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Regular Article

Risk of deep vein thrombosis in patients with cellulitis and erysipelas ☆ A systematic review and meta-analysis

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ABSTRACT

Introduction: The occurrence of deep vein thrombosis (DVT) is often considered in patients with cellulitis and erysipelas because of the common presentation of unilateral limb swelling, erythema and pain. Different authors however have reached different conclusions about the prevalence of DVT in these patients and for the need for compression ultrasound (CUS). The purpose of this study is to determine the prevalence of DVT in patients with cellulitis and erysipelas, and inform the utility of CUS.

Methods: A systematic literature search was conducted of Medline and Cochrane for studies that reported groups of patients with cellulitis or erysipelas who had CUS to evaluate for DVT. Study quality assessment was based on the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. The incidence rates from the included studies were pooled using a random-effects model to calculate an overall DVT rate. Individual and pooled DVT rates with corresponding upper and lower limits were graphed as a forest plot. Between-study heterogeneity was estimated using the I^2 statistic.

Results: Nine studies were included totaling 1054 patients with cellulitis or erysipelas with 18 DVTs. The overall pooled incidence rate was 2.1% (95% confidence interval, 0.5%-9.1%) for proximal DVT and 3.1% (95% confidence interval, 1.9%-4.9%) for any DVT. When analyzed separately, the pooled incidence rate for the three retrospective studies was 1.1% (95% CI, 0.6%-2.2%), while the rate for the six prospective studies was 7.8% (95% CI, 4.2%-14.2%).

Conclusion: The risk of DVT in cellulitis and erysipelas is low compared to the average risk of patients referred for CUS and comparable to low risk patients as determined by the commonly employed Wells criteria.

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Introduction

Cellulitis and erysipelas are common types of skin and soft tissue infection resulting in more than 600,000 hospitalizations per year in the United States [1]. Cellulitis is generally defined as any spreading infection involving the dermis and subcutaneous tissues [2], whereas erysipelas is a subtype of cellulitis involving the superficial dermal structures and distinguished clinically by raised borders and clear demarcation between involved and uninvolved skin [3]. The occurrence of deep vein thrombosis (DVT) is often considered in patients with these infections because of the common presentation of unilateral limb swelling, erythema and pain [4,5]. A recent prospective study from Denver for example reported that 42% of patients admitted with cellulitis received ultrasounds [6], primarily to rule out DVT (author personal communication). Other authors note that cellulitis and erysipelas are among the most common conditions in patients referred to assess for DVT [7,8], and account for up to 20% of ultrasound scans [9]. Despite this common practice, there is conflicting data about the prevalence of DVT in these infections and the need for CUS [10,11]. In order to better determine this risk, we undertook a systematic review and meta-analysis of the literature to determine the risk of DVT in patients with cellulitis or erysipelas.

Methods

Study Selection

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for conducting and reporting systematic reviews was used for our meta-analysis [12]. We searched for studies that reported the prevalence of DVT in groups of patients with cellulitis or erysipelas. OVID was used to search Medline using the subject headings "cellulitis", "erysipelas", "soft tissue infections", "venous thrombosis", "thrombophlebitis", and "lower extremity" from 1946 to present. The last search was done on December 1, 2012. References were limited to English language and humans. The Cochrane database was similarly searched. Each author independently screened all retrieved titles and abstracts for full text review. Selection for ultimate inclusion was based on full text review. Disagreement was resolved by mutual consensus.

Abbreviations: DVT, deep vein thrombosis; CUS, compression ultrasound; CI, confidence interval; SSTI, skin and soft tissue infection.

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All references that involved adult patients with cellulitis or erysipelas and reported rates of DVT were included in the review. We excluded pediatric series, case reports, and studies involving other skin and soft tissue infections such as abscess. We included observational studies of selected groups of patients with cellulitis or erysipelas referred for assessment of DVT. We included studies from varied clinical settings, including inpatient, emergency room, and outpatient. Cases were included if DVT was confirmed by compression ultrasound or venography. Cases diagnosed by impedance plethysmography were excluded.

