IMPORTANCE  The optimum antibiotic treatment for cellulitis and erysipelas lacks consensus. The available trial data do not demonstrate the superiority of any agent, and data are limited on the most appropriate route of administration or duration of therapy.

OBJECTIVE  To assess the efficacy and safety of antibiotic therapy for non-surgically acquired cellulitis.

DATA SOURCES  The following databases were searched to June 28, 2016: Cochrane Central Register of Controlled Trials (2016, issue 5), Medline (from 1946), Embase (from 1974), and Latin American and Caribbean Health Sciences Information System (LILACS) (from 1982). In addition, 5 trials databases and the reference lists of included studies were searched. Further searches of PubMed and Google Scholar were undertaken from June 28, 2016, to December 31, 2018.

STUDY SELECTION  Randomized clinical trials comparing different antibiotics, routes of administration, and treatment durations were included.

DATA EXTRACTION AND SYNTHESIS  For data collection and analysis, the standard methodological procedures of the Cochrane Collaboration were used. For dichotomous outcomes, the risk ratio and its 95% CI were calculated. A summary of findings table was created for the primary end points, adopting the GRADE approach to assess the quality of the evidence.

MAIN OUTCOMES AND MEASURES  The primary outcome was the proportion of patients cured, improved, recovered, or symptom-free or symptom-reduced at the end of treatment, as reported by the trial. The secondary outcome was any adverse event.

RESULTS  A total of 43 studies with a total of 5999 evaluable participants, whose age ranged from 1 month to 96 years, were included. Cellulitis was the primary diagnosis in only 15 studies (35%), and in other studies the median (interquartile range) proportion of patients with cellulitis was 29.7% (22.9%-50.3%). Overall, no evidence was found to support the superiority of any 1 antibiotic over another, and antibiotics with activity against methicillin-resistant Staphylococcus aureus did not add an advantage. Use of intravenous antibiotics over oral antibiotics and treatment duration of longer than 5 days were not supported by evidence.

CONCLUSIONS AND RELEVANCE  In this systematic review and meta-analysis, only low-quality evidence was found for the most appropriate agent, route of administration, and duration of treatment for patients with cellulitis; future trials need to use a standardized set of outcomes, including severity scoring, dosing, and duration of therapy.

Published online June 12, 2019.
Cellulitis is a common acute skin infection. Published guidelines for the management of cellulitis are mostly based on evidence from studies of skin and soft tissue infections, which have included cellulitis, or on expert opinion. Despite the published guidance, substantial variations in the antibiotic management of cellulitis have been identified.

This systematic review and meta-analysis aimed to inform the production of evidence-based guidelines that cover antibiotic choice, route of administration, duration of treatment, the role of combinations of antibiotics, and gaps in research.

Methods

We searched the following databases until June 28, 2016: Cochrane Central Register of Controlled Trials (2016, issue 5), Medline (from 1946), Embase (from 1974), and LILACS (Latin American and Caribbean Health Sciences Information System; from 1982). We also searched 5 trial databases and the reference lists of included studies. Further searches of PubMed and Google Scholar were undertaken from June 28, 2016, to December 31, 2018.

We included studies of adults or children with a cellulitis diagnosis that randomized participants to groups. We used the term cellulitis to include erysipelas, as the 2 conditions cannot be readily distinguished. The focus of this review was cellulitis requiring acute therapy with antibiotics rather than prophylaxis. We considered a randomized clinical trial if a comparison was made between different treatment regimens, including different antibiotics, routes of administration, and duration of therapy.

The primary outcome of the proportion cured, improved, recovered, or symptom-free or symptom-reduced at the end of treatment was commonly reported by patients or medical practitioners. No standard outcome measure was used because each trial applied different time points and criteria to assess patient recovery or improvement. The secondary outcome was any reported adverse events.

We identified relevant randomized clinical trials published in the English language. The databases we searched and the search strategies used are detailed in eAppendix 1 in the Supplement. We checked bibliographies of included studies for additional relevant trials. We did not perform a separate search for adverse effects of the target interventions, but we did examine data on adverse effects in the included studies.

All studies of antibiotic therapy included in the previous 2010 systematic review were included in this review. Potential studies for inclusion were independently reviewed by 2 of us (R.B. and O.M.W.) against the inclusion criteria. If both of us agreed that the study was not relevant to the objectives of this review, the study was excluded. If relevance was unclear from the abstract, the 2 of us reviewed the full text. Any disagreement between us was resolved by consensus and referred to a third author (P. F.) if necessary.

