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REVIEW

A systematic review of bacteremias in cellulitis and erysipelas

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Summary Objectives: Because of the difficulty of obtaining bacterial cultures from patients with cellulitis and erysipelas, the microbiology of these common infections remains incompletely defined. Given the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) over the past decade the proportion of infections due to *S. aureus* has become particularly relevant.

Methods: OVID was used to search Medline using the focused subject headings “cellulitis”, “erysipelas” and “soft tissue infections”. All references that involved adult patients with cellulitis or erysipelas and reported associated bacteremias and specific pathogens were included in the review.

Results: For erysipelas, 4.6% of 607 patients had positive blood cultures, of which 46% were *Streptococcus pyogenes*, 29% were other β -hemolytic streptococci, 14% were *Staphylococcus aureus*, and 11% were Gram-negative organisms. For cellulitis, 7.9% of 1578 patients had positive blood cultures of which 19% were *Streptococcus pyogenes*, 38% were other β -hemolytic streptococci, 14% were *Staphylococcus aureus*, and 28% were Gram-negative organisms.

Conclusions: Although the strength of our conclusions are somewhat limited by the heterogeneity of included cases, our results support the traditional view that cellulitis and erysipelas are primarily due to streptococcal species, with a smaller proportion due to *S. aureus*. Our results also argue against the current distinction between cellulitis and erysipelas in terms of the relative proportion of infections due to *S. aureus*.

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Introduction

Cellulitis is commonly defined as any spreading infection involving the dermis and subcutaneous tissues,^{1,2} while erysipelas is considered a specific type of cellulitis involving superficial dermal structures and distinguished by well-demarcated raised borders.³ Traditional teaching has maintained that most cases of cellulitis are due to β -hemolytic streptococci or *Staphylococcus aureus*, and that nearly all cases of erysipelas are due to streptococci.⁴ Citing data from studies of bacterial cultures based on needle aspirates and punch biopsies, as well as serologic studies using anti-streptococcal antibodies and immunofluorescent stains of skin biopsies, the most recent guideline from The Infectious Disease Society of America (IDSA) on skin and soft tissue infections states that most cases of cellulitis and nearly all cases of erysipelas are due to streptococci, often *Streptococcus pyogenes* but also groups B, C, or G.⁵ *S. aureus* is also noted to cause cellulitis, especially when associated with furuncles, carbuncles or abscesses.

Over the past decade numerous reports have noted the increasing prevalence of methicillin-resistant *Staphylococcus aureus*, particularly from the community (CA-MRSA).^{6,7} Recent studies have concluded that the majority of *S. aureus* skin and soft tissue infections are now methicillin-resistant,⁸ and that MRSA is the most common isolate from purulent skin and soft tissue infections in the United States.⁹ As a result of these reports, many physicians are now prescribing antimicrobials effective against CA-MRSA as first line treatment of skin and soft tissue infections,¹⁰ including cellulitis,¹¹ although it remains controversial whether antimicrobial management is effective in purulent soft tissue infections such as abscesses,¹² and it remains largely unknown to what extent MRSA is responsible for nonpurulent cases of cellulitis and erysipelas.¹³ The recently published guideline from the IDSA on the treatment of MRSA infections recommends that with purulent cellulitis therapy should be directed at CA-MRSA. In cases of nonpurulent cellulitis however, the guideline continues to recommend therapy directed at β -hemolytic streptococci and MSSA, with reservation of MRSA-active therapy for infections that fail to respond to β -lactam therapy.¹³ The guideline further notes the inherent difficulty of determining the etiology of nonpurulent cellulitis and calls for more research into its microbiology.

Given the uncertainty about the etiology of nonpurulent skin and soft tissue infections, we performed a systematic review of the literature of cellulitis and erysipelas for associated bacteremias, reasoning that although infrequently positive, these cultures offered unique evidence of the microbiology of these infections.

