National Institute for Health and Care Excellence

Diabetic foot problems: prevention and management

[A] Evidence review for diabetic foot infection: antimicrobial prescribing

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1 Context

1.1 Background

Diabetes is one of the most common chronic diseases in the UK with an estimated 3.7 million people diagnosed with diabetes as of November 2017 (Diabetes UK [online]). The life expectancy of people with diabetes is shortened by up to 15 years, and 75% die of macrovascular complications. Diabetes is the most common cause of non-traumatic limb amputation, with diabetic foot ulcers preceding more than 80% of amputations in people with diabetes (NICE 2016), and it is estimated that people with diabetes are 23 times more likely than a person without diabetes to have a leg, foot or toe amputation (Kerr, 2017). An estimated 60,000-75,000 people with diabetes in England will have a diabetic foot ulcer in any given week (Kerr 2017) and 10% of people with diabetes will experience a diabetic foot ulcer at some point in their lives. There are an estimated 7,000 lower limb amputations in people with diabetes in England each year (Diabetes UK [online]). Amputation and ulceration are associated with high mortality, with an estimated 50% of people with diabetes surviving only 2 years post major amputation, and 60% who have experienced ulceration surviving for 5 years or less (Diabetes UK [online].

A diabetic foot infection is defined as any type of skin, soft tissue or bone infection affecting tissues below the ankle in people with diabetes (Selva Olid et al 2015). Diabetic foot infection includes cellulitis (in deep skin), paronychia (around nails), abscesses, myositis (in muscle), tendonitis (in tendons), necrotising fasciitis (infection that kills tissue), osteomyelitis (in bone) and septic arthritis (in joints) (Lipsky 2004).

Diabetic foot infection is defined clinically by the presence of systemic signs of infection related to a foot lesion (usually an ulcer), purulent secretions, or at least 2 signs of inflammation including redness, warmth, pain or tenderness, and tissue hardening (Selva Olid et al 2015). The risk of foot problems in people with diabetes is increased, largely because of diabetic neuropathy and/or poor blood supply because of peripheral arterial disease.

The International Working Group on the Diabetic Foot (IWGDF) guidance on the diagnosis and management of foot infections in persons with diabetes (Lipsky et al 2016) outlines that diabetic foot infection is diagnosed clinically, based on local or systemic signs or symptoms of inflammation. The severity of infection can be assessed using the Infectious Diseases Society of America (IDSA)/IWGDF classification scheme or the perfusion, extent, depth, infection and sensation (PEDIS) system. The IDSA/IWGDF infection classification scheme has a scale from 1 to 4.

- 1 is defined as no systemic or local symptoms or signs of infection.
- 2 refers to a ‘mild infection’ where at least 2 of the following are present: local swelling or induration, erythema >0.5 cm around the wound, local tenderness or pain, local warmth or purulent discharge – with other possible causes of an inflammatory response of the skin excluded.
- 3 refers to a ‘moderate infection’ which involves only the skin or subcutaneous tissue, any erythema that extends <2 cm around any wound, with no systemic signs or symptoms of infection.
- 4 is a ‘severe infection’ defined by a systemic inflammatory response featuring 2 or more of the following: a temperature >38°C or <36°C, a heart rate >90 beats/min, a respiratory rate >20 breaths/min or $PaCO_2$ <4.3 kPa (32 mmHg), a white blood cell count >12,000/mm^3 or <4000/mm^3, or >10% immature (band) forms.

A recent cross-sectional study (n=400) in primary and secondary care in 27 English centres compared 2 methods of microbiological specimen taking (wound swab and tissue samples) and found that the most frequently reported groups of pathogens in the study were: Gram-

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positive cocci (70.6%); Gram-negative bacilli (36.7%); Enterobacteriaceae, including coliforms (26.6%); obligate anaerobes (23.8%); and Gram-positive bacilli (11.1%). The major cultured organisms in infected diabetic foot ulcer were *Staphylococcus aureus* (43.8%, of which 8.1% were methicillin resistant), Streptococcus (16.7%), Enterococcus (14.9%), Coagulase-negative Staphylococcus (12.2%), Corynebacterium (9.4%), and *Pseudomonas aeruginosa* (8.6%) (Nelson et al 2017).

