the study period 1998-2016, the most common serious infections in scleroderma were pneumonia (45%) and sepsis (32%), followed by SSTI (19%), UTI (3%) and OI (3%; Appendix 3). Scleroderma patients hospitalized with pneumonia or sepsis were 5 year older than those admitted with OI (Appendix 3).

The median length of hospital stay over the study period was the highest for OI hospitalizations at 6.1 days and the lowest for UTI at 2.8 days (Appendix 3). Serious infections led to above median length of hospital stay in 61-79% of discharges except for UTI, with 45% of the people. Median hospital charges were highest for hospitalizations with sepsis at $38,118 and lowest for UTI, $13,646 (Appendix 3).

Time-trends in serious infection hospitalization in Scleroderma

We noted a significant increase in the frequency and rate of sepsis, and possibly OI and UTI (Appendix 4 and 5; Figure 1). In 2013-14, sepsis surpassed pneumonia as the most common serious infection in people with scleroderma and by 2015-16, sepsis accounted for 1.8-times as many
hospitalized serious infections as pneumonia (Appendix 6; Figure 1).

We found a 3.6-fold increase in the overall mean hospital charges for composite serious infection in scleroderma patients from $23,152 in 1998-2000 to $87,095 in 2015-2016 (Appendix 7). On the other hand, the mean hospital stay decreased from 4.6 days in 1998-2000 to 4.2 days in 2015-2016. The reduction was the greatest for OI, from 9.5 to 5.8 days. In-hospital mortality also decreased from 10.3% for composite serious infection to 7.8%, respectively. The largest reductions were for OI, 21.2% to 7.7%, sepsis, 22.5% to 13.2%, and pneumonia, 9.8% to 2.8% (Appendix 7).

**Predictors of healthcare utilization and mortality in scleroderma admitted with serious infection**

Multivariable-adjusted analyses showed that compared to sepsis, other infections were significantly associated with lower healthcare utilization and mortality; Age ≥ 80 years and Deyo-Charlson score ≥ 2 were also significantly associated (Table 1). Medicare or Medicaid insurance payer. Northeast location, urban teaching or non-teaching status, medium or large hospital bed size were associated with higher odds of healthcare utilization only (Table 1).
Table 1
Multivariable-adjusted correlates of healthcare utilization and mortality for serious infections in scleroderma