Data Extraction and Quality Assessment

Two investigators assessed all studies meeting inclusion criteria. A standardized data extraction form was used to document patient characteristics such as age, type of soft tissue infection, clinical setting, type of diagnostic test for DVT and the specific definition of DVT used. Study quality assessment was based on the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [13], except that comparability was not relevant given the design of the included studies.

Data Synthesis and Analysis

The event rate of DVT in patients was estimated and the corresponding 95% confidence interval (CI) from each study was calculated before pooling data. The incidence rates from the included studies were pooled using a random-effects model to calculate an overall DVT rate. Individual and pooled DVT rates with corresponding upper and lower limits were graphed as a forest plot. Between-study heterogeneity was estimated using the I^2 statistic. Subgroup analysis was performed based on type of soft tissue infection, clinical setting, definition of DVT (proximal vs. distal), and study type (prospective vs. retrospective). Statistical significance was assumed for P values less than 0.05. All statistical analysis was performed using Comprehensive Meta Analysis software, version 2 (Biostat, Englewood, New Jersey).

Results

The primary literature search yielded 2,857 articles (Fig. 1). After review of the title and abstracts, 2695 articles were excluded, leaving 162 articles for full text review. Of these, 9 met study inclusion criteria. Tables 1 and 2 outline the characteristics and quality assessment of each study. No randomized controlled studies were identified. All studies were observational studies of patients that were reported as having either cellulitis or erysipelas and who had CUS to assess for DVT. Six of the studies were of patients with cellulitis whereas three were of erysipelas. Most restricted enrollment to patients with lower limb infections, although location wasn't reported in four of the studies. Six of the studies were prospective, with the type of soft tissue infection identified at the time of the ultrasound study, whereas three of the studies were retrospective, with the type of soft tissue infection being defined by record linkage. Other important study variables are shown in Table 1, including whether the study enrolled consecutive patients with cellulitis or erysipelas or whether patients were selected by referral, as well as clinical setting and the definition of DVT used. Of note, five of the studies used whole- leg compression ultrasound and included distal thromboses although only two of these five then reported whether found DVTs were in fact proximal or distal. As noted in Table 2, study quality was primarily limited by patient selection factors. In all of the retrospective studies and four of the prospective studies, reported patients were of select groups referred for ultrasound rather than of consecutive groups with cellulitis/erysipelas. Additionally, in the retrospective studies the presence or absence of DVT on CUS may have affected the enrollment of the patient in the cohort because the coded chart diagnosis may have been after the result of the CUS.

Fig. 2 reports the pooled and individual DVT incidence rates as determined by random-effects meta-analysis, grouped by study type. The total number of patients with either type of infection was 1054, and the total number of DVTs was 18. Eight of the DVTs were proximal, six were distal and 4 were unspecified. Individual study rates ranged from 12.5% (95% CI, 3.1%-38.6%) to 0.5% (95% CI, 0.1% to 1.8%). In general, the three retrospective studies, which contributed 87% of the patients but only half of the DVTs found low rates of DVT. The pooled rate for studies only reporting proximal DVT was 2.1% (95% CI, 0.5%-9.1%). The overall pooled DVT rate including distal DVT was 3.1% (95% CI, 1.9%-4.9%). We found evidence of significant statistical heterogeneity ($I^2 = 64.5\%$; $P = 0.0004$). We explored the heterogeneity by grouping analysis by study type (prospective vs. retrospective), and by clinical variables (proximal vs. whole leg CUS, SSTI type, and clinical setting). Despite the small number of studies in each of these groupings, none resolved the statistical heterogeneity except grouping by study type. When the three retrospective studies are analyzed separately, the pooled incidence rate for DVT is 1.1%