Among the information we recorded from each study was the population description, interventions, treatment duration, number of participants randomized into each treatment group, number of participants who were cured or did not respond to treatment, number of participants lost to follow-up, and duration of follow-up. For all potential studies, 2 of us (R.B. and O.M.W.) independently extracted and analyzed the data, and 1 (R.B.) entered the data into RevMan, version 5.3 (Nordic Cochrane Centre).

Six types of bias were assessed: selection, performance, detection, attrition, reporting, and other bias (eAppendix 2 in the Supplement). We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and categorized each included study as having high, low, or unclear risk of bias.

Statistical Analysis

For studies in which similar types of interventions were compared, we performed a meta-analysis to calculate a weighted treatment effect across trials. A Mantel-Haenszel fixed-effects model was used to calculate a treatment effect when heterogeneity was low and the advantages of small studies would be overestimated by the random-effects analysis. Because the number of included studies was low, we interpreted values of 50% or greater as representing substantial heterogeneity and applied a random-effects model. The results are expressed as risk ratios (RRs) with 95% CIs for dichotomous outcomes.

We assessed the reporting of withdrawals, dropouts, and protocol deviations as well as whether participants were analyzed in the group to which they were originally randomized (intention-to-treat population).

Results

The study selection process is summarized in Figure 1. A summary of findings, using the GRADE approach to assess the quality of evidence, is included in eTable 1 in the Supplement.

Of the 41 studies included, 2 consisted of 2 sets of comparisons and were then treated as separate studies (Bucko et al 2002 and Daniel 1991), increasing the number of studies to 43. One study was treated as 2 and thus is presented as 2 papers (Corey et al 2010 and Wilcox et al 2010).

The 43 studies included 5999 evaluable participants, whose age ranged from 1 month to 96 years. Details of the studies are summarized in eTable 2 in the Supplement. Cellulitis...
was the primary diagnosis in only 15 studies (35%), and in other studies the proportion of patients with cellulitis ranged from 8.9% to 90.9%, with a median (interquartile range) of 29.7% (22.9%-50.3%).

Most studies compared different antibiotics or treatment durations. No studies compared antibiotics with placebos. For most studies, the duration was allowed to vary, depending on clinical need. Some trials had different durations but not with the same antibiotic. Because of the wide range of antibiotics used, we could not analyze variations in antibiotic doses and outcomes.

Because every study reported outcomes in different ways, we accepted the proportion cured as equivalent to the proportion with improved or reduced symptoms. The criteria for determining improvement and the time points for assessment of cure or improvement varied widely. The quality of follow-up ranged from the assessment of all participants to the assumption that cure had occurred unless the participant returned.

The reason for the exclusion of most trials was they did not present results for the population with cellulitis, they were quasi-randomized clinical trials, or they had no obvious randomization process. The type of risk of bias for each study is shown in Figure 2 and eAppendix 2 in the Supplement.

### Effects of Interventions

#### Penicillin vs Cephalosporins

Three studies (n = 86) compared a penicillin with a cephalosporin. In 2 studies, intravenous (IV) ampicillin and sulbactam was compared with IV cefazolin, and a third study compared IV ceftriaxone with IV flucloxacillin. We found no difference between the 2 treatments. This outcome had high levels of heterogeneity (RR = 0.98; 95% CI, 0.68-1.42; P2 = 70%) (Figure 1.1 in the Supplement). Two studies reported on adverse events. No difference was found between the groups (RR = 0.48; 95% CI, 0.14-1.69; n = 68) (eFigure 1.2 in the Supplement).

#### Older vs Newer Cephalosporins

We identified 6 studies (n = 527) that were organized into 4 subgroups. No single cephalosporin was accepted as a standard for comparison. We defined the newer cephalosporin as cephalosporin A and the older as cephalosporin B. We found no difference between the 2 treatments (RR = 1.02; 95% CI, 0.96-1.09) (Figure 2.1 in the Supplement). Only 1 study reported data for adverse events for the cellulitis subgroup; the cefazolin-probenecid group experienced more adverse events compared with the IV ceftriaxone group (21% vs 10%), but this was not statistically different (RR = 0.50; 95% CI, 0.22-1.16; n = 134) (Figure 2.2 in the Supplement).

#### β-lactam vs Macrolide, Lincosamide, or Streptogramin

Two studies compared IV benzylpenicillin with an oral macrolide (roxithromycin) and a streptogramin (pristinamycin). Participants in both studies had uncomplicated erysipelas, presumed streptococcal, and were therefore penicillin sensitive. Another study compared oral cloxacillin with azithromycin, and a community study compared oral flucloxacillin with oral erythromycin. A small study, which included participants with cellulitis, compared cefalexin with azithromycin.