|                        | Hospital charges > median | Discharge to care facility | Length of Hospital Stay > 3 days | In-hospital Mortality |
|------------------------|---------------------------|-----------------------------|---------------------------------|-----------------------|
| Age category           | Adjusted odds ratio (95% CI) |                             |                                 |                       |
| <50 years              | Ref                        | Ref                         | Ref                             | Ref                   |
| 50 - <65 years         | 1.06 (0.95, 1.19)          | 1.39 (1.19, 1.62)           | 1.10 (0.99, 1.22)               | 1.54 (1.24, 1.90)     |
| 65-79 years            | 0.96 (0.85, 1.09)          | 2.01 (1.70, 2.38)           | 1.12 (0.99, 1.27)               | 2.08 (1.65, 2.63)     |
| ≥80 years              | 0.79 (0.68, 0.93)          | 4.17 (3.43, 5.08)           | 1.23 (1.05, 1.44)               | 3.23 (2.46, 4.24)     |
| Sex                    |                           |                             |                                 |                       |
| Male                   | Ref                        | Ref                         | Ref                             | Ref                   |
| Female                 | 0.99 (0.89, 1.11)          | 0.98 (0.85, 1.11)           | 1.03 (0.93, 1.14)               | 0.93 (0.78, 1.10)     |
| Race/ethnicity         |                           |                             |                                 |                       |
| White                  | Ref                        | Ref                         | Ref                             | Ref                   |
| Black                  | 1.10 (0.96, 1.26)          | 1.13 (0.96, 1.33)           | 1.07 (0.94, 1.22)               | 1.15 (0.93, 1.43)     |
| Hispanic               | 1.20 (1.03, 1.39)          | 0.79 (0.65, 0.96)           | 0.95 (0.83, 1.09)               | 1.15 (0.92, 1.44)     |
| Other/missing          | 1.09 (0.98, 1.21)          | 0.98 (0.86, 1.12)           | 1.14 (1.03, 1.27)               | 1.20 (1.00, 1.44)     |
| Deyo-Charlson score    |                           |                             |                                 |                       |
| 0                      | Not Est                    | Not Est                     | Not Est                         | Not Est               |
| 1                      | 1.54 (1.42, 1.68)          | 1.37 (1.23, 1.53)           | 1.44 (1.33, 1.57)               | 1.49 (1.28, 1.74)     |
| Income category        |                           |                             |                                 |                       |
| 0-25th percentile      | 0.81 (0.71, 0.91)          | 0.94 (0.81, 1.09)           | 1.00 (0.89, 1.13)               | 0.82 (0.68, 1.00)     |
| 25-50th percentile     | 0.83 (0.74, 0.93)          | 0.90 (0.78, 1.04)           | 1.01 (0.91, 1.13)               | 1.03 (0.86, 1.24)     |
| 50-75th percentile     | 0.85 (0.76, 0.96)          | 0.96 (0.84, 1.10)           | 1.00 (0.90, 1.12)               | 0.95 (0.80, 1.13)     |
| 75-100th percentile    | Ref                        | Ref                         | Ref                             | Ref                   |
| Primary Infection      |                           |                             |                                 |                       |
| Diagnosis              |                           |                             |                                 |                       |
| Sepsis                 | Ref                        | Ref                         | Ref                             | Ref                   |
| OI                     | 0.87 (0.66, 1.15)          | 0.38 (0.27, 0.54)           | 1.48 (1.11, 1.97)               | 0.46 (0.30, 0.70)     |
| SSTI                   | 0.42 (0.37, 0.47)          | 0.34 (0.29, 0.40)           | 0.65 (0.58, 0.73)               | 0.06 (0.04, 0.09)     |
| UTI                    | 0.28 (0.23, 0.36)          | 0.34 (0.25, 0.46)           | 0.32 (0.26, 0.41)               | 0.02 (0.00, 0.11)     |
| Pneumonia              | 0.64 (0.58, 0.70)          | 0.38 (0.34, 0.43)           | 0.72 (0.66, 0.79)               | 0.29 (0.25, 0.34)     |
| Insurance payer        |                           |                             |                                 |                       |
| Medicare               | 1.16 (1.05, 1.30)          | 1.76 (1.52, 2.03)           | 1.21 (1.10, 1.35)               | 0.80 (0.67, 0.95)     |
| Medicaid               | 1.22 (1.05, 1.42)          | 1.48 (1.20, 1.82)           | 1.12 (0.97, 1.29)               | 0.90 (0.68, 1.18)     |
| Other                  | 0.92 (0.69, 1.21)          | 1.29 (0.86, 1.93)           | 0.93 (0.71, 1.22)               | 1.46 (0.95, 2.25)     |
| Private                | Ref                        | Ref                         | Ref                             | Ref                   |
| Self                   | 1.28 (0.93, 1.77)          | 0.79 (0.46, 1.38)           | 1.06 (0.78, 1.43)               | 1.08 (0.60, 1.94)     |
| Hospital Region        |                           |                             |                                 |                       |
| Northeast              | Ref                        | Ref                         | Ref                             | Ref                   |
| Midwest                | 0.75 (0.66, 0.85)          | 1.00 (0.86, 1.16)           | 0.83 (0.73, 0.94)               | 0.66 (0.53, 0.81)     |
| South                  | 0.92 (0.82, 1.03)          | 0.83 (0.72, 0.95)           | 0.95 (0.85, 1.07)               | 0.86 (0.71, 1.03)     |
| West                   | 0.89 (0.78, 1.02)          | 0.85 (0.73, 1.00)           | 0.68 (0.60, 0.77)               | 0.83 (0.68, 1.01)     |
| Hospital Location/Teaching |                       |                             |                                 |                       |
| Rural                  | Ref                        | Ref                         | Ref                             | Ref                   |
| Urban Non-teaching      | 2.57 (2.26, 2.92)          | 0.74 (0.63, 0.87)           | 1.38 (1.21, 1.57)               | 1.18 (0.93, 1.49)     |
| Urban Teaching         | 2.25 (1.99, 2.54)          | 0.63 (0.54, 0.74)           | 1.31 (1.15, 1.48)               | 1.15 (0.91, 1.45)     |
| Hospital Bed size      |                           |                             |                                 |                       |
| Small                  | Ref                        | Ref                         | Ref                             | Ref                   |
| Medium                 | 1.46 (1.29, 1.65)          | 1.05 (0.90, 1.23)           | 1.20 (1.06, 1.36)               | 1.23 (0.99, 1.55)     |
| Large                  | 2.10 (1.89, 2.35)          | 1.01 (0.88, 1.16)           | 1.36 (1.22, 1.52)               | 1.35 (1.10, 1.66)     |

CI, Confidence Interval; Ref, reference category

Discussion

In this national study of people with scleroderma hospitalized with serious infection, we found that
compared to patients hospitalized with serious infection without scleroderma, people with scleroderma had higher healthcare utilization and in-hospital mortality. Hospital charges and the length of hospital stay were the highest for OI and/or sepsis and the lowest for UTI.

The frequency and rate of sepsis increased over time. Sepsis surpassed pneumonia as the most common serious infection in scleroderma in 2013-14. By 2015-16, sepsis was twice as common as pneumonia. This is an important observation. This trend in scleroderma cohort may reflect the increase in hospitalizations with sepsis in the general population [11]; systematic up-coding of severe infections to sepsis and misclassification error with sepsis diagnostic codes has been noted [12, 13]; and/or related to the increased infection risk related to scleroderma and its treatments.