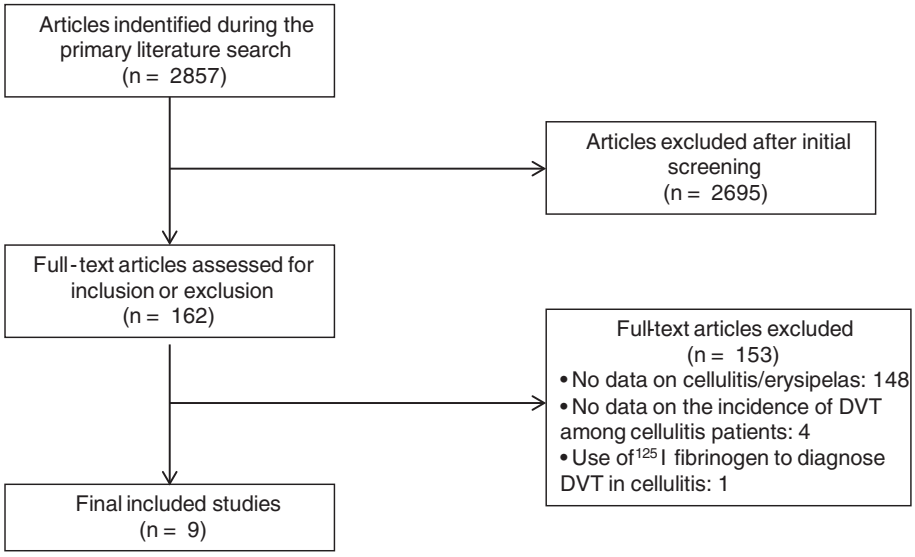

Fig. 1. Flow diagram of study selection process.

Table 1
Characteristics of included studies.

Author	*n*/*n*	Proximal?	Type of SSTI	Study type	Consecutive pt?	Limb?	Setting	Def. of DVT
1. Zaghdoudi [11]	3/30	1/3	Erysipelas	Prospective	yes	yes	ER	Whole leg
2. Lawall [21]	2/20	NR	Erysipelas	Prospective	yes	NR	Inpt	Whole leg*
3. Mazzolai [19]	1/27	NR	Erysipelas	Prospective	no	yes	Outpt	Whole leg*
4. Shields [7]	2/16	2/2	Cellulitis	Prospective	no	NR	ER	Proximal vein
5. Shitrit [9]	1/30	NR	Cellulitis	Prospective	no	NR	ER	Whole leg*
6. Birdwell [23]	0/15	0/0	Cellulitis	Prospective	no	NR	Outpt	Proximal vein
7. Maze [20]	3/240	3/3	Cellulitis	Retrospective	no	yes	Inpt	Proximal vein
8. Bersier [22]	2/431	2/2	Cellulitis	Retrospective	no	yes	NR	Proximal vein
9. Glover [10]	4/245	0/4	Cellulitis	Retrospective	no	yes	mix	Whole leg

Abbreviations: *n*/*n*, events/patients; Proximal, number of DVT that were proximal over total DVT; SSTI, skin and soft tissue infection; Limb?, study restricted to lower limb infections; Def. of DVT, definition of deep vein thrombosis; Inpt, inpatient; NR, not reported; ER, emergency room; Outpt, outpatient; CUS, compression ultrasound.
* Indicates that the particular study defined DVTs to include distal DVTs, but did not report whether DVTs were proximal or distal.

(95% CI, 0.6%-2.2%) and the I^2 is 8.2% ($p = 0.34$), and for the six prospective studies the pooled incidence is 7.8% (95% CI, 4.2%-14.2%) and the I^2 is 0.0% ($p = 0.75$). Due to the limited number of included studies we did not do meta-regression.

Discussion

DVT has long been considered to be part of the differential diagnosis of cellulitis and erysipelas since both conditions may present similarly [4]. Individual studies of the prevalence of DVT in these conditions have found contradictory results; in our study individual DVT rates ranged from 0.5% to 12.5%. The aim of our present study was to summarize the data to estimate the overall DVT rate in these types of infection. In total, we found nine studies that reported rates of DVT in groups of patients with either cellulitis or erysipelas, including a total of 1054 patients with 18 DVTS, yielding a pooled incidence of 2.1% and 3.1% for proximal and total DVT respectively.