Methods

OVID was used to search Medline using the focused subject headings "cellulitis", "erysipelas" and "soft tissue infections". As some authors have questioned the validity of distinguishing between cellulitis and erysipelas,^{3,14,15} we included erysipelas in our analysis. We restricted the search to human subjects, English language, publications since 1970 and to the subheadings diagnosis, epidemiology,

etiology, microbiology or pathophysiology. All references that involved adult patients with cellulitis or erysipelas and reported associated bacteremias and specific pathogens were included in the review. We excluded pediatric cases, case reports, case series involving only a single pathogen, and reports involving skin and soft tissue infections other than cellulitis or erysipelas, including abscess, necrotizing soft tissue infections, osteomyelitis, chronic diabetic foot infections, orbital cellulitis and surgical site infections. We also excluded cases of likely contaminants, including isolates of coagulase-negative staphylococci, *Viridans streptococci*, *peptostreptococcus* spp., *bacillus* spp., and diphtheroids. After the initial literature search the authors reviewed all titles and abstracts for potential articles for full text review. The bibliographies of all included studies as well as two identified review articles were examined for additional papers for inclusion. The resulting full text articles were then reviewed by both authors to determine final inclusion in the study. The last search was done on March 1, 2011.

The relative frequencies of positive cultures for β -hemolytic streptococci, *S. aureus*, and Gram-negative organisms were compared between cellulitis and erysipelas using the Fisher exact or chi-square test as appropriate. Statistical significance was assumed at *P* values less than 0.05.

Results

The primary literature search yielded 1784 articles (Fig. 1). After review of the titles and abstracts, 1684 articles were excluded, leaving 100 articles for full text review. Of these, 21 articles had specific blood culture results and described patients with cellulitis or erysipelas, and were therefore selected for inclusion. Additionally, two reviews of the utility of blood cultures in cellulitis were found, which described 16 articles with blood culture results, of which 3 met inclusion criteria for our study and were added. Review of the bibliographies of all the included studies led to the identification of an additional 4 articles, resulting in a total of 28 articles included in this systematic review.

Erysipelas

Five studies reported blood culture results for 607 patients with erysipelas, of which 28 (4.6%) were positive (Table 1). Three of the five studies specified a definition of erysipelas and were prospective studies with the diagnosis of erysipelas confirmed by one of the authors (Table 2). The other two studies were based on retrospective reviews of the medical records. Consistent with traditional teaching, streptococcal species were the predominant organism identified, constituting 75% of the isolates from positive blood cultures, while 14% were *S. aureus*, and 11% were Gram-negative rods. Of the three patients with blood cultures that were positive for Gram-negative organisms, one each consisted of *Citrobacter diversus*, *Escherichia coli*, and *Proteus morganii*. When restricting the analysis to only prospective studies, a similar distribution of microbes was identified, with 78% of cultures being streptococcus species, 13% *S. aureus*, and 9% Gram-negative rods.