A further study compared oral clindamycin with sequential IV and oral flucloxacillin. In total, 6 studies (n = 596) were found. We found no difference between the 2 treatments (RR = 0.94; 95% CI, 0.85-1.04; P2 = 44%) (Figure 3.1 in the Supplement). This has been independently published, including more studies but with similar findings. Three studies reported adverse events. No significant differences were observed between the groups (RR = 0.70; 95% CI, 0.45-1.08; n = 397) (Figure 3.2 in the Supplement).
Quinolone or Vancomycin vs Other Antibiotic
We found 3 studies (n = 160) comparing a quinolone with other antibiotics: 1 compared a novel fluoroquinolone with linezolid,44 1 compared moxifloxacin with a penicillin/beta-lactamase inhibitor combination,48 and 1 compared delafloxacin with tigecycline.36 We found no difference between the treatments (RR = 1.04; 95% CI, 0.94-1.16) (eFigure 4.1 in the Supplement). Data on adverse events could not be extracted.

We identified 10 studies (n = 2275), organized into 3 subgroups comparing vancomycin with other antibiotics. We found no difference between the 2 treatments (RR = 1.00; 95% CI, 0.98-1.02) (eFigure 5.1 in the Supplement).

Vancomycin Plus Gram-Positive, Plus Gram-Negative, or Alone vs Other Antibiotic
One study17 (n = 625) compared vancomycin followed by oral linezolid with dalbavancin. No difference was observed between vancomycin alone or in combination and other antibiotics (RR = 0.99; 95% CI, 0.94-1.04) (eFigure 5.1.1 in the Supplement).

Four studies (n = 853) compared vancomycin combined with a gram-negative antibiotic: vancomycin with oritavancin (aztreonam allowed in both arms),38 vancomycin plus aztreonam with ceftaroline fosamil,46,37 and vancomycin plus ceftazidine with ceftobiprole medocaril.39 No difference was found between vancomycin alone or in combination and other antibiotics (RR = 1.00; 95% CI, 0.96-1.05) (eFigure 5.1.2 in the Supplement).

We found 5 trials (n = 797) that compared vancomycin alone with other antibiotics: daptomycin,40,41 ceftobiprole,42 a new pleuromutilin,43 and linezolid.44 We found no evidence of a difference between the 2 treatments (RR = 1.00; 95% CI, 0.97-1.03) (eFigure 5.1.3 in the Supplement).

The only study (n = 101) with cellulitis-specific adverse events40 did not demonstrate a difference between the 2 treatments (RR = 1.02; 95% CI, 0.42-2.51) (eFigure 5.2 in the Supplement).

Linezolid vs Other Antibiotic
Four studies (n = 1024) compared linezolid with a variety of other antibiotics: a novel fluoroquinolone,34 tedizolid phosphate,45,46 and vancomycin.44 No difference was observed between linezolid and other antibiotics (RR = 1.00; 95% CI, 0.95-1.05) (eFigure 6.1 in the Supplement). Data on adverse events could not be extracted.

Clindamycin vs Trimethoprim Sulfamethoxazole
One study47 (n = 248) compared clindamycin with trimethoprim-sulfamethoxazole. This study was of uncomplicated skin infections and included participants with cellulitis in an area of high community prevalence of methicillin-resistant Staphylococcus aureus (MRSA). No difference was found between clindamycin and trimethoprim-sulfamethoxazole (RR = 1.05; 95% CI, 0.96-1.15) (eFigure 7.1 in the Supplement). Data on adverse events could not be extracted.

MRSA-Active vs Non-MRSA-Active Antibiotics
Two studies48,49 (n = 557) examined whether the addition of antibiotics active against MRSA affected outcome. The MRSA-
active arm (cephalosporin plus trimethoprim-sulfamethoxazole) was compared with cephalosporin plus placebo. There was no difference between MRSA-active and non-MRSA-active antibiotics (RR = 0.99; 95% CI, 0.92-1.06) (eFigure 8.1 in the Supplement). One study49 actively excluded patients with purulent cellulitis, whereas another48 included those with pustules less than 3 mm in maximal diameter. Although their numbers were small (n = 19), purulent cellulitis was not a factor in response to therapy.48 Both studies included data on adverse events. We found no difference between the 2 treatments (RR = 1.03; 95% CI, 0.92-1.14; n = 642) (eFigure 8.2 in the Supplement).

