**Decision making on the route and duration of antibiotic therapy in acute cellulitis: A systematic review and meta-analyses considering the effectiveness and harms of antibiotic treatment.**

**Running title:** Antibiotic treatment decision making for acute cellulitis

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## Abstract

### Objectives

Compared with guideline recommendations, antibiotic overuse is common in treating cellulitis. We conducted a systematic review and meta-analyses on antibiotic route and duration of treatment for cellulitis in adults and children.

### Methods

We searched MEDLINE, EMBASE and trial registries from inception to Dec 11, 2019 for interventional and observational studies of antibiotic treatment for cellulitis. Exclusions included case series/reports, pre-septal/orbital cellulitis and non-English language articles. Random-effects meta-analyses were used to produce summary relative risk (RR) estimates for our primary outcome of clinical response.

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### Results

We included 47/8423 articles, incorporating data from eleven trials (1855 patients) in two meta-analyses. The overall risk of bias was moderate. Only two trials compared the same antibiotic agent in each group. We found no evidence of difference in clinical response rates for antibiotic route or duration (RR(oral:IV)=1·12, 95%CI 0·98-1·27, $I^2$=32% and RR(shorter:longer)=0·99, 95%CI 0·96-1·03, $I^2$ = 0%, respectively). Findings were consistent in observational studies. Follow-up data beyond 30 days were sparse.

### Conclusions

The evidence base for antibiotic treatment decisions in cellulitis is flawed by biased comparisons, short follow-up and lack of data around harms of antibiotic overuse. Future research should focus on developing patient-tailored antibiotic prescribing for cellulitis to reduce unnecessary antibiotic use.

### Keywords

Cellulitis; Erysipelas; Soft tissue Infections; Anti-Bacterial Agents; Duration of Therapy; Administration, Intravenous; Administration, Oral

## Introduction

Cellulitis is the commonest form of acute skin and soft tissue infection (SSTI), characterised by spreading redness, oedema and induration, usually affecting the lower limb.[1] The term encompasses erysipelas, which is no longer considered a distinct entity, and does not apply to inflammation associated with collections of pus (e.g. around skin abscesses) for which the primary treatment is drainage rather than antibiotic therapy.[1] Cellulitis is predominantly a community onset infection, typically affecting older adults.[2] Recent data from the United States (US) show that SSTI incidence in older adults almost doubled between 2000 and 2012 (from 67-130 per 10,000 persons) with the associated healthcare costs tripling to 15 billion USD.[3] From 2000-2018, the proportion of emergency admissions due to cellulitis in England increased by more than one third (0·9 to 1·3%).[4] Over 90% of patients with cellulitis are treated in ambulatory care.[5]

The main causative organisms of cellulitis are beta-haemolytic streptococci, especially *Streptococcus pyogenes,* and *Staphylococcus aureus*[6,7] while other bacterial species are linked to specific patient risk factors.[2] Guidelines recommend antibiotic agents for cellulitis based on susceptibility of key pathogens, but clinicians then have three decisions as they seek to avoid antibiotic overuse whilst ensuring good treatment outcomes for their patients;[8] whether intravenous (IV) treatment is indicated; when to switch from IV to oral; and what total duration of treatment is needed. Decisions about whether to initiate IV or oral treatment should be based on severity of illness[9] but 30-50% of patients eligible for oral therapy receive IV antibiotics and then many remain on them for longer than necessary.[10-12] International recommendations for treatment duration in cellulitis are inconsistent and range from 5[1,13] to 10-14 days,[14,15] but in practice durations commonly exceed two weeks.[11,12] A recent review addressing antibiotic treatment of cellulitis in adults identified four randomised controlled trials (RCTs) comparing oral versus IV therapy, none focusing on IV-to-oral switch and five trials addressing treatment duration.[16]

We aimed to systematically review the literature on decisions about initial treatment with IV versus oral therapy, timing of IV-to-oral switch and duration of therapy in

cellulitis, considering both effectiveness and harms of antibiotic treatment. Where randomised trials exist, we conducted meta-analysis, and have also summarised relevant data from non-experimental studies. We considered studies involving both adults and children.

## Methods

### Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (checklist in appendix p1).[17] We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the ISRCTN registry, the U.S National Institute of Health ongoing trials register, the Australian and New Zealand Clinical Trials Registry and the World Health Organization International Clinical Trials Registry from database inception to Dec 11, 2019. Search terms covered the population (cellulitis/erysipelas/skin infection) and intervention (antibiotics/duration/route) (appendix p4). Only articles in the English language were considered. The protocol is available at www.crd.york.ac.uk/PROSPERO, CRD42018100602.

Studies were eligible if they investigated humans (adults or children) treated with oral or IV antibiotics for cellulitis. Those including only patients with pre-septal or orbital cellulitis were excluded. Studies assessing SSTIs in general were excluded, unless data for the cellulitis subpopulation could be separated. Studies that investigated antibiotic prophylaxis or solely topical antibiotic therapy were excluded. Both interventional and observational studies were included but case series and case reports were not. RCTs were restricted to comparisons of shorter versus longer antibiotic courses or oral versus IV antibiotics as initial treatment. Observational studies were required, as a minimum, to report the average duration of antibiotic therapy used and one of the outcome measures below.

### Data extraction and quality assessment

Titles and abstracts were screened by one author (ELAC) with a random 20% screened by another (HJ), calculating inter-observer agreement using Cohen's kappa.[18] All potentially eligible full text articles were independently reviewed by two of four authors (ELAC, HJ, RG, AS). Any disagreement was resolved by consensus, referring to a third author if necessary. Double data extraction was performed independently by the same authors on published reports using standardised, pre-piloted forms (appendix p3). Data were extracted on study methods, population and participant characteristics (setting, demographics, comorbidities, illness severity),

interventions (antibiotic agent, route, duration and co-interventions), individual patient-level outcomes (below), key conclusions drawn by authors, and study funding.

RCTs were assessed for risk of bias using the Cochrane Risk of Bias Tool.[19] Non-randomised studies were assessed using an abridged Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, focusing on items 4-12 to assess methodological quality.[20] Two authors (ELAC, IJO) independently assessed the risk of bias and quality of included studies; disagreements were resolved via consensus. The quality of the evidence for studies included in the meta-analyses was assessed using the Grading of Recommendation, Assessment, Development and Evaluation criteria.[21]

**Outcomes**

Our primary outcome measure was clinical response, defined as improvement or lack of progression of signs and symptoms, assessed as a measure of treatment effect at a timepoint specified by study authors. Additional secondary outcome measures of effectiveness included clinical/therapeutic failure, recurrence, microbiological cure/ bacteriological response, mortality, biochemical response and patient-focused outcomes. We also considered balancing outcomes e.g. length of stay (LOS), adverse events and development of antibiotic resistance.