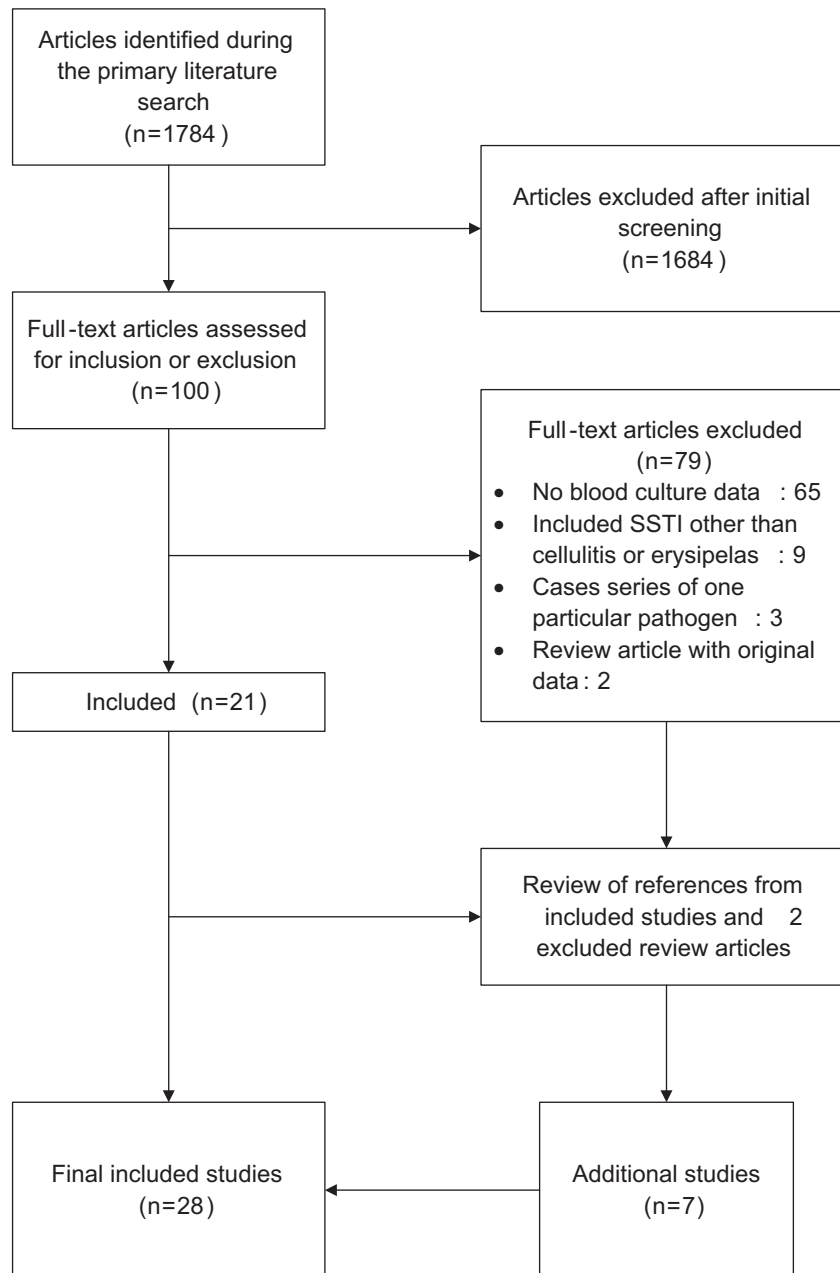


Figure 1 Flow diagram of study selection process. SSTI, skin and soft tissue infection.

Cellulitis

Nineteen studies of cellulitis reported a total of 1578 blood cultures, of which 125 (7.9%) were positive (Table 1). Overall, 58% of these positive blood cultures isolated β -hemolytic streptococci. Non-group A β -hemolytic streptococcal species were more common than group A streptococcus, which accounted for 19% of positive blood cultures. *S. aureus* accounted for 14% of patients, and Gram-negative organisms accounted for 28%. Lastly, two patients had blood cultures that were classified as miscellaneous organisms, including one each of a *clostridium* spp. and *enterococcus* spp. The Gram-negative isolates included a broad range of pathogens, including 6 each of *E. coli* and *Pseudomonas aeruginosa*, 3 *Klebsiella pneumoniae*,

and one each of *Acinetobacter* spp., *Enterobacter aerogenes*, and *Morganella morganii*. Other isolates of Gram-negative bacteremias included 4 isolates of *Haemophilus influenzae* and 2 of *Moraxella* spp., which may reflect cases of facial cellulitis arising from the sinuses, 5 cases of *Pasteurella multocida*, and single isolates each of *Vibrio vulnificus* and *Aeromonas hydrophilia* presumably reflecting aquatic exposures. The remaining four bacteremias included one case each of *Alcaligenes xylosoxidans*, *Comamonas* spp. (a member of *Pseudomonas* rRNA homology group 3), *Neisseria* species other than *Neisseria meningitidis* or *Neisseria gonorrhoeae*, and *flavobacterium* species.

Only seven of the included studies investigating cellulitis were prospective, and even these studies

Table 1 Bacteremias in cellulitis and erysipelas.