Once diagnosed diabetic foot infections require antibiotic treatment following clinical rather than microbiological identification of infection, so as to not delay antibiotic treatment (Selva Olid et al 2015). Antibiotic treatment is usually given in addition to other treatments, such as debridement, ulcer drainage, dressings and correction of any metabolic abnormalities.

The NICE guideline on diabetic foot problems outlines that people should receive advice about basic foot care and have their risk of developing diabetic foot problems assessed at diagnosis and at least annually thereafter, if any foot problems arise or on admission to hospital and if there is any change in their status whilst in hospital. People assessed as at low risk of developing a diabetic foot problem should continue to attend annual foot assessment and receive advice. Those at moderate or high risk of developing a diabetic foot problem should be referred to the foot protection service.

1.2 Antimicrobial stewardship

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks. This guideline also recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include: how long symptoms are likely to last with and without antimicrobials, what to do if symptoms get worse, what to do if they experience adverse effects from the treatment, and when they should ask again for medical advice.

Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship, both outline the need to consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.3 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

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- optimise therapy for individual people
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual people and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care prescribing. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017, and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and trimethoprim, and anti-*C. difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both in-patients (2.4%) and out-patients (14.7%) compared with 2013. Prescribing of co-amoxiclav, amoxicillin and piperacillin with tazobactam between 2013 and 2017 decreased by 11.3%, 7.4% and 30.2% respectively.

The use of cephalosporins has decreased by 21.4% due to reductions within primary care and is attributed to a decline in the use of cefalexin. However, the observed rate between 2016 and 2017 for cephalosporins overall remained unchanged.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use declined over the same period by 40.7%.

Between 2013 and 2017 fluoroquinolone use remained broadly stable but there was a 14.5% decline in use in primary care over the same period. Ciprofloxacin, norfloxacin and ofloxacin prescriptions have all declined from 2013 to 2017, but levofloxacin use increased by 98.0%.

The use of glycopeptides (vancomycin and teicoplanin) and daptomycin occurred almost exclusively in hospitals and most commonly in in-patients, with prescribing increasing by 40.1% over the 5-year period from 2013 to 2017.

Carbapenem use in secondary care remained stable from 2013 to 2017, but acute trusts and specialist and teaching trusts increased their use by 24.0% and 3.6%, respectively, between 2016 and 2017. A decline in use was seen in multiservice, small, medium and large trusts.

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2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for diabetic foot infection.

2.1 Literature search

Methods

Antimicrobial prescribing guidelines were commissioned to develop guidance on the use of antibiotics in diabetic foot infection. There is existing NICE guidance on the use of antibiotics in diabetic foot infection (NICE clinical guideline 19: Diabetic foot problems: prevention and management) published in 2015 and updated in 2016.

This antimicrobial prescribing guidance will update the recommendations on the use of antibiotics in diabetic foot infection in NG19. NG19 had an existing search strategy set up for this review question. For consistency, the same search strategy used for NG19 was used in this evidence review. The search was re-run from the cut- off of the previous guideline (2013) to present.

Studies included in NG19 were assessed against the criteria in the updated protocol for this evidence review (appendix B: review protocol), and were included if they matched the review protocol. If a study that was included in NG19 did not meet the criteria in the current review protocol, the study was excluded from this analysis.

Results

Twenty one studies were originally included in this review question in NG19. On review of the studies included in NG19, Lipsky et al. (2012) was excluded (appendix J: excluded studies) as it considered dressings (which is out of scope of this evidence review). A total of 20 studies from NG19 were included in this antibiotic prescribing evidence review.

In addition to the studies from NG19, the re-run literature search (see appendix C: literature search strategy for full details) identified 2707 references. These references were screened using their titles and abstracts and 121 full text references were obtained and assessed for relevance. Three full text references of systematic reviews and 2 full text references of randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

On review, the 3 systematic reviews were subsequently excluded because they included studies that had already been considered in NG19. The 2 RCTs were subsequently critically appraised, data extracted and considered alongside the identified 20 studies from NG19.

