Review article

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CPD

Clinical response to antibiotic regimens in lower limb cellulitis: a systematic review

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Summary

There is variation in the treatment of lower limb cellulitis (LLC) with no agreement on the most effective antibiotic regimen. Many patients with cellulitis fail to respond to first-line antibiotics. This can negatively affect patient care and result in unnecessary hospital admissions. The aim of this systematic review was to determine the clinical response and safety of antibiotic regimens for the management of LLC. A systematic review for randomized controlled trials (RCTs) was conducted using OVID MEDLINE, Ovid Embase and Cochrane Central Register of Controlled Trials in January 2019. Outcomes of interest included the clinical response to antibiotic regimens (type, dose, route, duration) and the safety of antibiotics in LLC. Trial quality was identified using the Cochrane Risk of Bias tool. Four RCTs were included. All included studies showed no significant differences between the clinical response to different antibiotic type, administration route, treatment duration or dose. LLC may be overtreated and shorter courses of oral antibiotics, possibly with lower doses, may be more suitable. There is a lack of published data on the clinical response and safety of antibiotics in LLC. Three studies were high risk for bias overall. Further high-quality studies may help determine whether less intensive antibiotic regimens can effectively treat LLC.

Introduction

During 2017, 88 664 National Health Service (NHS) patients were admitted to hospitals in the UK with cellulitis, receiving inpatient treatment costing £226m.[1,2] Without effective treatment, cellulitis may cause sepsis and recurrent disease.[3] Given the prevalence and consequences of cellulitis, it is essential to effectively manage this condition.

The antibiotic choice to treat cellulitis is influenced by hospital guidelines, causative bacteria and clinical experience.[4,5] One review identified 25 different antibiotic regimens across 5 emergency departments.[6] A study of over 100 hospitals showed that 16.6% of patients with acute cellulitis experienced initial antibiotic failure.[7]

A previous review highlighted a lack of high-quality studies and was unable to define best treatment for cellulitis.[4] However, it was conducted 9 years ago and did not focus on the lower limb, which is affected by cellulitis in 66% of cases.[8] Lower limb cellulitis (LLC) may behave differently from cellulitis at other sites, owing to differences in circulation and flora.

The 2017 Cellulitis Priority Setting Partnership (PSP), emphasized concern from patients and clinicians for more conclusive treatment guidelines.[9] This review aimed to better define how best to treat LLC.

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Methods

Reporting

This review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The protocol was registered with PROSPERO in January 2019 (CRD42019116416).

Outcome

The primary outcome was the clinical response to the antibiotic regimen (type, dose, route, duration). Clinical response was operationalized using validated outcome measures,[10,11] namely, symptom response, laboratory markers, therapeutic failure and quality of life. One of the authors (PS) is a patient expert, and ensured the review was patient-focused. The secondary outcome was the frequency of adverse events.

Study types

Studies included randomized conrolled trials (RCTs) of patients with LLC, in which the clinical response to antibiotics was evaluated. No restrictions on study date or patient demographics were applied. The exclusion criteria included: manuscript not in English; use of prophylactic antibiotics; and presence of eosinophilic cellulitis. Full eligibility and exclusion criteria are given in Table S1 online.

Search strategy

The search (Table S2) was developed with an information specialist (DG) and cellulitis expert (NJL). Ovid MEDLINE, Ovid Embase and the Cochrane Central Register were searched on 5 January 2019 using key terms (Table 1). Grey literature was identified using National Institute for Health and Care Excellence evidence and Google Scholar. The World Health Organization (WHO) International Clinical Trials Registry Platform was screened for unpublished studies. Deduplication was performed using EndNote X9 (https://endnote.com). The reference lists of included studies were scanned for eligible studies.

Table 1 PICOS framework for search strategy.

