REVIEWS

Do Patients with Cellulitis Need to be Hospitalized? A Systematic Review and Meta-analysis of Mortality Rates of Inpatients with Cellulitis

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BACKGROUND: Cellulitis is a common cause of hospitalization. In the USA, the *International Classification of Diseases* (ICD) code “other cellulitis and abscess” accounts for 1.4% of all admissions and \$5.5 billion in annual costs. The Infectious Disease Society of America recommends hospitalization for patients with cellulitis under certain circumstances but there is little actual clinical evidence to guide the decision to admit. The purpose of this study is to determine the mortality rate of patients hospitalized with cellulitis and to ascertain if the rate is comparable to the rate for low risk patients with community acquired pneumonia that are currently recommended for outpatient management.

METHODS: A systematic literature search was conducted for studies of consecutive patients hospitalized with cellulitis or erysipelas that reported inpatient mortality. Study quality was assessed using a modified Newcastle-Ottawa Quality Assessment Scale. The mortality rates from the included studies were pooled using a random effects model. Heterogeneity was estimated using the I^2 statistic.

RESULTS: Eighteen studies met inclusion criteria. The overall worldwide mortality rate was 1.1% (95% confidence interval (CI), 0.7–1.8). For studies from the USA, the rate was 0.5% (95% CI 0.3–0.9). The actual cause of death was generally poorly described, and only one third of deaths appeared to be due to infection.

DISCUSSION: The estimated mortality rate for patients currently being hospitalized for cellulitis is comparable to the mortality rate of patients with community-acquired pneumonia that are recommended for outpatient management by the Pneumonia Severity Index and CURB65 prediction models and strongly endorsed by major infectious disease societies. Outpatient management of these

patients could result in large cost savings and may be much preferred by patients.

KEY WORDS: Cellulitis; Mortality; Epidemiology; Hospitalization.

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INTRODUCTION

Cellulitis is a common cause of hospitalization. In the USA, for example, the *International Classification of Diseases* (ICD) code “other cellulitis and abscess” accounts for approximately 1.4% of all admissions and \$5.5 billion in annual costs.¹ The Infectious Diseases Society of America (IDSA) recommends that all patients with cellulitis and systemic signs of infection be considered for parenteral antibiotics, which for most patients requires hospitalization. The IDSA also recommends hospitalization for patients with altered mental status, hemodynamic instability, concern for deep infection, and poor adherence, who are severely immunocompromised, or who fail outpatient treatment.² Despite these recommendations, there is scant research to guide physicians about when to admit patients with cellulitis. It has been argued that the vast majority of patients with cellulitis could be managed as outpatients.³ In the case of community-acquired pneumonia, several validated risk stratification tools exist that identify patients with low mortality for outpatient management.^{4,5} We undertook a systematic review and meta-analysis of the literature of hospitalized patients with cellulitis to estimate the overall mortality of these patients and to assess whether the rate is low enough to potentially support alternatives to hospitalization.

METHODS

Data Sources and Search Strategy

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement for reporting systematic reviews was used for our study.⁶ We searched for observational studies that reported the rate of mortality for hospitalized patients with cellulitis or erysipelas. We searched Medline, Embase, and the Cochrane Library from database inception through February

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22, 2017. The search was limited to English language and adults. For Medline, we used the following search strategy: “Soft Tissue Infections/complications,” “Soft Tissue Infections/epidemiology,” “Soft Tissue Infections/mortality,” “Skin Diseases, Bacterial/complications,” “Skin Diseases, Bacterial/epidemiology,” “Skin Diseases, Bacterial/mortality,” “Cellulitis/epidemiology,” “Cellulitis/mortality,” “Erysipelas/diagnosis,” “Erysipelas/epidemiology,” or “Erysipelas/mortality.”

Study Selection

All observational studies of consecutive patients hospitalized with cellulitis or erysipelas were included. Studies of mixed cohorts of patients with skin and soft tissue infections (SSTI) that primarily included patients with cellulitis or erysipelas were also included but studies primarily of other types of SSTI such as abscess, diabetic foot, or complicated skin and soft tissue infection were excluded. Studies limited to patients treated with only one specific antimicrobial were not included as were studies limited to SSTI with specific comorbidities or limited to a specific pathogen. Studies with other selection criteria such as only culture-positive infections or only severe infections were also excluded. One author screened all titles and abstracts for full-text review which two authors (CG and AF) then independently reviewed for ultimate inclusion. Disagreement was resolved by consensus.