The main significance of this finding is that the risk of DVT in cellulitis or erysipelas appears to be relatively low. The median prevalence of DVT in all patients referred for ultrasound according to one meta-analysis of 51 studies is 24% [14], much higher than the rate in cellulitis/erysipelas. Even in studies using clinical prediction scores such as the Wells score or using D-dimer to exclude DVT, the resultant rate of DVT in "low risk" categories are comparable to the rate in cellulitis/erysipelas. For example, a systematic review of 22 studies that used the Wells score to predict DVT found that the average prevalence of proximal DVT in patients assessed as low risk by the Wells criteria is 6.5% (95% CI, 3.2%-11.4%)[14]. Similarly the overall prevalence of DVT in unselected patients referred for CUS who have a normal D-dimer is approximately 2.2% [15]. Unfortunately, the overall rate of DVT in cellulitis/erysipelas appears to be higher than typical rates for which no further testing is performed. The rate of DVT in patients with both low pretest probability and normal D-dimer levels for example is 0.7% (95% CI, 0.3%-1.3%)[16] while the rate for patients with negative whole limb lower extremity ultrasound is 0.6% (95% CI, 0.2%-0.9%)[17].

What should be the approach for assessing for DVT in patients with cellulitis or erysipelas then? Currently if a patient is suspected of DVT, the recommended approach is to use both a clinical risk assessment tool plus measurement of D-dimer to guide the overall approach [18]. Patients who are low risk and found to have a normal D-dimer are considered excluded and no further testing recommended [18]. The risk of DVT in cellulitis and erysipelas however, appears to be higher than this rate. One possible approach is simply to calculate the Wells score and obtain a D-dimer for these patients and if either the Wells score indicates that DVT is not low risk or the D-dimer is abnormal, then to obtain a CUS. The problem with this approach is that as mentioned, DVT and skin infections may have similar presentations; In particular, patients with skin infections may earn points on the Wells score for tenderness, calf swelling and edema which may exclude them from the low risk category and thus prompt an unnecessary CUS. Another approach would be to not calculate a pretest probability in patients with cellulitis or erysipelas but to merely obtain a D-dimer level. Given that the incidence of DVT in these patients appears to be similar to the rate in the low risk category as defined by the Wells score, it may be reasonable to consider DVT excluded if the D-dimer level was normal. If the D-dimer level was elevated, it would be reasonable to consider CUS to exclude DVT. The problem with this approach, however, is that it has not been tested and authors have reported that cellulitis and erysipelas may falsely elevate D-dimer levels, potentially limiting their usefulness in excluding DVT [11,19]. Ultimately, given the heterogeneity and limitations of the included studies in our review the optimal approach to assessing for DVT in cellulitis/erysipelas remains uncertain.

Our review has several important limitations. First, there was significant statistical heterogeneity for DVT rates between included studies, matching the clinical and methodological heterogeneity of the

Table 2
Study quality assessment using Newcastle-Ottawa Quality Assessment Scale.

Author	Study Cohort	Selection	Outcome	NOS score	Comment
Zaghdoudi et al. [11]	ER patients with erysipelas	**	***	5/9	Small study, only 1 proximal DVT
Lawal et al. [21]	Subgroup of patients with erysipelas of consecutive inpatients screened w/CUS	**	***	5/9	Small study, unclear if proximal or distal DVTs
Mazzolai et al. [19]	Outpatients with erysipelas referred for CUS	**	***	5/9	Small study, unclear if proximal or distal DVT; referred pts.
Shields et al. [7]	Adult ER patients with cellulitis referred for CUS	**	***	5/9	Small study, referred pts.
Shitrit et al. [9]	Adult ER patients with cellulitis referred for CUS	**	***	5/9	Small study, referred pts.
Birdwell et al. [23]	Adult outpatients referred for CUS	**	***	5/9	Small study, referred pts.
Maze et al. [20]	Inpatients with lower limb cellulitis who had CUS to exclude DVT	*	***	4/9	Retrospective. Cohort effected by outcome
Bersier et al. [22]	Patients with cellulitis referred for CUS	*	***	4/9	Retrospective. Cohort possibly effected by outcome
Glover et al. [10]	Subgroup of patients with cellulitis for CUS	*	***	4/9	Retrospective. Cohort possibly effected by outcome

Abbreviations: NOS, Newcastle-Ottowa Quality Assessment Scale; CUS, compression ultrasound; DVT, deep vein thrombosis; ER, emergency room; Pts, patients.