Parameter	Key terms
Population	Patients with lower limb cellulitis or lower limb erysipelas
Intervention	Antibiotics
Comparison	Another treatment for cellulitis, placebo, nothing
Outcome	Improved clinical outcomes such as symptom response, changes in laboratory markers, therapeutic failure or quality of life
Study design	Randomized controlled trial

Analysis

Eligibility screening, data extraction and quality assessment was performed independently by KM and SS. Disagreements were resolved through a third reviewer (NJL). Data was entered into Revman 5.3 (Cochrane Library). Studies were described in narrative synthesis. Methodological quality was assessed using a modified version of the Cochrane risk of bias (RoB) tool.[12] For each domain a study was assessed as 'low risk' if all signalling questions were 'yes', 'high risk' if at least one signalling question was 'no' or 'unclear' if not reported. If a study was 'high risk' in any domain, it was considered 'high risk of bias' overall. If a study was 'unclear risk' in multiple domains, it was considered to have 'some concerns of bias' overall.[12]

Results

The PRISMA diagram shows the search result (Fig. 1). Only four studies were eligible (Table 2).[13–16] In total, 529 patients were included across 13 countries. Two studies were based in hospitals.[13,15] No studies reported who had made the diagnosis or the duration of LLC. Two studies defined LLC diagnosis.[15,16] Two studies specified LLC severity and excluded patients with mild disease.[14,16] No studies compared the same antibiotic regimen, hence I^2 and meta-analysis was inappropriate.

Leman and Mukherjee showed that the addition of intravenous (IV) benzylpenicillin to IV flucloxacillin did not result in a more rapid clinical response (Tables 3 and 4).[13]

Peterson *et al.* demonstrated that 2 of 8 patients (25%) on ciprofloxacin 1500 mg and 6 of 8 (75%) on 2000 mg achieved a long-term satisfactory response [relative risk (RR) = 0.33, 95% CI 0.09–1.18].[16] This raises the possibility that in some patients lower doses of ciprofloxacin could potentially be used with no reduction in clinical response.[16]

Joseph *et al.*[14] performed a pooled analysis of the ESTABLISH 1 and 2 trials.[17,18] In the tedizolid group 114 of 162 patients (70.4%) achieved early clinical response compared with 115 of 158 (72.8%) in the

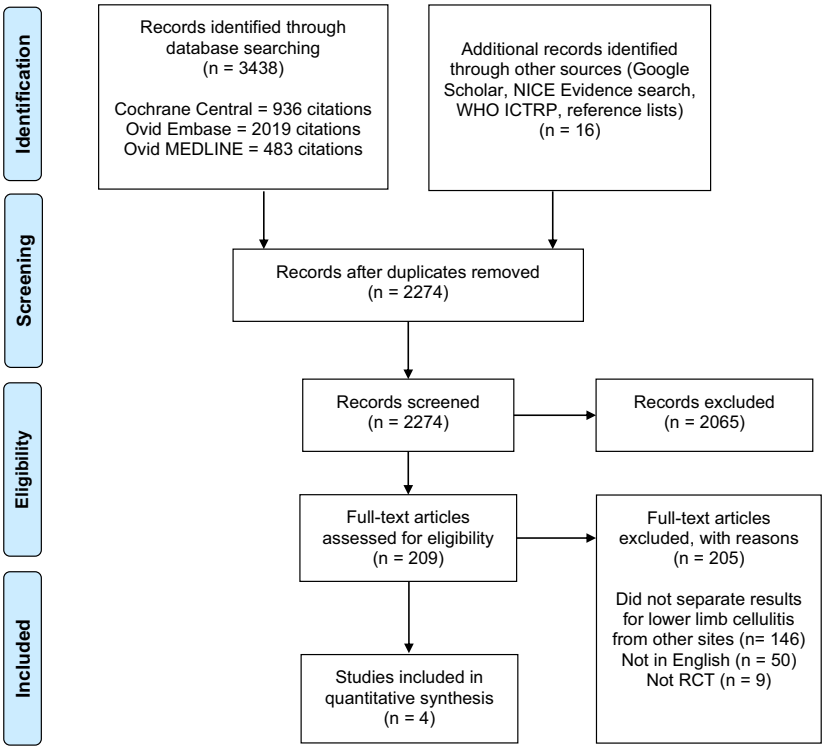

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of literature search and study selection.

linezolid group (RR = 0.97, 95% CI 0.84–1.1).[14] At post-therapy evaluation 139 of 162 (85.8%) in the tedizolid group and 136 of 158 (86.1%) in the linezolid group showed a clinical response (RR = 1.00, 95% CI 0.91–1.09), confirming noninferiority of tedizolid.[14] Tedizolid offered a short and well-tolerated treatment.[14]