Data Extraction and Quality Assessment

A standardized data extraction form was used to document study characteristics such as study methodology, patient descriptions, type of SSTI included, method used for data acquisition, definition of mortality used, rate of overall mortality, and attributable mortality if included. Two authors (CG and BC) independently assessed study quality using a modified Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies (see Supplementary File 1).⁷ Differences in assessments were resolved by consensus. The original NOS included eight elements but three of these are not relevant to the types of included studies so only five elements were assessed. Representativeness was judged as good if the study was prospectively performed and patients with cellulitis were individually identified or if the study was retrospective and used record linkage with codes that only included cellulitis. Retrospective chart reviews were judged to have fair representativeness as were studies that used record linkage with non-cellulitis codes or poor if they included multiple non-cellulitis-related codes. Ascertainment was judged favorably if the study was prospectively conducted or if it used a national database for record linkage.

Data Synthesis and Analysis

The mortality rate for hospitalized patients with cellulitis for each study was recorded and the 95% confidence interval (CI)

was calculated. Mortality rates from individual studies were pooled using a random effects model to calculate an overall mortality rate. Between-study heterogeneity was estimated using the I^2 statistic. Pre-specified subgroup analysis was performed based on study methodology (retrospective chart reviews vs. prospective studies vs. retrospective record linkage), study quality based on the NOS, and types of included infections (cellulitis only or mixed cohorts and whether necrotizing soft tissue infections were excluded). Meta-regression using these same variables was done to explore heterogeneity. Sensitivity analysis was done to assess the robustness of the overall pooled estimate after removal of individual studies. Statistical significance was assumed for p values less than 0.05. Statistical analysis was performed using Comprehensive Meta-Analysis, version 3 (Biostat, Englewood, NJ) and Stata/SE, version 14.2 (StataCorp, College Station, TX).

RESULTS

The initial electronic search found 2467 manuscripts (Fig. 1). Two thousand three hundred and fifty-five manuscripts were excluded based on title and abstract review, leaving 112 for full-text review. Of these, 13 met criteria for study inclusion. An additional five studies were found by review of the references from the included studies. The main reasons that studies were excluded after full-text review were that they included outpatients, did not report mortality, or did not enroll consecutive hospitalized patients but instead used selection criteria such as only enrolling culture-positive infections, severe infections, or patients treated with specific antibiotics.

Table 1 outlines the characteristics of the 18 included studies. Twelve of the studies were relatively small, occurred at a single hospital or institution, and used individual chart review for data acquisition. Seven of these 12 studies were conducted retrospectively and five prospectively. The remaining six studies used electronic coding for patient enrollment without chart review. Five of the six used ICD coding, and one was unspecified. In terms of types of infection included, the chart reviews and prospective studies purported to include only cellulitis and/or erysipelas, whereas the studies using coding included a more varied patient population; two included only cellulitis or erysipelas; two included a mix of infections including cellulitis, abscess, surgical site infection, ulcer-associated infections, and necrotizing infections; one included cellulitis, abscess, and surgical site infections; and one did not specify what types of infections were included. Of the 18 studies, eight were from Europe, four were from the USA, two were from China or Taiwan, two were from Australia-New Zealand, and one each from Israel and Canada.

Table 2 describes the study quality assessment based on the modified NOS. Study quality was assessed based on five elements, each of which could earn one point if certain standards were met. Studies that scored favorably in all five

Figure 1 Study flow diagram of literature search.

elements received five points, which was achieved by seven studies. Ten studies scored four points and one three points. The main reason studies lost points were for retrospective chart reviews with poor ascertainment and for studies that used poorly representative coding.