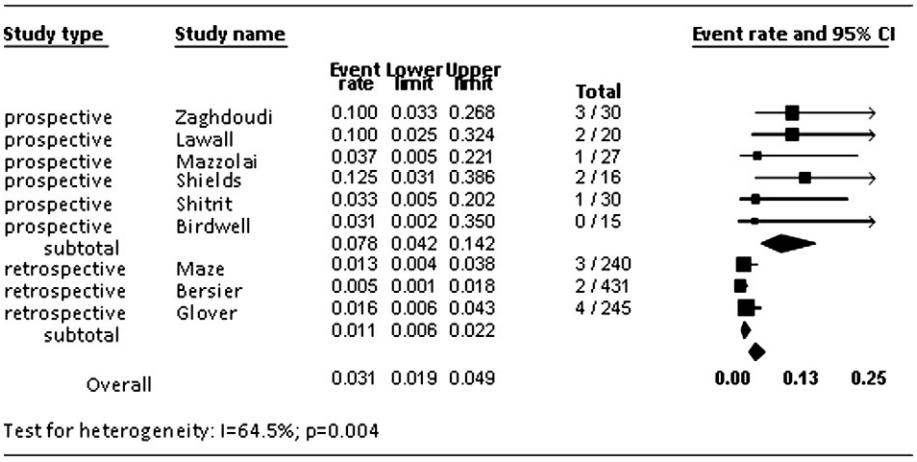

Fig. 2. Individual and pooled DVT incidence rate.

included studies. As can be seen in Fig. 2, the three retrospective studies all found relatively low rates of DVT, while the prospective studies generally found higher rates. We hypothesize several possible reasons for this difference. First, the retrospective studies used record linkage to record the occurrence of DVT and soft tissue infection type. Jenkins et al. have shown that many cases coded as cellulitis have in fact other types of complicated soft tissue infection such as abscess or diabetic foot infection [6], which may not have a similar association with DVT, and for which ultrasound has a different clinical role. This may mean that in the retrospective studies, if many of the cases recorded as cellulitis were in fact abscesses for which ultrasound was ordered to confirm the extent of abscess, that it would be unsurprising to find a low rate of DVT. Another potential bias from the use of record linkage is that the reported cohort of patients may also have been affected by the occurrence of the outcome. It is possible in other words, that if patients were found to have a DVT that they would have been recorded as having the diagnosis of DVT rather than cellulitis and not included in the study. Although the use of record linkage may have biased the retrospective studies, the prospective studies were all small which may be associated with publication bias and most were of non-consecutive patients referred for CUS which may also overestimate the effect size. Three of the prospective studies, furthermore, used whole-leg CUS to detect DVTs but didn't report whether found DVTs were proximal or distal, the latter of which are of uncertain clinical significance.

Another important limitation of our study is the clinical heterogeneity of included studies. We included studies with different types of soft tissue infection (cellulitis and erysipelas), different definitions of DVT (whole leg versus proximal leg), and different clinical settings (inpatient, outpatient, emergency room and mixed). All of these may have impacted the incidence of DVT. Ultimately we decided to do meta-analysis however despite these sources of heterogeneity because we felt it would be clinically useful to have some estimate of the overall incidence of DVT in these infections. Larger prospective studies of consecutive patients with cellulitis/erysipelas who are systematically evaluated for DVT are needed. Future studies should also distinguish between proximal and distal DVTs given the uncertain significance of the later, and should be limited to limb infections given that it is unlikely that infections of the torso or face would be related to underlying DVT.

In summary, the prevalence of DVT in patients with cellulitis or erysipelas appears to be low, comparable to the low risk group as defined by the Wells criteria. Given the limitations of the literature the optimal approach to assessing for DVT in patients with these infections remains uncertain. Prospective studies of consecutive patients with limb infections which assess for proximal DVT are needed.

Conflict of Interest Statement

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

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