**Data analysis**

Where there was evidence of substantial clinical heterogeneity, narrative synthesis was performed. Where pooling of results was feasible, meta-analysis was performed using the random-effects model. One author (IJO) entered the data onto RevMan,[22] which was independently cross-checked by a second author (ELAC). Statistical heterogeneity of included studies was assessed using the Chi-square test (threshold $P<0{\cdot}1$) and the $I^2$ statistic. $I^2$ values <25% were considered to represent low heterogeneity, values 25-75% moderate heterogeneity, and values >75% high heterogeneity. Results from meta-analyses are presented as RR, with 95% confidence intervals (95% CI) and two-sided P values (threshold $P<0{\cdot}05$). An assessment of publication bias was not performed due to the small number of studies included in each meta-analysis (<10).

## Results

The initial search yielded 8423 articles. Title and abstract screening identified 604 articles for full-text screening of which 557 were excluded. Inter-observer agreement was moderate at title and abstract screening (Kappa=0·66, 95%CI 0·59-0·73). Among the 47 included articles, one described two RCTs yielding a total of 48 studies (figure 1): 16 RCTs (including one quasi-RCT),[23-37] two non-randomised interventional studies[38,39] and 30 observational studies.[40-68] Eleven RCTs were included in two separate meta-analyses.

Figure 2 summarises the risk of bias across the RCTs. In eight RCTs, the method of sequence generation or allocation concealment was not adequately reported. Nine RCTs were either open-label or failed to report that they were blinded. The overall risk of bias across the RCTs was considered moderate. For non-randomised studies; five were considered high quality, 19 moderate quality and eight low quality. The risk of bias and quality assessment of each individual study are in appendix tables 1-5.

Only eight studies measured clinical outcomes beyond 30 days. In the remainder, outcomes were assessed within 30 days (12/48), within two weeks (12/48), within the first 48-72 hours (4/48); 12 studies did not clearly report the timing of outcome assessment.

### Evidence for selecting oral versus IV antibiotics

Five RCTs compared oral versus IV route of initial treatment for adults with cellulitis (table 1). All studies were conducted in high-income countries. Four of the five studies included patients with cellulitis who were admitted to hospital. All trials included non-necrotising cellulitis, but various descriptions were used to indicate the severity of disease. One study specifically stated included patients must have a severity of cellulitis that warranted treatment with IV antibiotics,[23] another study stated that included patients had to have 'severe local findings'.[27] All studies required patients to have a fever of ≥38°C (with one trial also requiring tachycardia of >90 beats/min),[23] but all trials excluded patients with features of severe sepsis. Two studies compared antibiotics of the same class in both oral and IV groups. The remainder compared oral agents likely to have good efficacy in cellulitis (clindamycin, roxithromycin and pristinamycin) with IV penicillin.

In terms of treatment effectiveness, three of the five RCTs assessed clinical response rates and were included in the meta-analysis (N=397) (figure 3). There was no evidence of difference in clinical response rates between oral versus IV groups (RR(oral:IV)=1·12, 95%CI 0·98-1·27, $I^2$=32%). The two remaining studies were not included in the meta-analysis since they reported different outcome measures. Aboltins found no evidence of a difference in mean days until no advancement of the area of cellulitis (mean difference -0·49, 95%CI -1·02 to +0·04) and in treatment failure rates between oral and IV groups (4% versus 22%, P=0.10).[23] Jorup-Rönström assessed efficacy by the time to body temperature reduction to ≤37·5°C and found no evidence of difference between groups.[27] Two RCTs reported similar rates of relapse or recurrence of 16% versus 14% at 4 weeks[26] and 11% versus 16% at 6 months[27] for oral versus IV treatment respectively. The single RCT that reported patients' pain scores and satisfaction with treatment found no evidence of differences between groups.[23]

In terms of treatment-associated harms, all studies reported data on adverse events with only one finding evidence of differences between treatment groups; namely a higher rate of adverse events in the oral (pristinamycin) versus IV (penicillin) group, 28% versus 17% (P=0·03).[25] However, there was no evidence of difference in the proportions of adverse events necessitating discontinuation of study medication between the two groups (11% versus 17%, respectively, P=0·17). Two studies reported *C. difficile*-associated diarrhoea as an outcome, but no cases occurred.[26,27] Three studies compared average hospital LOS, which ranged between 3 and 11 days, and found no evidence of difference between randomised groups.[25-27] No trials reported on the development of antibiotic resistance.

**Evidence for timing of intravenous-to-oral switch**

A single RCT compared efficacy of early (24h) versus later (≥72h) switch to oral antibiotics in uncomplicated cellulitis requiring IV antibiotics (table 2).[28] Resolution of cellulitis was achieved in 79% and 84% of patients in the of shorter (24h and longer (>72 hour) treatment groups respectively but the study sample size was too small to demonstrate non-inferiority. Decreases in patient-reported pain scores were similar between groups. The only treatment-associated harm reported was from a patient in the shorter group who experienced headaches and non-*C. difficile* diarrhoea.

We did not identify any non-randomised comparative studies of different IV to oral switch timing. However, six observational studies reported average durations of IV antibiotics for both adult and paediatric patients with complicated cellulitis;[40-45] these were consistently around 1-3 days prior to oral-switch but often ranged up to 14 days (table 2, appendix table 6). None of the studies reported relationships between timing of IV-to-oral switch and adverse events, frequency of *C. difficile* infection or antibiotic resistance.

**Evidence for overall duration of therapy**

Data on clinical outcomes among patients with cellulitis randomised to either shorter versus longer antibiotic durations were available for 1508 patients in 10 RCTs (table 3). Seven studies recruited only adults, only one outside Europe and North America. Most trials reported outcomes for cellulitis as a subset of patients with SSTIs, two of these included patients with complicated SSTIs[32,33] but most of the other studies lacked detail regarding the severity of cellulitis. As part of the inclusion criteria, the minimum total lesion surface area was 75cm$^2$ accompanied by at least one regional or systemic sign of infection (10-30% of patients had fever at baseline). Four used antibiotics of the same class in both groups (macrolides and oxazolidinones) and four compared different classes of antibiotics in each group. In each the choice of short-course agent was based on anticipated longer duration of action. Five used azithromycin and three used tedizolid. The difference between shorter and longer treatment groups ranged from two to seven days.