Zeglaoui *et al.* revealed that 11 of 55 patients (20%) on IV benzylpenicillin and 8 of 57 (14%) on intramuscular (IM) bipenicillin had failure of treatment at Day 10 based on their symptoms (RR = 1.43, 95% CI 0.62–3.27).[15] Mean time to recovery was 6.3 days in patients on IV benzylpenicillin compared with 6.5 days in patients on IM bipenicillin (*t*-test, $P = 0.75$).[15] This suggested that IM bipenicillin could be a possible alternative to IV benzylpenicillin.[15]

Zeglaoui *et al.* also found that 9.1% (4/44) on IV benzylpenicillin and 7% (3/44) on IM bipenicillin experienced local skin complications such as cutaneous necrosis (RR = 1.33, 95% CI 0.32–5.61).[15] The authors reported that 14/44 (25.5%) patients on IV benzylpenicillin experienced venitis, whereas no patients on IM bipenicillin did (RR = 29.00, 95% CI 1.78–471.58).[15] By contrast, Leman and Mukherjee identified no adverse effects for benzylpenicillin.[13]

RoB was high for three of these studies,[13,15,16] and there were some concerns about RoB in the fourth[14] (Fig. 2). One study did not provide the baseline characteristics.[16] Leman and Mukherjee reported that 18 of 99 participants (18%) withdrew from the study, and identified deviation from standard practice due to the early discharge of participants.[13] The study of Peterson *et al.* was underpowered to show a significant difference.[16] Two studies used subjective outcome measures.[15,16]

Discussion

All included studies showed no significant differences between groups related to antibiotic types, administration routes (IV and alternative routes), durations of treatment (long vs. short) or dosages (high vs. low). This suggested that LLC may be overtreated in some patients. Another review, which included sites other than the lower limb also showed oral route, lower dosages and shorter durations of antibiotics to be equally effective.[19]

The first surveillance data by the WHO on antimicrobial resistance, published in 2018, revealed that penicillin resistance ranged from 0 to 51% globally.[20] The first-line antibiotic in the UK is flucloxacillin,[5] but this is ineffective against methicillin-resistant *Staphylococcus aureus* (MRSA) and its broad-spectrum action potentiates resistance.[21,22] Flucloxacillin can also be

Table 2 Characteristics of the four included studies.

Reference	Leman and Mukherjee, 2005[13]	Joseph *et al.*, 2017[14]	Zeglaoui *et al.*, 2004[15]	Peterson *et al.*, 1989[16]
Country, setting	Single tertiary emergency department at an inner-city teaching hospital in the UK	ESTABLISH 1 – North America, South America, Europe ESTABLISH 2 – South America, Oceania, Europe, New Africa, North America	Department of Dermatology, Charles Nicolle Hospital, Tunisia	Minneapolis Veterans Administration Medical Center, MN, USA
Years of study	2001–2003	ESTABLISH 1: 2010–2011 ESTABLISH 2:2011–2013	1994–1999	Unclear
Study type	Double-blind, randomized, placebo-controlled trial	ESTABLISH 1 and 2: randomized, double-blind, phase III trials	Prospective, randomized, monocentric trial	Double-blind, randomized controlled trial
Diagnoses explored in the study	LLC	Cellulitis, erysipelas, major cutaneous abscess, wound infection	Erysipelas of leg	Cellulitis or osteomyelitis with comorbid peripheral vascular disease
Funding source	Unclear	ESTABLISH 1: Trius Therapeutics ESTABLISH 2: Cubist Pharmaceuticals	Unclear	Miles Pharmaceuticals
Patients with LLC analysed, *n*	81–41 (I); 40 (C)	320–162 (I); 158 (C)	112–57 (I); 55 (C)	16–8; 8 (C)
Mean age of patients with LLC, years	44.9 (I); 46.4 (C)	47.6* (I); 47.9* (C)	44 (I); 41.4 (C)	64[a]
Male patients with LLC, *n* (%)	35 (85%) (I); 30 (75%) (C)	158 (58.5%) (I)[a]; 159 (56.4%) (C)[a]	29 (50.9%) (I); 28 (51%) (C)	47* (98%)[a]
Intervention	IV flucloxacillin 1 g four times daily plus IV[a] benzylpenicillin 1.2 g once daily	Oral tedizolid 200 mg once daily for 6 days	IM bipenicillin (benzylpenicillin + procaine penicillin) 2 MU twice daily for 10 days	Oral ciprofloxacin 1000 mg twice daily 3 weeks
Control	IV flucloxacillin 1 g four times daily plus normal saline placebo	Oral linezolid 600 mg twice daily for 10 days	IV benzylpenicillin 4 MU 4 h for 10 days	Oral ciprofloxacin 750 mg twice daily for 3 weeks
Outcome	Number of doses received prior to clinical response defined as reduction to either < 100 mm or < 50% of the initial diameter and resolution of fever; diameter decrease; pain VAS[b]; patient subjective improvement	Early clinical response ESTABLISH 1: temperature < 37.6 °C, cessation of lesion spread, no concomitant antibiotics and no mortality ESTABLISH 2: ≥ 20% reduction in lesion area, no concomitant antibiotics, no mortality Clinical response at post-therapy evaluation ESTABLISH 1: as per early response, no pain, mild or no tenderness ESTABLISH 2: as per early clinical response	Recovery: symptom rating score of zero for erythema, oedema and pain and normal temperature. Failure: no clinical improvement in symptom ratings	Long-term satisfactory response: immediate satisfactory response and no rehospitalization related to LLC within 12 months
Timeframe for follow-up	When clinical resolution criteria met; diameter decrease, VAS change and patient subjective improvement at Days 1 and 2	Early clinical response 48–72 h; post-therapy evaluation 7–14 days after end of treatment	10 days	1 year