See also appendix D: study flow diagram.

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2.2 Summary of included studies

A summary of the included studies is shown in Table 1 to Table 3. Details of the study citation can be found in appendix E: included studies. An overview of the quality assessment of each included study is shown in appendix F: quality assessment of included studies.

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Table 1: Summary of included studies: antibiotic choice

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Penicillin with beta-lactamase inhibitor vs penicillin with beta-lactamase inhibitor					
Tan et al. 1993 USA Multi centre double blind RCT, follow-up at 10-14 days	n=111 (n=35 had diabetic foot infection)	Hospitalised adults with complicated skin and skin structure bacterial infections; mean age 54 years	Piperacillin with tazobactam (IV) for at least 5 days and at least 48 hours after resolution of symptoms	Ticarcillin with clavulanic acid (IV) for at least 5 days and at least 48 hours after resolution of symptoms.	Cured or improved condition of ulcer
Harkless et al. 2005 USA Multi-centre, open-label RCT, follow-up at 14-21 days	n=185	Adults with diabetes and open infected foot ulcers; mean age 61 years	Piperacillin with tazobactam (IV) for between 4 and 14 days, which can be extended to a maximum 21 days	Ampicillin with sulbactam (IV) for between 4 and 14 days, which can be extended to a maximum 21 days	Cured or improved condition of ulcer; adverse events; withdrawals due to adverse event
Glycycline vs carbapenem					
Lauf et al. 2014 USA Multicentre, double-blind RCT, follow-up at 12-92 days (non- osteomyelitis) and 25-27 days (osteomyelitis)	n=944	Hospitalised adults with diabetes and foot infection; mean age 59 years	Tigecycline (IV) for up to 42 days	Ertapenem (IV) with or without vancomycin (IV) for up to 42 days	Clinical cure; adverse events
Carbapenem vs penicillin					
Bouter et al. 1996 Netherlands Double-blind RCT, follow-up at 10 days	n=185	Hospitalised adults with Wagner classified diabetic foot lesions stage II, III or IV; mean age 59 years	Imipenem with cilastatin (IV) for at least 10 days	Piperacillin/clindamycin combination therapy (IV) for at least 10 days	Cured or improved condition of ulcer; adverse events

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Grayson et al. 1994 USA Double-blind RCT, follow-up at 6 days	n=93	Diabetic adults with limb-threatening infection of a lower-extremity; mean age 60 years	Imipenem with cilastatin (IV) for 4-32 days	Ampicillin with sulbactam (IV) for 5-45 days	Cured or improved condition of ulcer; adverse events
Lipsky et al. 2005a USA Multicentre, double-blind RCT	n=445	People with diabetes and a foot infection requiring IV antibiotics; mean age 58	Ertapenem (IV) for 5-28 days	Piperacillin with tazobactam (IV) 5-28 days	Cured or improved condition of ulcer
Saltoglu et al. 2010 Turkey Open-label RCT, follow-up at 2 months	n=62	Hospitalised adults with moderate to severe diabetic lower-extremity infection; mean age 58 years	Imipenem with cilastatin (IV) for 14 days	Piperacillin with tazobactam (IV) for 14 days	Cured or improved condition of ulcer; adverse events
Zhang-Rong et al. 2016 China non-inferiority RCT, follow-up at 14 days after the last dose of antibiotic	n=443	Diabetic adults with moderate to severe foot infection requiring IVI antibiotics; mean age 61 years	Ertapenem (IV) for 5-28 days[1]	Piperacillin with tazobactam (IV) 5-28 days[1]	Clinical response
[1] Investigators could administer vancomycin if Enterococcus spp and/or MRSA organisms were known or suspected; After 5 days of IV treatment (ertapenem or piperacillin with tazobactam) the investigator could switch adults to co-amoxiclav (oral) 875/125 mg every 12 hours					
Cephalosporin vs cephalosporin					
Hughes et al. 1987 USA, Dual centre RCT, follow-up at up to 3 months	n=63 (n=46 had diabetic foot infection)	Adults with peripheral arterial insufficiency or diabetes and 2 or more signs of lower extremity infection; mean age 64 years	Cefoxitin (IV) (duration of treatment unclear)	Ceftizoxime (IV) (duration of treatment unclear)	Cured or improved condition of ulcer; adverse events
Bradsher et al. 1984 USA	n=84	Hospitalised adults with suspected serious skin and soft tissue	Ceftriaxone (IV or IM) (duration of treatment unclear)	Cefazolin (IV) (duration of treatment unclear)	Cured or improved condition of ulcer;