Two trials specifically studied patients with cellulitis and used the same antibiotic agent (flucloxacillin) in both shorter and longer duration groups. One included mostly outpatients with uncomplicated cellulitis who received oral therapy, the mean age was 40 years, 16% had diabetes mellitus, 10% had a fever and the average cellulitis severity score was 6.5.[31] The other trial included hospitalised patients requiring IV therapy who were on average 20 years older (mean age 60 years), 24% had diabetes, 47% had fever and the average severity score was 8.5.[35]

In terms of treatment effectiveness, the eight RCTs that studied mainly adults were included in the meta-analysis (N=1458, figure 4). Clinical response rates varied from 49-100% between trials and there was no evidence of difference in response rates between shorter versus the longer antibiotic groups (RR(shorter:longer)=0·99, 95%CI

0·96-1·03, $I^2$ = 0%). Three RCTs examined bacteriological response to antibiotic therapy, defined as the disappearance of a pathogen that was identified from culture at baseline after treatment with antibiotic therapy.[29,36] One found higher responses in the shorter (macrolide) versus the longer (penicillin) group (33% versus 15%, P=0·04).[29] Another RCT comparing two macrolides found a trend towards a higher response rate in the shorter (89%) versus the longer (78%) group.[29] In the third RCT, 100% of patients achieved bacteriological response in both groups.[36]

The two trials to describe patient-reported outcomes found no evidence of differences in pain and swelling scores between the shorter and longer groups.[31,35]This was the same for the physician reported clinical scores.

The only RCT to measure clinical outcomes beyond 30 days was the Duration of ANtibiotic Therapy for CEllulitis “DANCE” trial which randomised 151 hospitalised patients to receive 6 versus 12 days of flucloxacillin and followed patients to day 90.[35] Although there was no evidence of differences between groups at day 28, more recurrences occurred in the shorter treatment group compared to the longer group between day 28 and day 90 (24% versus 6%, P=0·045).

Four non-randomised comparative studies reported effectiveness outcomes for patients with cellulitis receiving shorter versus longer durations of antibiotic therapy (table 4, appendix table 7). Two were non-randomised interventional studies and achieved modest reductions in antibiotic duration after implementing new management guidelines/ protocols for cellulitis.[38,39] Three studies found no evidence of a reduction in effectiveness with shorter treatment durations.[38,39,46] Conversely, one study that focused on children reported a significantly higher odds ratio (OR) of treatment failure for patients treated with short-course IV therapy versus inpatient IV therapy (OR=7·2, 95%CI 1·6-33·1), and outpatient oral antibiotics (OR=3·2, 95%CI 1·3-8·3).[47] The duration of short-course IV therapy was not clearly defined but 73% of patients in this group received ≤2 doses of IV antibiotics.

We identified a further twenty-two studies which reported the average length of antibiotic treatment for patients with cellulitis and at least one relevant outcome measure (appendix tables 8 and 9). These studies included populations that were generally older, with a higher illness severity and more comorbidities than those recruited to the RCTs. For instance, studies of inpatients had a mean age range from

48 to 70 years and 20-35% had diabetes. Eleven studies included inpatients and reported an average length of antibiotic treatment of 5-17 days.[40,46,48,49,52-54,57,58] Clinical response rates were all above 85%, failure rates ranged from 5-12% and recurrence rates from 0-17%. Eleven studies, including those treated as outpatients/OPAT, reported an average length of IV therapy of 2-7 days and an average overall treatment duration of 6-10 days.[59-69] Clinical response rates ranged from 85-97%, failure rates from 5-22% and recurrence rates from 0-6%.

Across these studies, patient factors emerged as the key determinants of clinical response, while no evidence of associations between duration of therapy and outcome was reported. In studies comparing patients with better versus worse outcomes, groups with poorer outcomes had higher proportions of patients with prior cellulitis, sepsis at presentation and comorbidities (including diabetes, immunosuppression, obesity and venous insufficiency).[40,48,50,55,60,62]

With regards to treatment-associated harms, data on adverse events were not reported separately for cellulitis patients within SSTI trials, but overall, three trials found a higher incidence of gastrointestinal side-effects among patients receiving longer treatment (linezolid and erythromycin) versus shorter treatment (tedizolid and azithromycin).[29,32,33] One trial found no difference in gastrointestinal side effects between groups.[34] Only two of these reported that no cases of diarrhoea were associated with *C. difficile*.[33,34] One RCT found a higher proportion of side-effects in the shorter (azithromycin) versus the longer (cloxacillin) group, but severe events requiring study withdrawal were more frequent in the longer group.[29] No trials reported on the development of antibiotic resistance.

**Evidence from paediatric studies**

There were 7 studies that focused on paediatric populations.[36,37,44,45,47,58,68] Overall, the paediatric studies included a lower proportion of patients with lower limb cellulitis (~40%) compared to adult studies. Only three of the studies stated the severity of infection, which was reported as uncomplicated moderate/severe cellulitis.[44,45,68] None of the paediatric studies compared oral to IV antibiotic therapy.

Two of the paediatric observational studies reported average IV-to-oral switch durations between 1.8-2.5 days with a maximum duration of 2.6 days,[44,45] compared to adult studies where the maximal average duration was 15 days. The average total

duration of antibiotic therapy reported in paediatric studies was 8-11 days with treatment failure rates of 0-5%, compared to an average duration of 5-17 days in adults with failure rates from 5-22%.

Two RCTs compared shorter versus longer duration of antibiotic therapy in children.[36,37] The trials were conducted in low- and middle-income countries as opposed to adult studies where the majority were conducted in high-income countries. They both compared different classes of antibiotics in each group. Similar to the adult studies, the choice of short-course agent was based on anticipated longer duration of action. However, the short-course therapy duration was shorter at 3 days versus 5-6 days in adult studies. The clinical response rates of 81-100% were comparable to response rates seen in adult populations.