Figure 2 presents the pooled and individual study mortality rates for hospitalized patients with cellulitis using random effects meta-analysis. The overall pooled rate was 1.1% (95% CI, 0.7–1.8). Individual studies ranged from 0 deaths to 2.9% mortality. The pooled result for important subgroups is listed in Table 3. The pooled rate for studies that used chart review was 1.2% (95% CI, 0.6–2.8) whereas the rate for

studies that used record linkage was 1.3% (95% CI, 0.7–2.4). The pooled result for studies that purported to include only patients with cellulitis was 1.1% (95% CI, 0.7–1.8) whereas for studies with mixed cohorts, the rate was 1.3% (95% CI, 0.7–2.5). The only subgroup with a statistically significant different rate of mortality when compared to the remaining studies was of studies from the USA for which the pooled rate was 0.5% (95% CI, 0.3–0.9). Overall, there was statistically significant evidence for heterogeneity ($I^2 = 98\%$, $p < 0.001$). We explored the heterogeneity by subgroup analysis but most subgroups also had high heterogeneity with the exception of the three studies of leg cellulitis only ($I^2 = 0\%$,

Table 1 Characteristics of Included Studies

Author	Year	Country	Setting	Data acquisition	SSTI types included	Mortality, N (%)
Jorup-Ronstrom ⁸	1986	Sweden	Single hospital	Prospective	Cellulitis	1/233 0.4%
Eriksson ⁹	1997	Sweden	Single hospital	Prospective	Cellulitis	2/229 0.9%
Cox ¹⁰	1998	England	Two hospitals	Retrospective chart review	Cellulitis	0/92
Peri ¹¹	1999	Israel	Single hospital	Retrospective chart review	Cellulitis	0/757
Carratala ¹²	2003	Spain	Single hospital	Retrospective Hospital EMR with chart review	Cellulitis, ulcer, NSTI	8/332 2.4%*
Lazzarini ¹³	2005	Italy	Single hospital	Retrospective chart review	Cellulitis	0/200
Morpeth ¹⁴	2005	New Zealand	Single hospital	Prospective	Cellulitis	0/51
Goettisch ¹⁵	2006	Netherlands	National	Primary ICD-9 code	Cellulitis	65/3473 1.9%
Edelsberg ¹⁶	2008	USA	National	Primary ICD-9 codes	Cellulitis, abscess, SSI, ulcer, other	365/47,219 0.8%
Figtree ¹⁷	2010	Australia	Single hospital	Primary ICD-10 codes with chart review	Cellulitis, ulcer	10/395 2.5%
Jenkins ¹⁸	2010	USA	Single hospital	Primary ICD-9 codes with chart review	Cellulitis, abscess, NSTI	0/322
Shen ¹⁹	2010	Taiwan	National	Primary ICD-9 codes	Cellulitis, abscess, DFI, SSI, NSTI, ulcer, other	306/11,390 2.7%
Lipsky ²⁰	2012	USA	National	Prospective	Cellulitis, abscess, DFI, SSI	4/1033 0.4%
Marwick ²¹	2012	Scotland	Single hospital	Prospective	Cellulitis, NSTI	2/79 2.5% 30 days
Perello-Alzamora ²²	2012	Spain	Single hospital	Retrospective chart review	Cellulitis, Ulcer	2/70 2.9%
Baiber-genova ²³	2014	Canada	National	Primary ICD-10 Code	Cellulitis	654/65,454 1.0%
Kaye ¹	2015	USA	National	Primary ICD-9 codes	Cellulitis, abscess, SSI	22,140/4,891,187 0.45%
Li ²⁴	2016	China	Four hospitals	Data collected from the EMR corresponding to cSSTI	Cellulitis, abscess, SSI, NSTI, ulcer	14/575 2.4%

*Mortality rate at 72 h of hospitalization

Table 2 Study Quality Assessment

Author	Representativeness	Ascertainment	Outcome assessment	Follow-up duration	Adequacy of follow-up	NOS
Jorup-Ronstrom ⁸	Good*	Prospective*	Independent assessment*	Yes*	Yes*	5/5
Eriksson ⁹	Good*	Prospective*	Independent assessment*	Yes*	Yes*	5/5
Cox ¹⁰	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Perl ¹¹	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Carratala ¹²	Fair*	CR	Independent assessment*	72 h and 30 days	Yes*	3/5
Lazzarini ¹³	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Morpeth ¹⁴	Fair*	Prospective*	Independent assessment*	Yes*	Yes*	5/5
Goettsch ¹⁵	Fair*	Coding*	Record linkage*	Yes*	Yes*	5/5
Edelsberg ¹⁶	Poor	Coding*	Record linkage*	Yes*	Yes*	4/5
Figtree ¹⁷	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Jenkins ¹⁸	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Shen ¹⁹	Poor	Coding*	Record linkage*	Yes*	Yes*	4/5
Lipsky ²⁰	Good*	Prospective*	Independent assessment*	Yes*	Yes*	5/5
Marwick ²¹	Good*	Prospective*	Independent assessment*	30 days	Yes*	4/5
Perello-Alzamora ²²	Fair*	CR	Independent assessment*	Yes*	Yes*	4/5
Baibergenova ²³	Good*	Coding*	Record linkage*	Yes*	Yes*	5/5
Kaye ¹	Fair*	Coding*	Record linkage*	Yes*	Yes*	5/5
Li ²⁴	Poor	Coding*	Record linkage*	Yes*	Yes*	4/5