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Dual centre RCT, follow-up at 7 days.		infections; mean age 55 years			adverse events; surgeries required
Cephalosporin vs penicillin with beta-lactamase inhibitor					
Erstad et al. 1997 USA Double-blind RCT, follow-up at: at least 5 days	n=36	Adults hospitalised for diabetic foot infection; mean age 59 years	Cefoxitin (IV) for at least 5 days	Ampicillin with sulbactam (IV) for at least 5 days	Cured or improved condition of ulcer; length of hospital stay;
Fluoroquinolone vs penicillin with beta-lactamase inhibitor					
Schaper et al. 2013 Europe and USA Multicentre, double-blind RCT, follow-up at 7-21 days	n=206	Hospitalised adults with diabetic foot infection requiring surgery and antibiotics; mean age 64 years	Moxifloxacin (IV or oral) for 7 to 21 days	Piperacillin with tazobactam (IV) then co-amoxiclav (oral) for 7 to 21 days	Cured or improved condition of ulcer; adverse events
Siami et al. 2001 Canada Multicentre, parallel group, single-blind RCT, follow-up at 12 days,	n=409 (n=76 had diabetic foot infection)	Adults with a severe or limb-threatening skin and soft tissue infection; mean age 58 years	Clinafloxacin (IV then oral): IV for a minimum of 3 days before switch to oral; total no longer than 14 days unless advised otherwise	Piperacillin with tazobactam (IV) then co-amoxiclav (oral) plus vancomycin if MRSA suspected: IV for a minimum of 3 days before switch to oral; total no longer than 14 days unless advised otherwise	Cured or improved condition of ulcer
Lipsky et al. 1997 USA Multicentre RCT, 7 days	n=88	Hospitalised Adults with diabetes and foot infection; mean age 62 years	Ofloxacin (IV then oral), with metronidazole added if no improvement, for up to 25 days.	Ampicillin with sulbactam (IV) then co-amoxiclav (oral), with gentamicin, co-trimoxazole, or another agent added for broader coverage of Gram-negative bacilli if needed, for up to 25 days.	Cured or improved condition of ulcer; adverse events

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Vick-Fragoso et al. 2009 Worldwide Multicentre, parallel group, open-label RCT, follow-up at 14-28 days	n=427 (n=112 had diabetic foot infection)	Adults with a diabetic foot infection; mean age 52 years	Moxifloxacin (IV then oral) for 7 to 21 days	Co-amoxiclav (IV then oral) for 7 to 21 days	Cure rates; treatment duration; adverse event
Lipsky et al 2007 6 countries Multicentre, double-blind RCT, follow-up at 10-42 days	n=127	Hospitalised adults with diabetic foot infection; mean age 57 years	Moxifloxacin (IV) for at least 3 days then switched to moxifloxacin (oral). The total treatment duration of 7 to 14 days	Piperacillin with tazobactam (IV) for at least 3 days then switched to co-amoxiclav (oral). The total treatment duration of 7 to 14 days	Cure rates; adverse events; withdrawals due to adverse event
Other antibiotic comparisons					
Lipsky et al. 1990, USA, Double blind RCT, follow-up at 14 days	n=56	Adults with lower-extremity infections; mean age 61 years	Clindamycin (oral) for 2 weeks.	Cefalexin (oral) for 2 weeks.	Cure or complete healing of ulcer
Lipsky et al. 2004, 8 countries (not specified), Multi centre open label RCT follow-up at 15-21 days	n=361	Adults with diabetes mellitus and a foot infection; mean age 63 years	Linezolid (IV or oral) for at least 7 days but not longer than 28 days	Ampicillin with sulbactam (IV) or co-amoxiclav (oral) for at least 7 but not longer than 28 days	Cured or improved condition of ulcer; Adverse events; Withdrawals due to adverse event
Lipsky et al. 2005b, 5 countries (USA, Europe, South Africa, Australia, Israel), Multi centre single blind RCT, follow-up at 6-20 days	n=52	Hospitalised adults with a complicated skin and skin structure infection (with and without diabetes); mean age 62 years	Daptomycin (IV) for 7 to 14 days	Semi-synthetic penicillin (IV) for 7 to 14 days	Cured or improved condition of ulcer
Lipsky et al. 2005b,	n=43	Hospitalised adults with a complicated skin and skin structure	Daptomycin (IV) for 7 to 14 days	Vancomycin (IV) for 7 to 14 days	Cured or improved condition of ulcer