## Discussion

We have undertaken a comprehensive systematic review of all available published evidence supporting decisions about the initial route of administration and duration of antibiotic therapy for adults and children with cellulitis. Our findings expand on those of a recent review which concluded there is a lack of evidence to support use of IV over oral antibiotics and treatment for longer than 5 days in cellulitis.[16] The findings of a recent trial by Cranendonk *et al.* highlight that more patients can achieve good long-term outcomes with more prolonged therapy.[35] We have also considered data from non-randomised studies and paediatric studies but crucially we have considered potential harms of antibiotic therapy, highly relevant to clinicians aiming to optimise antibiotic treatment in cellulitis. We have identified 48 relevant studies, many of low or very low quality, whose interpretation is further hampered by the heterogeneity of outcome measures, highlighted previously as a major limitation in this area.[70] Further general limitations of the evidence are vagueness of the case definition of cellulitis, a potential misdiagnosis rate of ~30%,[71] and the fact that participants had often received antibiotics prior to enrolment, minimising differences in treatment effectiveness between groups.[72,73]

Currently, the available evidence suggests that for adults with cellulitis clinical response rates are similar for initial oral and IV antibiotic treatment. While this is the consistent finding of five trials, all are of low or very low quality. None provide data relevant to patients with complicated disease or markers of sepsis. Another key limitation is that studies often compare agents of different classes. Only two trials compare antibiotic route using drugs of the same class and two trials compare oral to IV agents with different anti-staphylococcal activity. Therefore, their findings can only be applied in clinical practice with great caution and may be affected in settings with differing epidemiology of *S. pyogenes* and *S. aureus*. Nevertheless, overall, these trials indicate that if initial oral therapy is less effective than initial IV the difference is likely to be <2%. However, they do not provide evidence that oral treatment is superior to IV treatment through any balancing treatment-related harm outcomes such as side-effects, *C. difficile* infection or antibiotic resistance.

The question of timing of IV-to-oral switch has been addressed in only a single trial which was too small to demonstrate non-inferiority and again included only a subset of patients with uncomplicated cellulitis.[28]

Although we identified ten randomised trials providing evidence on duration of therapy, a major limitation of this evidence base is that eight of the trials use short-course treatment with agents anticipated to have longer durations of action compared to the longer-course agent used. For instance, azithromycin is used as the short-course agent in half of the trials on duration but is known to have a longer serum half-life than the other antibiotics. The comparisons are therefore severely flawed and their findings of limited relevance to clinical decision making. Current guidelines recommending 5 days treatment of cellulitis[1,13] are based on a single trial that used levofloxacin, which is not a recommended first-line treatment.[31] Overall these trials indicate that for early clinical cure, if short-duration treatment of cellulitis is associated with any loss of effectiveness, this is likely to be small (<4%). The one study which found shorter treatment to be associated with reduced early clinical cure reported 7.2% failure for the cohort overall.[47] This illustrates an important point. Across all the studies reviewed, the overwhelming majority of patients achieved clinical success irrespective of the initial route or duration of therapy. Patients with comorbidities, such as diabetes or who have experienced previous cellulitis, may be at increased risk of treatment failure but the value of IV or prolonged treatment in these patients remains unproven.

There is a particular lack of data around outcomes beyond 30 days to allow an assessment of the impact on recurrence. A particularly striking finding of the DANCE trial was increased recurrence up to 90 days among patients receiving shorter initial therapy.[35] These results suggest that recurrence may be due in part to recrudescence of infection rather than reinfection and that long-term recurrence may be tractable to optimised initial therapy.[35]

The paediatric studies we have identified illustrate important differences compared with adult disease. In particular that fewer patients have lower limb disease and that treatment durations and recurrence rates are lower. That two paediatric trials were conducted in low- and middle-income countries reflects the greater incidence of paediatric streptococcal skin infection in hotter climates and overcrowded communities. Nevertheless, findings of the paediatric studies that short duration oral therapy is highly effective in cellulitis are entirely consistent with those of studies in adults.

Our study has major strengths. We conducted an extensive literature search across all major relevant databases including observational studies. This allowed us to

include evidence which informs clinical practice but is not captured in existing overviews of this literature, and to include patients who would not ordinarily have been enrolled into trials because of significant comorbidities and illness severity. By addressing both effectiveness and treatment-related harms our analysis highlights a major gap in the evidence in this field. Unless antibiotic-reduction strategies are superior in ways which are meaningful to individual patients (e.g. fewer adverse effects, less antibiotic resistant infections) even marginal concern about loss of effectiveness will limit translation of findings into practice.[74]

Our study has several limitations. We have only searched for articles in English and did not search unpublished/grey literature. It is possible but unlikely that we have missed evidence which would have changed our conclusions. We have been unable to assess the impact of publication bias due to the small number of studies included in each meta-analysis (<10). The small number of studies available may make the random-effects meta-analysis approach we have used unreliable, but this remains the most appropriate method.[75] There is a risk that some relevant studies could have been incorrectly excluded as only 20% of identified papers underwent dual title and abstract screening. However, there was substantial agreement between reviewers for dual screened studies (1465/1550, 95%) and it is unlikely we have missed evidence which would have changed our conclusions. We chose to use an abridged STROBE statement to assess the quality of observational studies as there is no consensus on the optimal tool to use. While STROBE was not designed for this purpose, it provides a useful recommendation of the essential information required to assess the conduct of observational studies.[76]

In summary although the efficacy of oral antibiotics in cellulitis is long established,[77,78] there is a striking lack of evidence that initial IV therapy or treatment beyond 5-7 days are more effective than initial oral or short course treatment. However, this does not preclude initial IV treatment and prolonged therapy being more effective in some scenarios. This is particularly the case for commonly used agents such as beta-lactams, since most studies have used less widely used agents, and for patients with complicated disease, who have been excluded from most studies. Indeed, the DANCE trial highlights that although most patients achieve lasting cure with short durations of therapy, a small number of patients do require longer treatment.[35] The challenge for future research is personalising treatment decisions about duration of therapy. The

evidence is further limited by inappropriate comparisons, heterogenous outcomes, and lack of long-term follow up. In particular, the lack of data around the harms of IV and prolonged antibiotic treatment hampers clinical decision making. It is likely this contributes to clinicians choosing to exceed guideline recommendations. Observational data suggest that prior cellulitis, illness severity and the presence of certain comorbidities are likely to be important in influencing clinical outcomes. Future research should focus on developing patient-tailored recommendations for antibiotic treatment in cellulitis and establishing the individual patient benefits of reduced antibiotic exposure.

**Declarations of interest:** None

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**Contributors**

ELAC, IJO, KF and MJL designed the study. EC, RG, HJ, IJO and AS were responsible for collecting and analysing the data, under the guidance of KF, TEAP, SAW and MJL. ELAC and MJL were responsible for drafting the manuscript, with support and input from the other co-authors. All authors critically reviewed and approved the final manuscript.