Other Studies Not Already Included
One study50 (n = 19) compared cefalexin 500 mg twice a day with 250 mg 4 times a day. No difference was observed between the groups (RR = 1.00; 95% CI, 0.81-1.23) (eFigure 9.1 in the Supplement).

One study51 compared meropenem with imipenem-cilastatin for skin and skin-structure infection. No statistically significant differences were found within the cellulitis subgroup (RR = 0.88; 95% CI, 0.68-1.15; n = 81) (eFigure 9.2 in the Supplement).

One study52 (n = 81) examined the addition of benzylpenicillin to the regimen of those who receive flucloxacillin (temperature, pain, or diameter of infected area were assessed on days 1 and 2 of treatment). No statistically significant effect on symptoms (RR = 0.98; 95% CI, 0.87-1.09) (eFigure 9.3 in the Supplement) was found. No adverse effects were reported in either arm of the study.

One study53 (n = 410) compared flucloxacillin plus clindamycin with flucloxacillin plus placebo and found no statistically significant difference between the 2 allocations at day 5 follow-up (RR = 1.07; 95% CI, 0.98-1.18) (eFigure 9.4.1 in the Supplement). A statistically significant difference in adverse events was observed, specifically diarrhea, occurring twice as frequently in the clindamycin group (RR = 1.87; 95% CI, 1.23-2.86; P = .004) (eFigure 9.4.2 in the Supplement).

One study54 (n = 18) compared ticarcillin and clavulanic acid with moxalactam. No difference between the groups was found (RR = 1.00; 95% CI, 0.82-1.22) (eFigure 9.5 in the Supplement).

One study55 compared oral gatifloxacin with oral levofloxacin as part of a skin and skin-structure infection trial. A small but statistically significant difference was found, favoring gatifloxacin (RR = 1.17; 95% CI, 1.01-1.35; n = 82; P = .03; low-quality evidence) (eFigure 9.6 in the Supplement).

One study56 (n = 112) compared IV benzylpenicillin with intramuscular penicillin (benzylpenicillin and procaine penicillin) for 10 days. No difference in outcome was observed (RR = 0.93; 95% CI, 0.79-1.10) (eFigure 9.7.1 in the Supplement), but more adverse events occurred in the IV group (RR = 7.25; 95% CI, 1.73-30.45; P = .007) (eFigure 9.7.2 in the Supplement).

Shorter vs Longer Courses of Antibiotics
We identified 5 studies (n = 916) that compared a shorter with a longer duration of treatment. Only 1 study57 compared the duration for the same antibiotic. One study58 compared a single dose of oritavancin, a glycopeptide with a long half-life, with 7 to 10 days of vancomycin. The 2 studies by Daniel55 compared 5 days of azithromycin with 7 days of either cloxacillin or erythromycin. One study37 compared 5 days of oral levofloxacin with a 10-day regimen. Another study55 compared 6 days of tedi-zolid with 10 days of linezolid. No difference was found between short and long antibiotic courses (RR = 0.99; 95% CI, 0.94-1.04) (eFigure 10.1 in the Supplement). Only 1 study57 (n = 87) reported adverse events that led to participant withdrawal, which was not statistically significant (RR = 0.33; 95% CI, 0.01-7.79) (eFigure 10.2 in the Supplement).

Intravenous vs Oral Antibiotics
We identified 4 studies (n = 550), although the only study58 designed specifically to compare oral with IV antibiotics was small (n = 47) and showed no statistical difference in outcomes. Two studies (n = 357) investigated an oral macrolide28 or an oral streptogramin29 against IV benzylpenicillin. The oral agents were shown to be more effective than the IV benzylpenicillin. Pallin et al48 included data on route of administration, although the study was not designed to examine this route.

For this outcome, we found low-quality evidence that IV administration was inferior compared with oral administration (RR = 0.83; 95% CI, 0.75-0.93; P < .001) (eFigure II.1 in the Supplement). Although more adverse events occurred in the oral administration group, no statistically significant difference was observed between the groups (RR = 1.11; 95% CI, 0.73-1.68; n = 549; I² = 46%) (eFigure II.2 in the Supplement).