Reference	#Culture	#Positive	#GAS	#BHS	# <i>S. Aureus</i>	#Gram-neg	#Other
Studies of patients identified as Erysipelas							
Bergkvist et al., 1997 ²⁶	107	3	3	0	0	0	0
Bishara et al., 2001 ²⁷	176	4	1	1	1	1	0
Eriksson et al., 1996 ²⁸	161	8	5	3	0	0	0
Jorup-Ronstrum, 1986 ²⁹	149	12	4	3	3	2	0
Masmoudi et al., 2005 ³⁰	14	1	0	1	0	0	0
Subtotal (n)	607	28	13	8	4	3	0
Subtotal (%)		4.6%	46%	29%	14%	11%	—
Studies of patients identified as Erysipelas or Cellulitis							
Bernard et al., 1989 ³¹	42	1	0	1	0	0	0
Figtree et al., 2010 ³²	275	20	5	6	5	4	0
Lazzarini et al., 2005 ¹⁵	141	3	1	1	1	0	0
Siljander et al., 2008 ³³	88	2	0	2	0	0	0
Subtotal (n)	546	26	6	10	6	4	0
Subtotal (%)		4.8%	23%	38%	23%	15%	—
Studies of patients identified as Cellulitis							
Baddour et al., 1984 ³⁴	13	1	1	0	0	0	0
Bjornsdottir et al., 2005 ³⁵	81	12	4	4	0	4	0
Goldgeier, 1983 ³⁶	13	1	0	0	0	1	0
Ho et al., 1979 ³⁷	66	1	1	0	0	0	0
Hook et al., 1986 ³⁸	50	2	1	0	1	0	0
Jeng et al., 2010 ²¹	82	8	1	6	1	0	0
Jenkins et al., 2010 ¹¹	38	3	0	1	2	0	0
Kielhofner et al., 1988 ³⁹	87	6	1	0	2	2	1
Kulthanan et al., 1999 ⁴⁰	116	20	8	0	2	10	0
Lentino et al., 1984 ⁴¹	39	1	1	0	0	0	0
Liles et al., 1985 ⁴²	21	1	0	0	0	1	0
Lutomski et al., 1988 ⁴³	25	1	0	0	1	0	0
Peralta et al., 2006 ⁴⁴	308	45 ^a	2	24	6	14	0
Perl et al., 1999 ⁴⁵	553	11	3	5	1	2	0
Rescigno et al., 1994 ⁴⁶	7	1	0	1	0	0	0
Sachs, 1990 ⁴⁷	25	1	1	0	0	0	0
Simon et al., 1992 ⁴⁸	14	4	0	3	0	0	1
Stalnikowicz et al., 2001 ⁴⁹	30	3	0	1	1	1	0
Woo et al., 2000 ⁵⁰	10	3	0	3	0	0	0
Subtotal (n)	1578	125 ^a	24	48	17	35	2
Subtotal (%)		7.9%	19%	38%	14%	28%	2%
Total (n)	2731	179	43	66	27	42	2
Total (%)		6.5%	24%	37%	15%	23%	1%

#culture, Total number of cases with blood cultures; #positive, number of cases with positive blood cultures; #GAS, number of cases with blood cultures positive for group A streptococcus; #BHS, number of cases with blood cultures positive for non group A β -hemolytic streptococci; #*S. aureus*, number of cases with blood cultures positive for *Staphylococcus aureus*; #Gram-neg, number of cases with blood cultures positive for Gram-negative organisms; #other, 2 blood cultures were classified as miscellaneous organisms, including one each of a *clostridium* spp. and *enterococcus* spp.

^a Number of positive blood cultures is one less than individual number of pathogens because of one case of polymicrobial bacteremia caused by *S. aureus* and *P. aeruginosa*.

inconsistently excluded other types of soft tissue infections, such as abscess, diabetic foot infections and necrotizing infections (Table 2). If only the prospective studies are considered, the total number of positive blood cultures is 31 of 389 (8%). Streptococcal spp. accounted for 61% of these, *S. aureus* 16%, Gram-negative rods 19%, and miscellaneous 3%. Of the six Gram-negative isolates from prospective studies, two were *H. influenzae*, and one each was *P. multocida*, *E. coli*, *Comamonas* spp., and *Neisseria* species.