C, control; I, intervention; IM, intramuscular; IV, intravenous; LLC, lower limb cellulitis; VAS, visual analogue scale. [a]All patients, not LLC specifically; [b]VAS is a validated pain scale from 0 to 100, with 0 representing no pain and 100 maximal pain.

Table 3 Summary of findings from outcome measures of clinical response in Leman and Mukherjee.[13]

	Flucloxacillin + benzylpenicillin		Flucloxacillin alone			
Outcome	*n*	Mean (95% CI)	*n*	Mean (95% CI)	Mean difference (95% CI)	*P*[a]
Doses to achieve clinical response	38	8.47 (7.09 to 9.86)	38	8.71 (6.90 to 10.5)	−0.24 (−2.48 to 2.01)	0.83
Temperature drop, °C (Day 1 minus Day 0)	35	0.36 (−0.24 to 0.95)	32	0.42 (0.06 to 0.80)	−0.07 (−0.76 to 0.62)	0.84
Decrease in diameter, mm						
Day 1 minus Day 0	26	36 (−20 to 92)	22	69 (33 to 105)	−34 (−99 to 31)	0.30
Day 2 minus Day 0	13	95 (35 to 135)	12	46 (−6 to 99)	48 (−27 to 124)	0.20
VAS[b]						
Day 1 minus Day 0	24	2.6 (1.6 to 3.6)	23	2.5 (1.6 to 3.6)	0.10 (−1.26 to 1.42)	0.91
Day 2 minus Day 0	16	3.0 (1.4 to 4.7)	16	2.9 (1.6 to 4.2)	0.15 (−1.86 to 2.16)	0.88

[a]Two-sample *t*-test; [b]Visual Analogue Scale (VAS)is a validated pain scale from 0 to 100, with 0 representing no pain and 100 maximal pain.

Table 4 Patient assessment of clinical response in Leman and Mukherjee.[13]

Patient subjective assessment, *n* (proportion)	Flucloxacillin + benzylpenicillin	Flucloxacillin alone	RR (95% CI)[a]
Day 1			
Improving	25 (0.74)	21 (0.68)	1.09 (0.79–1.49)
No change	9 (0.26)	8 (0.26)	
Worse	0 (0)	2 (0.06)	
Day 2			
Improving	18 (0.82)	16 (0.84)	0.97 (0.74–1.28)
No change	1 (0.05)	0 (0)	
Worse	3 (0.14)	3 (0.16)	

RR, relative risk; [a]'No change' and 'worse' scores were combined to calculate RR.

complicated by allergic reactions and *Clostridium difficile*.[23] With the increase in rates of resistance and adverse events, it is important to identify new antibiotics. Fear of MRSA and poor outcomes may have driven overtreatment in the cases reported.[24] A previous review revealed 14% of cellulitis admissions were overtreated.[25]

The main limitation of this review was the number and quality of included studies. Although an abundance of cellulitis literature existed, few focused on the lower limb. As this is the first systematic review focused on the antibiotic treatment of LLC, the less stringent eligibility criteria provided a comprehensive scope of the current literature.