Discussion
From the data presented, defining the most effective antibiotic treatment for cellulitis was not possible, given that no 1 antibiotic was superior over another. The use of a cephalosporin rather than a penicillin was not supported despite trials that showed equivalence.23-25,54 Similarly, glycopeptide,37,38 oxazolidinone,44 and daptomycin41 did not show superiority to the other antibiotics. The use of combination therapy was not supported, as the trials with combination therapy did not demonstrate better outcomes.48,49,52,53

The use of oral therapy was supported by the limited data for oral vs IV antibiotics and by trials in which only oral antibiotics were used with good outcome. The earliest studies of antimicrobials for erysipelas administered the drugs orally with good outcomes.21,22 In this review, when oral antibiotics were compared with IV treatments, the oral treatments appeared more effective.28,29,48,58

Identifying the optimum duration of antibiotic therapy was not possible, with only 1 trial designed to look specifically at duration,57 but no supporting evidence was found for antibiotic therapy longer than 5 days.15 The trial by Hepburn et al57 only randomized to longer treatment at day 5, which did not clarify whether prolonged antibiotic treatment for those patients who were slow to improve made any difference to the rate of improvement or final outcome. An antibiotic with
activity against MRSA in cellulitis was investigated in 2 trials. Neither trial showed the advantage of this antibiotic, however, supporting the view that cellulitis is primarily a streptococcal infection.

Limitations
This study has several limitations. Most of the included studies lacked consistent, clear, and precise end points for cellulitis therapies, making comparison between treatments difficult. Standard end points are needed with which assessment is made and to which subsequent trials should all adhere. These end points must be objective (eg, no further swelling, neutrophil level within the normal range) and not subjective (eg, discharge from hospital, IV to oral switch). According to interviews with participants, the outcomes of interest to them were time to resolution of unpleasant symptoms, such as pain, yet only 6 studies gave information on symptom reduction. A more common outcome was the proportion of patients cured or improved, an assessment often timed at the end of treatment or up to 2 weeks after treatment and defined as the reduction or absence of the original signs or symptoms. This timing or definition does not allow discrimination between treatments, which may affect the duration of symptoms or the length of hospital stay.

Older studies either did not specify or did not exclude participants who had received previous antibiotic therapy and included people who did not respond to community treatment. In contrast, 17 studies excluded participants who had received antibiotics before enrollment, although the exclusion period varied between studies.

Many trials included mixed populations with a range of skin and skin-structure infections; unless they presented subgroup data for those with cellulitis, we were unable to include these studies. The decision to show these data may be biased, because researchers may prefer to show data for specific disease groups if the response to the treatments varied.

In most trials, the causative organisms were not isolated. Many studies with mixed-disease populations reported subgroup data for causal organisms but not the type of tissue involvement. Isolation rates for causal organisms were generally low for cellulitis, rarely higher than 25%. This rate means that, in some studies, 75% of participants with cellulitis would be excluded.

A number of studies did not adequately explain the process of allocation concealment or blinding (Figure 2), and only more recent studies provided sample size calculations. Eleven studies were described as open, with 5 additional studies presumed to be not blinded (their design was not specified). This lack of blinding, in combination with a lack of objective outcome measures, could increase the risk of bias.

Implications for Research
In light of the low quality of evidence we identified, additional research is required to define the optimum management of cellulitis. Future clinical trials should only include participants with cellulitis and address specific issues associated with therapy. Trials need to clarify the duration of therapy and whether longer durations are necessary with more severe disease. None of the trials included dose comparisons, and the tendency may be to increase the dose to resolve treatment failures without testing this hypothesis. Future trials need to clarify dosing and whether dosing should be based on actual or ideal body weight.

Randomized clinical trials should be conducted comparing IV with oral antibiotics for participants within a community setting; the results of such trials would have implications for the delivery and cost-effectiveness of home therapy, minimizing the involvement of home IV services or frequent outpatient hospital visits. In addition, trials need to have standardized criteria for severity scoring (eg, Systemic Inflammatory Response Syndrome criteria, renal function, and area of erythema) to allow the examination of treatment route, dosing, and duration. A standardized set of outcomes needs to be established for these trials. These outcomes should include systemic features (eg, heart rate, blood pressure) as well as local (eg, inflammation, swelling), blood (eg, neutrophils, urea), and patient-focused (eg, nausea, pain, mobility) measures. Trial exclusions (eg, duration of antibiotics prior to trial entry) and times of follow-up (eg, early, late, and back-to-normal activities) should be standardized whenever possible.

Conclusions
Current evidence does not support the superiority of any 1 antibiotic over another, and the use of a combination of antibiotics is not supported by clinical trial data. There is a lack of evidence favoring the use of intravenous over oral antibiotics or for treatment durations longer than 5 days.
For the treatment of cellulitis and erysipelas, the efficacy and safety of daptomycin vs. vancomycin were evaluated in a randomized, double-blind, phase 3, non-inferiority trial. *Clin Infect Dis.* 2013;57(5):1093-1103. doi:10.1093/cid/cit122