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**Figure 1. Study selection**

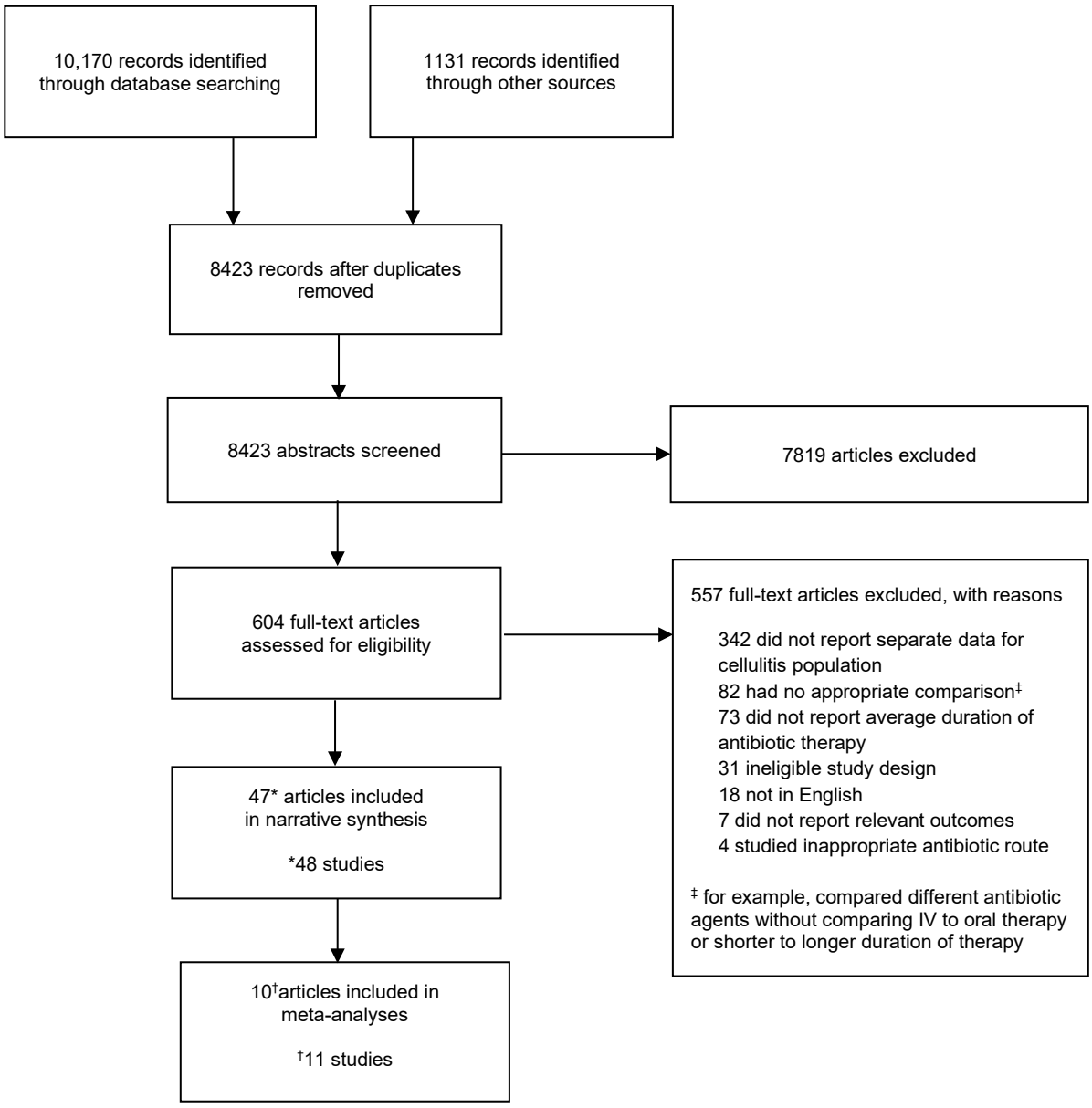


**Figure 2. Summary of risk of bias across RCTs.**

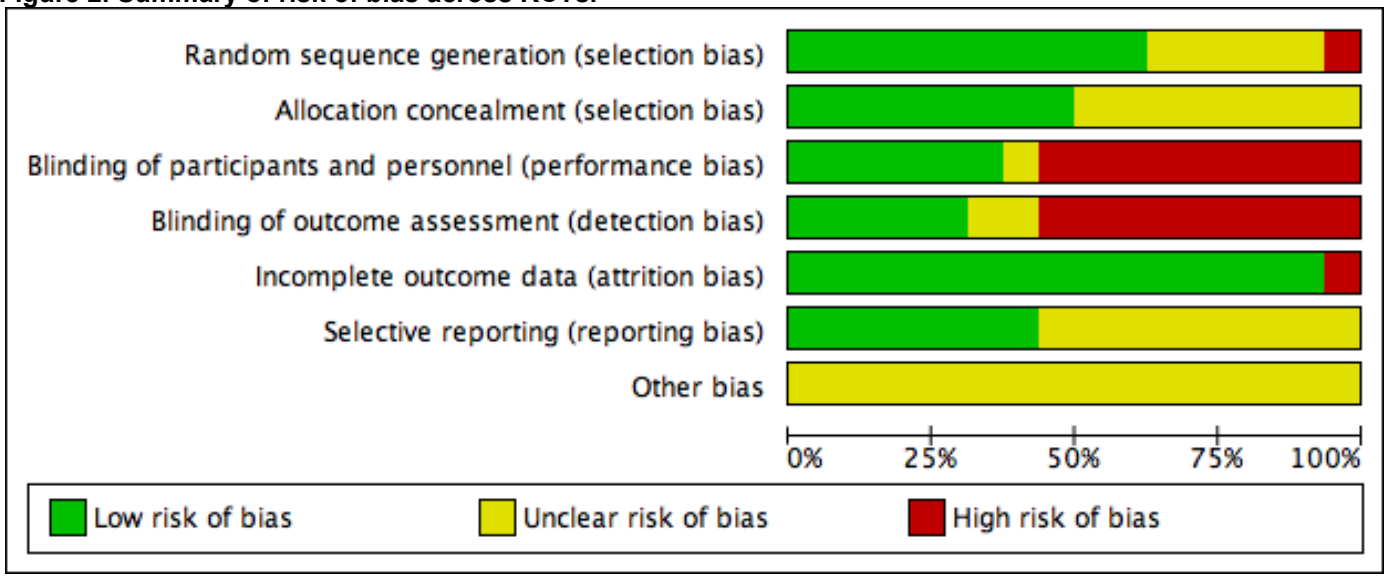


**Table 1. Characteristics of studies comparing oral versus IV with step down to oral treatment**

| Author & year | Study design | Setting | Population | Severity & site | Oral antibiotic arm | IV antibiotic arm | Primary outcome | Findings | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Oral arm | IV arm |
| Aboltins 2015 | RCT | Single tertiary teaching hospital, Australia<br><br>Inpatients & OPAT | 47 adults with cellulitis | Uncomplicated (not mild)<br><br>- 87% lower limb<br>- 13% upper limb | Oral cephalexin*<br><br>10 days | IV-to-oral cefazolin to cephalexin *<br><br>10 days | Mean days until no advancement of the area of cellulitis | 1.29 (SD 0.62) days (n=24) | 1.78 (SD 1.13) days (n=23) |
| | | | | | | | | Mean difference -0.49 (95% CI, -1.02 to +0.04) | |
| Bernard 1992 | RCT | 6 dermatological departments, France<br><br>Inpatients | 69 adults with erysipelas | Non-gangrenous erysipelas<br><br>- Site NR | Oral roxithromycin<br><br>Average duration (range)<br>13 days (2 to 29) | IV-to-oral penicillin<br><br>Average IV duration (range) 6 days (2 to 17)<br><br>Average oral duration<br>7 days (0 to 21) | Efficacy rate<br><br>Timing NR (some point within 30 days) | 26/31 (84%) | 29/38 (76%) (P=0.43) |