NOS the Newcastle-Ottawa Scale, CR chart review

*Item achieves one point on the NOS

$p = 0.61$) and the five prospective studies ($I^2 = 22\%$, $p = 0.28$). On meta-regression, 93% of the heterogeneity was explained

by the covariates of NOS of five ($R^2 = 0.35$) and studies from the USA ($R^2 = 0.58$). Sensitivity analysis removing individual

Figure 2 Forest plot of individual study and pooled mortality rates.

studies or subgroups did not have an effect on the overall pooled result or on heterogeneity.

Only five of the 18 studies included information about the actual cause of death. In these five studies, a total of 27 patients died including ten who were reported to have died directly from their infection (37%). Seven of these ten infectious deaths were from a single study.¹² Of the remaining 17 patients who died, two died from heart failure,²⁵ one from respiratory failure,¹² and 14 were not specified other than that they did not die from infection.²⁴

DISCUSSION

In total, we found 18 studies of consecutive patients hospitalized for cellulitis or associated infections. The estimated pooled mortality rate worldwide for these patients using random effects meta-analysis was 1.1%. For studies from the USA, the rate was 0.5%. Although poorly described, only about one third of this mortality appeared to be attributable to cellulitis. The overall rate is comparable to common thresholds to recommend outpatient management for community-acquired pneumonia. For example, a systematic review of 31 studies that assessed the mortality rate of class 1–2 patients as defined by the PSI found that the pooled mortality rate for these low-risk patients was 0.75%.²⁶ The same systematic review found that the pooled mortality rate from 17 studies of the CURB65 score for patients with 0–1 risk factors was 2.0%. The IDSA and the British Thoracic Society (BTS) both recommend use of these prediction tools to identify patients for outpatient management. In the case of cellulitis, there are no well-described clinical models to predict mortality in hospitalized patients. The most widely known system classifies patients into four groups based on systemic signs of infection and comorbidity, but the actual mortality for the different groups has not been well defined.²⁷ Our findings show that the pooled mortality rate of patients currently being hospitalized for cellulitis is comparable to the mortality rate of patients with community-acquired pneumonia that is strongly recommended for outpatient management by the IDSA and BTS.

Talan et al. reported that in 85% of cases, the reason emergency room physicians hospitalize patients with SSTI is to administer intravenous antibiotics.³ The main significance of our study is to support the potential use of alternatives to hospitalization for these patients. The use of outpatient parenteral antimicrobial therapy (OPAT) for example has been shown to be a safe alternative to hospitalization and to be preferred by patients.^{28, 29} Another alternative is to briefly admit patients with cellulitis for observation. It has been estimated that the use of observation admission in the USA for low acuity conditions such as cellulitis could save individual patients \$1500, individual hospitals \$4.5 million, and the country \$3.1 billion.³⁰ Lastly, several antibiotics are now

Table 3 Subgroup Analysis

Subgroup	Heterogeneity (I^2)	Mortality rate and 95% CI
Overall pooled estimate	99%	1.1% (0.7–1.8)
Studies using chart review	55%	1.2% (0.6–2.8)
Studies using record linkage	99%	1.3% (0.7–2.4)
Cellulitis only cohorts	74%	1.1% (0.7–1.8)
Mixed cohorts	99%	1.3% (0.7–2.5)
Leg cellulitis only cohorts	0%	1.8% (1.5–2.3)
Prospective studies only	22%	0.8% (0.4–1.6)
Studies that include NSTI ($n = 3$)	52%	1.9% (0.7–5.2)
Studies that exclude NSTI ($n = 6$)	99%	1.0% (0.6–1.5)
Studies with NOS ≥ 4	99%	1.1% (0.7–1.7)
Studies with NOS ≥ 5	99%	0.8% (0.4–1.4)
U.S. studies only	97%	0.5% (0.3–0.9)*