Comparison of erysipelas and cellulitis

The relative frequencies of streptococcal, staphylococcal and Gram-negative etiologies were compared between patients with erysipelas and cellulitis. Erysipelas was more likely to be due to group A streptococcus ($p = 0.002$) and less likely to be due to Gram-negative organisms ($p = 0.05$). There was also a nonsignificant trend for erysipelas to be due to β -hemolytic streptococci ($p = 0.09$). Both infections had similar rates of *S. aureus*.

Table 2 Characteristics of included studies.

Reference	Location	Date Range	Setting	Def ^a	Method	Types of SSTI excluded?
Studies of patients identified as Erysipelas						
Bergkvist et al., 1997 ²⁶	Sweden	N.R.	Hospital	Yes	Prospective	Diabetics
Bishara et al., 2001 ²⁷	Israel	10/93–12/96	Hospital	Yes	Retrospective	TSS, bullous erysipelas
Eriksson et al., 1996 ²⁸	Sweden	11/88–10/90	Hospital	Yes	Prospective	Wound infections
Jorup-Ronstrum, 1986 ²⁹	Sweden	81–83	Hospital	Yes	Prospective	Not specified
Masmoudi et al., 2005 ³⁰	Tunisia	1/91–12/00	Hospital	Yes	Retrospective	Not specified
Studies of patients identified as Erysipelas or Cellulitis						
Bernard et al., 1989 ³¹	France	N.R.	Hospital	Yes	Prospective	Abscess, NSTI, facial infections
Figtree et al., 2010 ³²	Australia	1/99–12/06	Hospital	Yes	Retrospective	Abscess, NSTI, diabetic foot infections
Lazzarini et al., 2005 ¹⁵	Italy	1/95–12/02	Hospital	Yes	Retrospective	Not specified
Siljander et al., 2008 ³³	Finland	4/04–3/05	Hospital	Yes	Prospective	Abscess, NSTI, septic arthritis, osteomyelitis
Studies of patients identified as Cellulitis						
Baddour et al., 1984 ³⁴	Tennessee	8/78–11/82	Hospital	No	Not specified	Not specified
Bjornsdottir et al., 2005 ³⁵	Iceland	10/00–2/04	Hospital	Yes	Prospective	Abscess, NSTI
Goldgeier, 1983 ³⁶	New York	79–81	Hospital	Yes	Retrospective	Abscess, ulcers, pustules, lacerations
Ho et al., 1979 ³⁷	Hawaii	6/73–12/78	Hospital	No	Retrospective	Not specified
Hook et al., 1986 ³⁸	Seattle	N.R.	E.R.	Yes	Prospective	Head or neck infections, abscess, deep SSTI
Jeng et al., 2010 ²¹	California	12/04–6/07	Hospital	Yes	Prospective	Any culturable SSTI, including abscess, wounds
Jenkins et al., 2010 ¹¹	Denver	1/07–12/07	Hospital	Yes	Retrospective	Abscess, SSTI with complicating factors
Kielhofner et al., 1988 ³⁹	Missouri	N.R.	Hospital	Yes	Prospective	Abscess, ulcers, osteomyelitis
Kulthanan et al., 1999 ⁴⁰	Thailand	92–95	Hospital	Yes	Retrospective	Abscess, ulcers, osteomyelitis
Lentino et al., 1984 ⁴¹	Illinois	1/82–3/83	Hospital	No	Prospective	Gangrenous or necrotic lesions
Liles et al., 1985 ⁴²	Missouri	N.R.	Hospital	Yes	Retrospective	Pustular lesions
Lutowski et al., 1988 ⁴³	Ohio	N.R.	E.R.	Yes	Prospective	Diabetics
Peralta et al., 2006 ⁴⁴	Spain	1/97–1/05	E.R.	yes	Retrospective	Hospital acquired cellulitis
Perl et al., 1999 ⁴⁵	Israel	4/95–8/98	Hospital	No	Retrospective	Facial cellulitis
Rescigno et al., 1994 ⁴⁶	New York	8/89–10/92	Mix	No	Not specified	Not specified
Sachs, 1990 ⁴⁷	Philadelphia	N.R.	Hospital	Yes	Prospective	Fluctuant or purulent infections
Simon et al., 1992 ⁴⁸	Michigan	N.R.	N.R.	No	Not specified	Not specified
Stalnikowicz et al., 2001 ⁴⁹	Israel	1/98–3/98	E.R.	No	Retrospective	Not specified
Woo et al., 2000 ⁵⁰	Hong Kong	96–98	Hospital	No	Retrospective	Not specified