| Bernard 2002 | RCT | 22 dermatology centres, France<br><br>Inpatients | 289 adults with erysipelas | Superficial, non-necrotising<br><br>- 94% lower limb | Oral pristinamycin<br><br>14 days | IV-to-oral benzylpenicillin to phenoxymethylpenicillin<br><br>14 days | Clinical cure rate Day 25 to 45 | 90/138 (65%)† | 79/150 (53%)† |
| Thomas 2014 | RCT | Single hospital, New Zealand<br><br>Inpatients | 40 adults with cellulitis | Severity NR<br><br>- 78% lower limb<br>- 10% upper limb | Oral clindamycin<br><br>Median no. of doses of IV 'treatment'‡ (range)<br>11 (0 to 15) | IV-to-oral flucloxacillin<br><br>Median no. of doses of IV treatment (range)<br>8 (0 to 21), (P=0.23) | Clinical efficacy<br><br>Daily review at 'completion of treatment' | 21/21 (100%)<br>Cured 18/21 (86%)<br>Improved 3/21 (14%) | 18/19 (95%)<br>Cured 7/19 (37%)<br>Improved 11/19 (58%) |
| | | | | | Median oral duration (range) 9 days (0 to 21) | Median oral duration<br>8 (0 to 18), (P=0.81) | | | |
| Jorup-Rönström 1984 | Quasi-RCT | Single hospital, Sweden<br><br>Inpatients | 73 adults with erysipelas | 'severe local findings'<br><br>- Site NR | Oral phenoxymethylpenicillin ± flucloxacillin<br><br>For at least 10 days | IV-to-oral Benzylpenicillin ± cloxacillin<br><br>For at least 10 days | Time to temperature fall to ≤37.5°C (median fever duration) | 2 days | 3 days |

NR = Not reported. Primary outcome defined by study authors, where not defined the first outcome measure of clinical response to be reported was selected. *Clindamycin if penicillin allergic. †In the intention-to-treat (ITT) analysis. ‡Placebo IV treatment given in the oral clindamycin arm.