C.I. confidence interval, NOS the Newcastle-Ottawa Scale, U.S. United States

* p value < 0.05 for comparison between subgroup and the remaining studies

available for SSTI that have long half-lives allowing once-weekly outpatient administration.^{31–33}

Another significance of the low pooled mortality rate for cellulitis relates to antibiotic stewardship. Current guidelines recommend relatively narrow spectrum antibiotics for most patients with cellulitis, targeting the most common organisms which are β -hemolytic streptococci and methicillin-susceptible *Staphylococcus aureus*.² Studies over the past decade, however, have shown that most patients in the USA when hospitalized with cellulitis are receiving combinations of broad-spectrum antibiotics, including frequent coverage of MRSA and resistant Gram-negative organisms as well as anaerobes.^{18, 20, 34} This practice likely reflects uncertainty about the true microbiology of these infections which are frequently unculturable and also promotion of broad-spectrum antibiotics for severe infections such as septic shock.³⁵ Studies showing that inappropriate antibiotics are associated with higher mortality originate largely from studies of patients with bacteremia with severe illness hospitalized in the ICU.³⁶ One systematic review for example found the pooled mortality rate for ICU patients with septic shock to be 46%.³⁷ As shown by our study, the estimated mortality rate for hospitalized patients with SSTI is a magnitude lower and supports an initial narrow approach to empiric antibiotics.

Our review has several limitations. First, there was significant statistical heterogeneity for mortality between studies. This likely reflects both methodologic and clinical differences between studies. In particular, most of the studies purported to include only patients with cellulitis or erysipelas, but most of these were retrospective studies in which it may be difficult to distinguish cellulitis from other SSTI including abscess, bursitis, and ulcer-associated infections. It has also been pointed out that the terms cellulitis and erysipelas have been used

differently by different authors so studies of these infections may in fact report heterogeneous SSTI.³⁸ We also included studies of hospitalized patients that used coding without individual chart review to identify patients. Several of these studies included ICD codes other than cellulitis and erysipelas, including for different types of SSTI such as abscess, surgical site infection, and diabetic foot infections. To try to understand the heterogeneity of the included studies, we did subgroup analysis and meta-regression and found that most of the heterogeneity was due to the lower rates of mortality found in studies that had low risk of bias as measured by the NOS or originated from the USA. Ultimately, because of the heterogeneity of included studies and the limits in reporting for most of the studies, we used random effects meta-analysis to estimate the pooled mortality rate and we emphasize that different populations of patients with cellulitis likely have somewhat different rates of mortality.

Another potential weakness of our study is that only three of the included studies specifically included necrotizing soft tissue infections (NSTI) and most of the studies did not specify whether NSTI were included. The pooled mortality rate for the three studies that included NSTI was 1.9% and it is possible that to the extent that studies excluded NSTI that much of the attributable mortality rate for cellulitis was removed. Ideally, to answer our research question, studies would have included NSTI and reported the frequency and outcomes of these infections both separately and included with full cohort.

Lastly, our study does not by itself show that patients that are currently being hospitalized with cellulitis would have the same low rate of mortality if managed as outpatients. In addition to intravenous antibiotics, hospitalized patients also undergo monitoring and supportive care. After the PSI was derived, for example, three separate randomized controlled studies were conducted which confirmed that low-risk patients had in fact good outcomes when treated as outpatients.^{39–41} Ideally, a randomized trial would be the next step to demonstrate that patients currently being hospitalized with cellulitis did equally well when managed as outpatients.

In summary, the estimated rate of mortality for patients hospitalized with cellulitis worldwide is approximately 1% and for patients in the USA, 0.5%. Attributable mortality is even lower. This rate is similar to the mortality rate of low-risk patients with community-acquired pneumonia that is currently strongly recommended for outpatient management by major infectious disease societies. If confirmed by a randomized controlled trial, outpatient management of patients currently being hospitalized for cellulitis could result in large cost savings to patients and payers and may be much preferred by patients.

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Compliance with Ethical Standards:

Conflict of Interest: The authors have no conflicts to disclose.

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