^a Def, did authors describe a specific definition of cellulitis or erysipelas; N.R., not reported. E.R., emergency room; NSTI, necrotizing soft tissue infection; SSTI, skin and soft tissue infection.

Discussion

Traditional teaching holds that most cases of cellulitis are due to β -hemolytic streptococci or *S. aureus*, and that nearly all cases of erysipelas are streptococcal.^{4,5} Over the past decade numerous reports have highlighted the increasing prevalence of CA-MRSA, leading many authorities to include recommendations for considering CA-MRSA as a cause of cellulitis,^{5,16,17} and some to recommend empiric

coverage for MRSA for all skin and soft tissue infections.¹⁸ A recent study by Jenkins et al. for example, found that 85% of patients admitted for cellulitis at a Denver hospital were treated with vancomycin or other therapy effective against MRSA, whereas only 20% were treated with cefazolin and 8% with nafcillin respectively. At discharge, 48% of patients in this study continued therapy with trimethoprim-sulfamethoxazole compared with only 6% on cephalexin and 3% on dicloxacillin.¹¹ This use of trimethoprim-sulfamethoxazole as monotherapy for nonpurulent cellulitis

has been questioned by some authorities however because of the lack of published efficacy data and concern about effectiveness against streptococci.^{19,20}

Our data support the primary role of streptococcal species in both erysipelas and cellulitis. *S. aureus* accounted for a relatively small proportion of bacteremias associated with these infections. Similar findings were recently reported by Jeng et al. using acute and convalescent serologies of anti-streptococcal antibodies. These authors found evidence of streptococcal infection in 73% of cases of nonpurulent cellulitis.²¹ Older studies using needle aspiration or punch biopsy for diagnosis, on the other hand, appear to support a primary staphylococcal etiology in cellulitis. A recent review of these studies found that *S. aureus* accounted for 51% of cases of cellulitis, compared with only 27% for group A streptococcus.¹⁸ This review however did not specifically exclude cases with purulence and also included pediatric cases.

S. aureus accounted for 15% of the bacteremias in cellulitis and erysipelas in our study. Some authorities have recommended that empiric coverage for *S. aureus* should be considered when rates of infection are greater than 10%,¹⁷ in which case our data support the inclusion of anti-staphylococcal therapy for these infections. In areas with high rates of MRSA, this would entail empiric therapy effective against MRSA. Alternatively, it may be preferable to continue to treat stable patients with cellulitis or erysipelas with β -lactam antibiotics, and to reserve empiric therapy for MRSA for severely ill patients or patients failing antibiotics after 48 h, as has been suggested by others.^{13,21} Given the similar microbiology of cellulitis and erysipelas, our results argue against the current distinction between these infections in terms of empiric antibiotic therapy. Currently the IDSA guidelines recommend empiric treatment for only β -hemolytic streptococci for erysipelas with penicillin (a class A-1 recommendation), but recommend empiric therapy for both β -hemolytic streptococci and *S. aureus* for patients with cellulitis (methicillin-sensitive *S. aureus* (MSSA) for nonpurulent cellulitis, CA-MRSA for purulent cellulitis).^{5,13} Our results suggest that the decision to broaden empiric therapy to include *S. aureus* should be the same for both infections.