This review identified a profound gap in the literature regarding high-quality studies to identify best treatment of LLC. Future studies could explore whether we can effectively treat mild LLC with less intensive antibiotic regimens. Such regimens would save health services money, reduce treatment complications and contribute to guidelines based on patient characteristics.

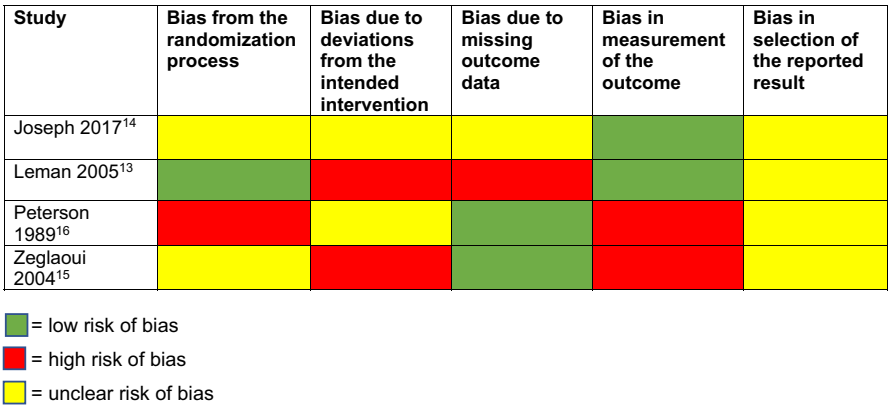

Figure 2 Cochrane risk of bias assessment to illustrate the risk of bias for each domain in individual studies.

Conclusion

The evidence for the clinical response to antibiotics for LLC is limited; however, there is low-quality evidence to support the possible use of shorter courses of lower doses of oral antibiotics in some patients. Further trials comparing lower-intensity antibiotic regimens are warranted.

Acknowledgement

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Learning points

- Cellulitis is a common condition that can have a negative impact on patients; however, the clinical response of different antibiotic treatment regimens remains unclear.
- There is variation in the treatment of LLC, with many patients failing to respond to first-line antibiotics, and an increase in antibiotic resistance.
- There is weak evidence that LLC may be overtreated in some patients, for whom shorter courses of lower-dose, oral antibiotics may be suitable.

References

1 Department of Health and Social Care. NHS reference costs 2015 to 2016. National schedule of reference costs: the main schedule. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/577084/National_schedule_of_reference_costs_-_main_schedule.xlsx (accessed 15 July 2020).
2 NHS Digital. Hospital admitted patient care activity, 2017–2018. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 (accessed 15 July 2020).
3 Mistry KM, Sutherland M, Levell NJ. Lower limb cellulitis: low diagnostic accuracy and underdiagnosis of risk factors. *Clin Exp Dermatol* 2019; **44**: 193–5.
4 Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev* 2010; (6): CD004299.
5 Clinical Resource Efficiency Support Team. Guidelines on the management of cellulitis in adults, 2005. Available at: http://www.acutemed.co.uk/docs/Cellulitis%20guidelines,%20CREST,%2005.pdf (accessed 15 July 2020).
6 Dong SL, Kelly KD, Oland RC *et al*. ED management of cellulitis: a review of five urban centers. *Am J Emerg Med* 2001; **19**: 535–40.
7 Berger A, Oster G, Edelsberg J *et al*. Initial treatment failure in patients with complicated skin and skin structure infections. *Surg Infect (Larchmt)* 2013; **14**: 304–12.
8 Lazzarini L, Conti E, Tositti G *et al*. Erysipelas and cellulitis: clinical and microbiological spectrum in an Italian tertiary care hospital. *J Infect* 2005; **51**: 383–9.
9 Thomas KS, Brindle R, Chalmers JR *et al*. Identifying priority areas for research into the diagnosis, treatment and prevention of cellulitis (erysipelas): results of a James Lind Alliance Priority Setting Partnership. *Br J Dermatol* 2017; **177**: 541–3.
10 Talbot GH, Powers JH, Fleming TR *et al*. Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. *Clin Infect Dis* 2012; **55**: 1114–21.
11 Yadav K, Suh KN, Eagles D *et al*. Predictors of oral antibiotic treatment failure for nonpurulent skin and soft tissue infections in the emergency department. *Acad Emerg Med* 2019; **26**: 51–9.
12 Higgins JPT, Sterne JAC, Savocic J *et al*. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev* 2016; **10**: 29–31.
13 Leman P, Mukherjee D. Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulitis: a randomised controlled trial. *Emerg Med J* 2005; **22**: 342–6.
14 Joseph WS, Culshaw D, Anuskiewicz S *et al*. Tedizolid and linezolid for treatment of acute bacterial skin and skin structure infections of the lower extremity versus non–lower-extremity infections pooled analysis of two phase 3 trials. *J Am Podiatr Med Assoc* 2017; **107**: 264–71.
15 Zeglaoui F, Dziri C, Mokhtar I *et al*. Intramuscular bipenicillin vs. intravenous penicillin in the treatment of erysipelas in adults: randomized controlled study. *J Eur Acad Dermatol Venerol* 2004; **18**: 426–8.
16 Peterson LR, Lissack LM, Canter K *et al*. Therapy of lower extremity infections with ciprofloxacin in patients with diabetes mellitus, peripheral vascular disease, or both. *Am J Med* 1989; **86**: 801–8.
17 Prokocimer P, De Anda C, Fang E *et al*. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections. *JAMA* 2013; **309**: 559–69.
18 Moran GJ, Fang E, Corey GR *et al*. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2014; **14**: 696–705.
19 Brindle R, Williams OM, Barton E, Featherstone P. Assessment of antibiotic treatment of cellulitis and erysipelas a systematic review and meta-analysis. *JAMA Dermatol* 2019; **155**: 1033–40.