**Figure 3. Forest plot of comparison: Oral versus IV antibiotics, outcome clinical response**

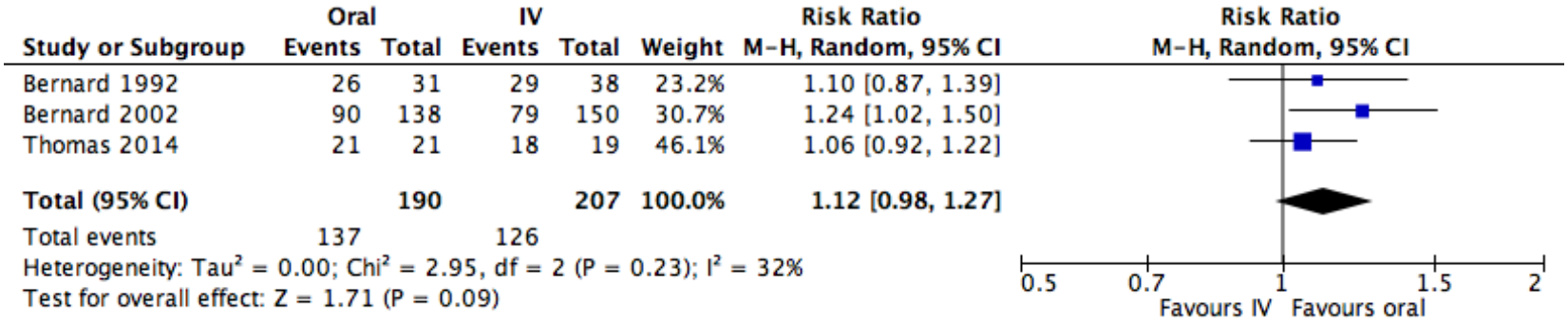


**Table 2. Summary of studies reporting on timing of IV-to-oral switch**

| Study | Design | Setting | Population | Relevant Outcome | Finding |
|---|---|---|---|---|---|
| Clarke 2019 Switch Trial | RCT comparing early (24h) vs later (≥72h) oral switch | 10 sites, Australia & New Zealand<br><br>Inpatients & OPAT | 80 adults with cellulitis requiring IV therapy (39 in shorter, 41 in longer group) | Resolution of cellulitis at the end of therapy (10 days after randomisation) | Cellulitis resolution achieved in 31 (79%) in shorter group and 35 (85%) in longer group (difference of -5.8% (95%CI, -22.5% to 10.7%) |
| Bogner 2013 | Prospective, multicentre cohort study describing outcomes among patients treated with moxifloxacin | >600 sites, Europe, the Middle East and Asia-Pacific region<br><br>Inpatients | 5444 adults and children with complicated SSTIs, 820 with cellulitis | Effectiveness (improvement and resolution of cellulitis) at follow-up | Mean IV-to-oral switch time of 3.4 days associated with 'very good' (68%), 'good' (26%) and 'sufficient' (3%) effectiveness ratings |
| Lipsky 2012 | Prospective, multicentre cohort study describing patient characteristics and treatment outcomes in cellulitis | 56 hospitals, USA<br><br>Inpatients | 1033 adults with complicated SSTIs, 278 with cellulitis | Clinical response at the end of IV treatment | Mean IV duration of 2 to 3 days associated with cure in 11.9% and improvement in 78.4% |
| Morpeth 2005 | Prospective cohort study assessing determinants of LOS, length of IV antibiotic therapy and outcomes in cellulitis | Single hospital, New Zealand<br><br>Inpatients | 51 adults with cellulitis | Recurrence of cellulitis within six weeks of discharge | Median IV duration of 3 days, 12% were readmitted to hospital for recurrence |
| McNamara 2007 | Retrospective cohort to examine risk factors and develop a predictive model for recurrent lower limb cellulitis | Multicentre, USA<br><br>Inpatients and outpatients | 209 adults with cellulitis | Recurrence of cellulitis within 2 years | Mean IV duration of 1.1 days, 35 (16.7%) experienced a recurrence within 2 years |
| Gouin 2008 | Prospective cohort study assessing outcomes of children with cellulitis managed at a day treatment centre | Single hospital, Canada<br><br>OPAT/day treatment centre | 92 children with cellulitis | Relapse of cellulitis within 14 days | Mean IV duration of 2.5 days at which point 19 children received further 4.5 days IV therapy and 73 were discharged on oral therapy. 1/73 relapsed |
| Ibrahim 2017 | Prospective cohort study describing outcomes of children with cellulitis treated on an admission avoidance pathway | Single hospital, Australia<br><br>OPAT & inpatients | 115 children with cellulitis (47 OPAT, 68 inpatients) | Treatment failure within 48 hours | Median duration of IV therapy similar between OPAT and inpatient groups (1.9 vs. 1.8 days, P=0.31) as was treatment failure (4% vs. 14%, P=0.10) |

**Table 3. Characteristics of RCTs comparing shorter versus longer duration antibiotics**

| Author & year | Setting | Population | Severity & site | Shorter arm | Longer arm | Primary outcome | Findings | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Shorter arm | Longer arm |
| Daniel 1991 part 1 | 29 centres, 6 European countries<br><br>In-/outpatient, unclear | 122 adults with cellulitis (308 SSTIs) | Severity & site NR | 5 days of oral azithromycin | 7 days of oral erythromycin | Clinical cure 7-10 days after treatment completion | 52/72 (72%) | 37/50 (74%) |
| Daniel 1991 part 2 | 15 centres, 4 European countries<br><br>In-/outpatient, unclear | 62 adults with cellulitis (323 SSTIs) | Severity & site NR | 5 days of oral azithromycin | 7 days of oral cloxacillin | Clinical response 4-9 days post treatment completion | 41/41 (100%)<br>Cured 27/41 (66%)<br>Improved 14/41 (34%) | 21/21 (100%)<br>Cured 11/21 (52%)<br>Improved 10/ 21 (48%) |
| Kiani 1991 | 22 centres, USA<br><br>Inpatients & outpatients | 47 adults with cellulitis (366 SSTIs) | Severity & site NR | 5 days oral azithromycin | 10 days of oral cephalexin | Clinical response Day 11 (10-13) | 23/24 (96%)<br>Cured 12/24 (50.0%)<br>Improved 11/24 (45.8%) | 22/23 (96%)<br>Cured 14/23 (60.9%)<br>Improved 8/23 (34.8%) |
| Hepburn 2004 | Single tertiary care military hospital, USA<br><br>Inpatients & outpatients | 87 adults with cellulitis | Uncomplicated<br><br>Face, trunk or extremity | 5 days of levofloxacin* | 10 days of levofloxacin* | Resolution of infection Day 14 (without symptom recurrence by day 28) | 43/44 (98%) | 42/43 (98%) |
| Prokocimer 2013 *(ESTABLISH 1)* | 81 centres, North America, Latin America and Europe<br><br>In-/outpatient, unclear | 275 adults with cellulitis (667 SSTIs) | Complicated<br><br>Site NR | 6 days oral tedizolid | 10 days oral linezolid | Early clinical response 48-72hrs after the start of treatment | 101/135 (74.8%) | 100/139 (71.9%) |
| Moran 2014 *(ESTABLISH 2)* | 58 centres, various countries†<br><br>In-/outpatient, unclear | 334 adults & children (age range 15-89) with cellulitis (666 SSTIs) | Complicated<br><br>Site NR | 6 days IV-to-oral tedizolid | 10 days IV-to-oral linezolid | Early clinical response 48-72hrs after the start of treatment | 134/166 (81%) | 135/168 (80%) |
| | | | | | | | Treatment difference 0.3% (95% CI, -8.2 to 8.9%) | |
| Lv 2019 | Multicentre, USA, China, Taiwan and the Philippines<br><br>In-/outpatient, unclear | 383 adults with cellulitis (598 SSTIs) | Complicated<br>- 59% lower limb<br>- 12% upper limb | 6 days IV-to-oral tedizolid | 10 days IV-to-oral oral linezolid | Early clinical response 48-72hrs after the start of treatment | 135/192 (70.3%) | 150/191 (78.0%) |
| Cranendonk 2019 | 11 centres, the Netherlands<br><br>Inpatients | 149 adults with cellulitis | 'High severity'<br>- 84% lower limb<br>- 9% upper limb | 6 days IV-to-oral flucloxacillin | 12 days IV-to-oral flucloxacillin | Cure by day 14 without relapse by day 28 | 36/73 (49%) | 38/76 (50%) |
| **Paediatric studies** | | | | | | | | |
| Rodriguez-Solares 1993 | 5 centres, Costa Rica, Guatemala, Panama, Venezuela Outpatients | 16 children with cellulitis (118 with SSTIs) | Severity & site NR | Oral azithromycin for 3 days | Oral dicloxacillin or flucloxacillin for 7 days | Clinical response 7-10 days after the start of treatment | 5/5 (100%)<br>Cured 4/5 (80%)<br>Improved 1/5 (20%) | 11/11/ (100%)<br>Cured 11/11 (100%)<br>Improved 0/11 (0%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Montero 1996 | 'Multicentre', Colombia, Guatemala, Panama, South Africa Inpatients | 34 children with cellulitis (200 SSTIs) | Severity & site NR | Oral azithromycin for 3 days | Oral cefaclor for 10 days | Clinical efficacy (cured/improved) 10-14 days after the start of treatment | 13/16 (81%) | 16/18 (89%) |

NR = Not reported. Primary outcome defined by study authors, where not defined the first outcome measure of clinical response to be reported was selected. *Mostly oral (12 IV-to-oral). †Argentina, Australia, Germany, New Zealand, Poland, Russia, South Africa, Spain, and the USA.