One surprising result from our data is that Gram-negative organisms appear to account for as large a percentage of erysipelas and cellulitis as *S. aureus*. Although recognized as a potential cause of cellulitis, particularly in immunocompromised patients,⁵ cirrhotics,²² and with certain exposures such as animal bites and aquatic lacerations, Gram-negative organisms have not been commonly associated with erysipelas, and empiric coverage for Gram-negative organisms is not recommended for either infection by the IDSA, except possibly for immunocompromised patients that are severely ill. Unfortunately, our data is not sufficient to determine which cases of Gram-negative bacteremia involved immunocompromised or cirrhotic patients, and even after discounting the 13 cases of bacteremia due to organisms that reflect specific exposures such as animal bites or that may have originated from sinusitis, there were still substantial numbers of patients with Gram-negative bacteremia. Based on our results, it may be reasonable to recommend that Gram-negative empiric therapy be considered for patients who

fail empiric therapy against Gram-positive organisms, and should be considered in all patients with cellulitis that are severely ill.

Our study has several important limitations. First, we rely on the pathogens found from associated bacteremias to reflect the distribution of pathogens in cellulitis and erysipelas. Clearly, this may be biased for several reasons, including the common practice of obtaining blood cultures from sicker patients, particularly upon hospitalization. This may mean that our findings more accurately reflect the distribution of pathogens in more severely ill patients with cellulitis and erysipelas than less sick patients. Similarly, certain groups of pathogens may be more likely to result in bacteremia, possibly biasing our results towards these organisms. As far as we know, however, there is no evidence that streptococcal species have a greater propensity to cause bacteremias than *S. aureus*.

Another important limitation to our study is that many of the included studies are retrospective, which likely include cases of skin and soft tissue infections other than cellulitis or erysipelas. In the study by Jenkins, for example, more than 90% of cases of hospitalized patients with skin and soft tissue infections were coded as "abscess or cellulitis", which share the same ICD-9 code. On review of the individual cases, the authors only considered 20% of these to have been uncomplicated cellulitis, while 32% had cutaneous abscesses and 48% were classified as "soft tissue infection with complicating factors", including recent surgery, deep tissue infection, chronic ulcers, bite wounds, periorbital infections, and infections associated with severe peripheral artery disease.¹¹ Studies that rely only on previously recorded diagnoses, therefore, likely include a significant number of other types of skin and soft tissue infection, including purulent infections such as abscess, that are more likely to be due to *S. aureus*^{9,13,16} and infections such as diabetic ulcers or post-surgical infections, which are more likely to involve *S. aureus* or Gram-negative organisms.²³ To address this potential bias we performed a subgroup analysis of data from the subset of prospective studies in which patient diagnoses were confirmed by study authors. With the analysis restricted to this subset of higher quality studies, results were consistent with those from the primary analysis.

Another potential limitation of our analysis is that most of the studies were performed before this past decade and the broad recognition of CA-MRSA. It is possible that there has been a shift in the predominant etiology of cellulitis and erysipelas given that strains of CA-MRSA recognized over the recent years may have genetic components that both impact on the pathogenesis of related disease and the epidemiology of CA-MRSA.¹⁹ If only the 4 studies with data from the past decade are included however, 25 positive blood cultures are reported, of which 18 are streptococcal (72%), 3 are *S. aureus* (12%), and 4 are Gram-negative organisms (16%).^{11,21,24,25}

In conclusion, this systematic review of cases of bacteremia associated with erysipelas and cellulitis supports the traditional teaching that streptococcal species are the predominant pathogens for both cellulitis and erysipelas. *S. aureus* appears to account for a much smaller proportion of cases. Importantly, Gram-negative organisms appear to be at least as common as *S. aureus*. Our review of the

literature also highlights the limited data on the subject and the need for additional well-designed studies of cellulitis and other skin and soft tissue infections to better define the microbiology of these infections and changes in the prevalence of specific pathogens over time.

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Conflict of interest statement

The authors have no relationship, condition, or circumstance that presents a potential conflict of interest related to this report.

Authorship

This manuscript represents original work and is not under consideration for publication elsewhere. All authors participated in the design of the study and in the writing of the manuscript and have seen and approved the submitted version.

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