20 World Health Organization. Global Antimicrobial Surveillance System (GLASS) Report (2017–18). Available at: https://www.who.int/mediacentre/news/releases/2018/antibiotic-resistance-found/en/ (accessed 15 July 2020).
21 Guenthner SH, Wenzel RP. In vitro activities of teichomycin, fusidic acid, flucloxacillin, fosfomycin, and vancomycin against methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother* 1984; **26**: 268–9.
22 Neu HC. The crisis in antibiotic resistance. *Science* 1992; **257**: 1064–73.
23 Centers for Disease Control and Prevention. Antibiotic prescribing and use in the U.S. Available at: https://www.cdc.gov/antibiotic-use/stewardship-report/index.html (accessed 15 July 2020).
24 Boothe WD, Diven D. Antibiotic stewardship: the treatment of uncomplicated lower limb cellulitis. *Am J Emerg Med* 2019; **37**: 139–1.
25 Gunderson CG, Cherry BM, Fisher A. Do patients with cellulitis need to be hospitalized? A systematic review and meta-analysis of mortality rates of inpatients with cellulitis. *J Gen Intern Med* 2018; **33**: 1553–60.

CPD questions

Learning objective

To demonstrate up-to-date knowledge in the management of lower limb cellulitis.

Question 1

Which of the following is the most common location of cellulitis?

(a) Face.
(b) Umbilicus.
(c) Genitals.
(d) Upper limb.
(e) Lower limb.

Question 2

Which of the following is an antibiotic used to treat lower limb cellulitis, but may increase the risk of methicillin-resistant *Staphylococcus aureus*?

(a) Vancomycin.
(b) Linezolid.
(c) Flucloxacillin.
(d) Clindamycin.
(e) Trimethoprim.

Question 3

Which of the following adverse effects is more common with antibiotics administered through the intravenous rather than intramuscular route?

(a) Venitis.
(b) Cutaneous skin necrosis.
(c) Nausea and vomiting.
(d) Anaphylaxis.
(e) Headache.

Question 4

Which of the following antibiotics are considered first line in the UK for the treatment of cellulitis?

(a) Ciprofloxacin.
(b) Gentamicin.
(c) Fusidic acid.
(d) Chloramphenicol.
(e) Flucloxacillin.

Question 5

Which of the following statements regarding the treatment of lower limb cellulitis is based on evidence in the international literature?

(a) Intravenous benzylpenicillin results in a shorter time to recovery compared with intramuscular bipenicillin.
(b) The addition of intravenous benzylpenicillin to intravenous flucloxacillin results in a more rapid clinical response.
(c) Ciprofloxacin has no clinical response against lower limb cellulitis.
(d) There appears to be no difference in the clinical response to intravenous vs. oral antibiotics in the treatment of cellulitis for some patients.
(e) Tedizolid has no clinical response against lower limb cellulitis.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures.
- Reflect on the article.
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions.
- Complete the required evaluation component of the activity.

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Eligibility citeria.
Table S2. Detailed search strategy.