We noted a reduction in the in-hospital mortality from 10.3% in 1998–2000 to 7.8% in 2015–2016 for composite serious infection in people with scleroderma. Not surprisingly, the largest reductions were noted for the serious infections with the highest mortality in 1998–2000. We noted large reductions of in-hospital mortality for OI, 21.2–7.7%, sepsis, 22.5–13.2%, and pneumonia, 9.8–2.8%, from 1998–2000 to 2015–2016, respectively. To our knowledge, these are important novel findings in a scleroderma cohort hospitalized with serious infections. Survival rates in scleroderma have improved over time [14], which our findings further validate. As expected, in-hospital mortality of 9% in people with serious infections and scleroderma in our study is slightly higher than the reported overall in-hospital mortality rates in scleroderma of 7.1% using the 1995 NIS [10] and 6.3% using the 2002–2003 NIS [3].

We noted a 3.6-fold increase in the mean hospital charges with a 9% concomitant decrease in the mean/median hospital stay for serious infections in scleroderma patients, from 1998–2000 to 2015–2016. These trends over time are consistent with the general trends in the overall NIS cohort. The reduction in median hospital stay was the greatest for OI, from 9.5 to 5.8 days, and minimal for sepsis, from 5.5 to 5.3 days.

Multivariable-adjusted analyses showed that lower odds for healthcare utilization and in-hospital mortality for all serious infections compared to sepsis. The reduction in odds were 28–62% for healthcare utilization and 54–98% for in-hospital mortality. These important differences separate
sepsis from other serious infections in scleroderma, with regards to outcomes. Several other factors were also independently associated with poorer healthcare utilization and in-hospital mortality outcomes. A higher Deyo-Charlson score ≥ 2 was associated with higher healthcare utilization and in-hospital mortality, odds were increased by 37-54%. Our finding validates findings from another study that showed that diabetes, anxiety and depression increased in-hospital mortality in hospitalized scleroderma patients [15], and extends it to scleroderma patients hospitalized with serious infections. Our finding of an independent association of unmodifiable factors such as older age, Medicare or Medicaid insurance payer. Northeast location, urban teaching or non-teaching status, medium or large hospital bed size with higher odds of healthcare utilization can help in a better understanding of associated healthcare utilization.

Our study has several limitations. Misclassification bias is possible, since we used the ICD-9-CM or ICD-10-CM codes to identify people with scleroderma and infections. However this bias may be minimal since the diagnostic codes for scleroderma [10] and serious infections [7-9] have been shown to be valid in previous studies. Since the NIS counts discharges, longitudinal outcome analyses were not possible at a patient-level, including 30- and 90-day post-discharge readmission and mortality risk. The NIS does not include data from the military or Veterans Affairs hospitals, which can lead to some selection bias.

The strengths of our study are the use of national U.S. data that can produce national estimates of mortality, charges and healthcare utilization, the inclusion of several covariates and confounders in regression analyses resulting in robust estimates of association, and inclusion of a large sample size.

Conclusions
In conclusion, we found important differences in hospitalized serious infection patients between scleroderma vs. non-scleroderma. In the U.S., the most common serious infection in hospitalized scleroderma patients was pneumonia followed by sepsis; sepsis was the most common in the most recent study-period. We noted a significant increase in the rate of sepsis, and possibly OI and UTI. Hospital charges increased, and the duration of hospital stay and in-hospital mortality decreased from
1998–2000 to 2015–2016. We identified several modifiable and non-modifiable independent risk factors for poorer outcomes, that can help policy makers and spark new interventions for improving outcomes.

Abbreviations
NIS, National Inpatient Sample
HR, Hazard ratio
CI, confidence interval
SD, standard deviation
UTI, urinary tract infection
SSTI, skin and soft tissue infections
OI, opportunistic infections
CCS, Clinical Classifications Software
UAB, University of Alabama at Birmingham
ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Declarations

**Ethics/IRB approval and consent to participate:** The University of Alabama at Birmingham’s Institutional Review Board approved this study and all investigations were conducted in conformity with ethical principles of research (UAB X120207004). The IRB waived the need for an informed consent for this database study.

**Consent for publication:** No individual person’s data were presented in any form in this study and therefore no consent to publish is required.

**Availability of Data and materials:** These data are easily available from the Agency for Healthcare Research and Quality (AHRQ’s) “Healthcare Cost and Utilization Project (HCUP)” and can be obtained after completing an on-line Data Use Agreement training session and signing a Data Use Agreement. The contact information for requesting the data is as follows:

HCUP Central Distributor
Phone: (866) 556-4287 (toll-free)
Fax: (866) 792-5313

E-mail: HCUPDistributor@ahrq.gov

**Competing Interests:** There are no financial conflicts related directly to this study. JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Spherix, Practice Point communications, the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in Amarin pharmaceuticals and Viking therapeutics. JAS is on the speaker’s bureau of Simply Speaking. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies. JAS is a member of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS served as a member of the American College of Rheumatology’s (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee. JDC has no conflicts. There are no non-financial competing interests for either author.

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**Author contributions:** Jasvinder A. Singh designed the study, developed study protocol, reviewed analyses and wrote the first draft of the paper. John D. Cleveland performed the data abstraction and data analyses. All authors revised the manuscript, read, and approved the final manuscript.

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Figures
Figure 1

Rate of hospitalized infection in people with scleroderma per 100,000 total NIS claims (1A) and per 100,000 overall scleroderma claims (1B)

Supplementary Files

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Scleroderma_appendix1.docx