**Figure 4. Forest plot of comparison: Shorter versus longer duration antibiotics, outcome clinical response**

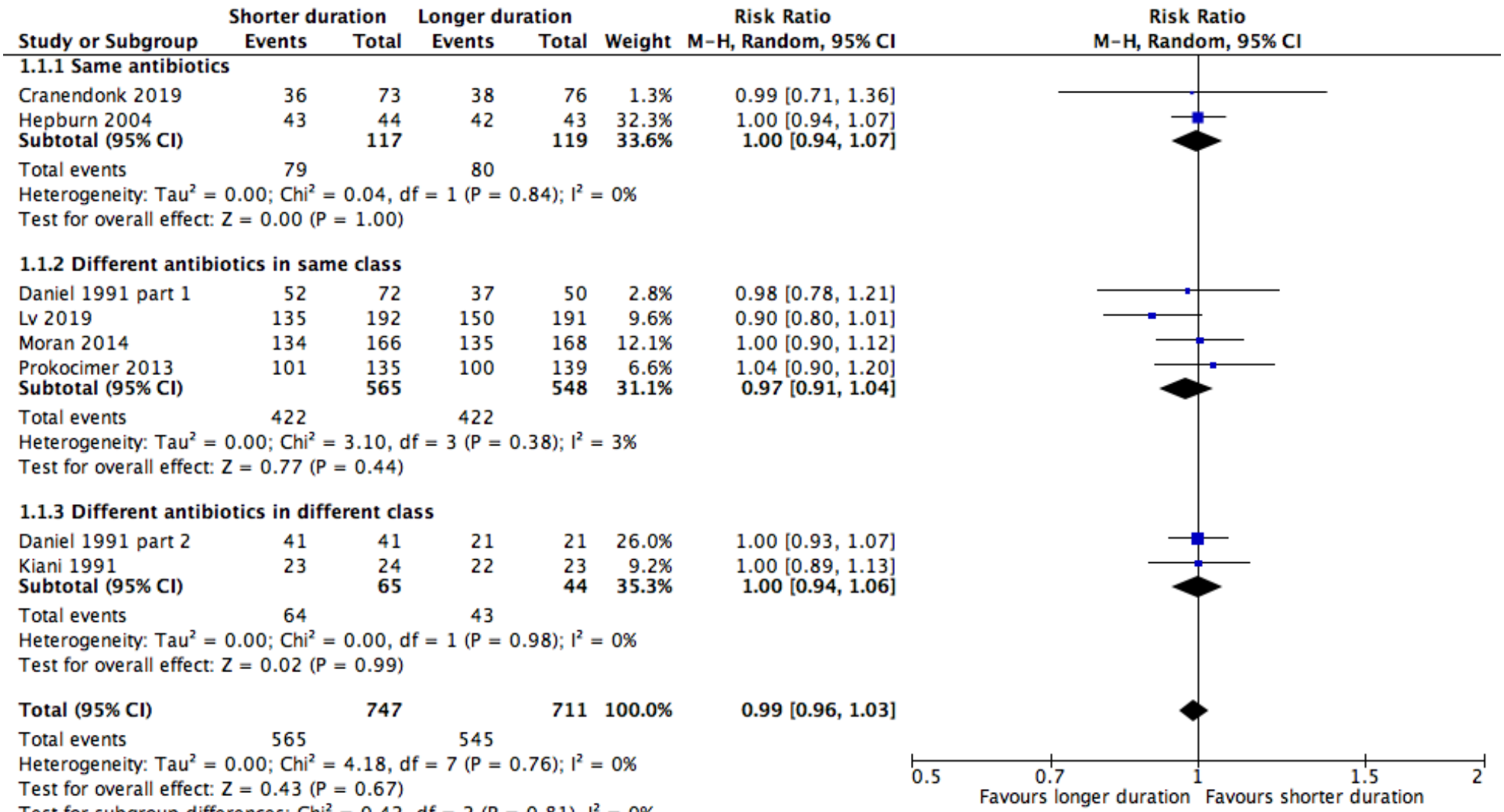


**Table 4. Summary of non-randomised studies reporting on shorter versus longer duration antibiotics**

| Study | Design | Setting | Population | Relevant Outcome | Finding |
|---|---|---|---|---|---|
| Jenkins 2011 | Retrospective pre- and post-intervention study evaluating a guideline for the inpatient management of cellulitis | Single hospital, USA<br><br>Inpatients | 148 adults with cellulitis (66 pre-, 82 post-intervention) | Composite endpoint of clinical failure within 30 days of discharge | From pre-to post-intervention, median antibiotic duration decreased from 13 to 10 days (P<0.001) and clinical failure rates remained similar 12.1% vs. 9.8% (P=0.65), respectively |
| Seaton 2005 | Pre- and post-intervention study evaluating a new protocol for specialist nurse management of cellulitis through an OPAT service | Single centre, Glasgow<br><br>OPAT | 342 adults & children with cellulitis | Clinical response (cure/improved) at 'completion of treatment' | From pre-to post-intervention, median antibiotic duration decreased from 5 to 4 days (P=0.01) and clinical response rates remained similar 99% vs. 97%, respectively |
| Aly 1996 | Retrospective observational study examining the management of cellulitis in a teaching hospital | Tertiary teaching hospital, Australia<br><br>Inpatients | 118 adults with cellulitis | Clinical response (not clearly defined) within 5 days | Most patients (93%) had a clinical response within 5 days. However, 40% of the cohort continued IV therapy for >5 days and in 10% for >10 days, with no evidence of difference in outcomes |
| Kam 2010 | Retrospective observational study comparing emergency department short-course IV therapy vs. inpatient IV therapy or outpatient oral antibiotics | Single hospital, Canada<br><br>Inpatients and outpatients | 321 children with cellulitis | Treatment failure within 7 days of index visit | The odds of treatment failure were higher for short-course IV therapy compared to inpatient IV therapy (7.2, 95% CI 1.6 to 33.1) and outpatient oral antibiotics (3.2, 95% CI 1.3 to 8.3) |