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
5 countries (USA, Europe, South Africa, Australia, Israel), Multi centre single blind RCT, follow-up at 6-20 days		infection (with and without diabetes); mean age 62 years			
Abbreviations: RCT, randomised controlled trial; IV, intravenous; IM, intramuscular					

Table 2: Summary of included studies: antibiotic dual treatment (treatment with more than 1 antibiotic)

Clay et al. 2004, USA, Open label RCT, follow-up at 4 days	n=70	Hospitalised adult males with diabetes mellitus & a lower extremity infection; mean age 64 years	Metronidazole (IV) plus ceftriaxone (IV) (duration of treatment unclear)	Ticarcillin with clavulanic acid (IV) (duration of treatment unclear)	Cured or improved condition of ulcer; mean duration of treatment
File et al. 1983, USA, Single blind open label RCT, follow-up at 14 days	n=41 (n=32 had diabetes or osteomyelitis)	Hospitalised people with clinical evidence of bacterial soft tissue infection; mean age 56 years	Amdinocillin (IV) plus cefoxitin (IV) for a mean duration of 14 days	Cefoxitin (IV) for a mean duration of 13 days	Cured or improved condition of ulcer; people needing amputations
Abbreviations: RCT, randomised controlled trial; IV, intravenous; IM, intramuscular					

Table 3: Summary of included studies: antibiotic course length

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Tone et al 2015, France, Open-label multi-centre RCT, follow-up at end of treatment (6 or 12 weeks) and at 1 year	n=40	People with diabetic foot osteomyelitis treated non-surgically; mean age 64 years	Short-course (6 weeks) empirical[1] antibiotic (IV or oral)	Long-course (12 weeks) empirical[1] antibiotic (IV or oral)	Remission of diabetic foot osteomyelitis
Abbreviations: RCT, randomised controlled trial;					

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
[1]For Gram-positive cocci infections: rifampin was used in combination with levofloxacin, co-ceazole, doxycycline, linezolid, or any other antimicrobial agent active against bone pathogens for the entire duration of treatment; for Gram-negative bacilli infections: levofloxacin or ciprofloxacin was used in combination with cefotaxime, ceftriaxone, or cefepime for the first 2 weeks of treatment and then continued for the rest of the treatment as monotherapy.					

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3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults, young people and children with diabetic foot infection (with or without osteomyelitis).

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

3.1 Antibiotics in adults

3.1.1 Choice of antibiotic in adults

The evidence review for choice of antibiotic treatment for diabetic foot infections is based on 1 newly identified RCT (Zhang-Rong et al. 2016) and 20 RCTs identified in NICE clinical guideline 19: Diabetic foot problems: prevention and management (2015). The following comparisons were included:

- Penicillin with beta-lactamase inhibitor versus penicillin with beta-lactamase inhibitor (piperacillin with tazobactam (IV) versus ticarcillin with clavulanic acid (IV):Tan et al. 1993; piperacillin with tazobactam (IV) versus ampicillin with sulbactam (IV): Harkless et al. 2005)
- Carbapenem versus glycycline (Ertapenem with or without vancomycin (IV) versus tigecycline (IV): Lauf et al. 2014)
- Carbapenem versus penicillin (imipenem with cilastatin (IV) versus piperacillin/clindamycin (IV): Bouter et al. 1996; imipenem with cilastatin (IV) versus ampicillin with sulbactam (IV): Grayson et al. 1994; ertapenem (IV) versus piperacillin with tazobactam (IV): Lipsky et al. 2005a; imipenem with cilastatin (IV (IV) versus piperacillin with tazobactam): Saltoglu et al. 2010; ertapenem (IV) versus piperacillin with tazobactam (IV): Zhang-Rong et al. 2016)
- Cephalosporin versus cephalosporin (cefoxitin (IV) versus ceftizoxime (IV): Hughes et al. 1987; ceftriaxone (IV or IM) versus cefazolin (IV): Bradsher et al. 1984)
- Cephalosporin versus penicillin with beta-lactamase inhibitor (cefoxitin (IV) versus ampicillin with sulbactam (IV): Erstad et al 1997)
- Fluoroquinolone versus penicillin with beta-lactamase inhibitor (moxifloxacin (IV or oral) versus piperacillin with tazobactam or co-amoxiclav (IV or oral): Schaper et al. 2013; clinafloxacin (IV and oral) versus piperacillin with tazobactam (IV) and co-amoxiclav (oral): Siami et al 2001; ofloxacin (IV and oral) versus ampicillin with sulbactam and co-amoxiclav (IV) and co-amoxiclav (oral): Lipsky et al. 1997; moxifloxacin (IV and oral) versus co-amoxiclav (IV and oral): Vick-Fragoso et al. 2009; moxifloxacin (IV) versus piperacillin with tazobactam and co-amoxiclav (IV and oral): Lipsky et al. 2007)
- Other antibiotic comparisons (clindamycin (oral) versus cefalexin (oral): Lipsky et al. 1990; linezolid (IV or oral) versus ampicillin with sulbactam or co-amoxiclav (IV or oral): Lipsky et al. 2004; ; daptomycin (IV) versus vancomycin (IV): Lipsky et al. 2005b; semi synthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin) (IV): Lipsky et al. 2005b)

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- Antibiotic dual treatment (metronidazole plus ceftriaxone (IV) versus ticarcillin with clavulanic acid (IV): Clay et al. 2004; amdinocillin plus cefoxitin (IV) versus cefoxitin (IV): File et al. 1983)

Two included studies (Lauf et al. 2014; Zhang-Rong et al. 2016) were non-inferiority trials. However, the committee considered that the reasons for the choice of non-inferiority margin differed between studies and were not well reported in one study. Therefore the committee decided to treat non-inferiority trials as superior head to head trials. Clinical effectiveness was assessed using a minimal important difference of 1.0 and imprecision was assessed using the standard GRADE minimal important difference of a relative risk (RR) of 0.75 and 1.25 for all outcomes.

3.1.2 Penicillin with beta-lactamase inhibitor versus penicillin with beta-lactamase inhibitor

3.1.2.1.1 Piperacillin with tazobactam versus ticarcillin with clavulanic acid

Tan et al. (1993) assessed the efficacy and safety of piperacillin with tazobactam (IV) compared with ticarcillin with clavulanic acid (IV) in people aged 16 years or over (mean age 54) with complicated skin or skin structure infections, of which 35/111 had diabetic foot infection confirmed by clinical symptoms. People randomly received piperacillin with tazobactam 3 g/375 mg (n=18) or ticarcillin with clavulanic acid 3 g/100 mg (n=17) every 6 hours for 5 days and at least 48 hours after resolution of signs and symptoms. People were evaluated for their clinical responses to treatment daily for the duration of treatment in hospital, at 24 to 72 hours after treatment completion, and at 10 to 14 days after the completion of treatment.

Overall, there was no significant difference between piperacillin with tazobactam and ticarcillin with clavulanic acid in clinical response at 10 to 14 days after the completion of treatment (n=35, 38.9% versus 35.3%, RR 1.10, 95% CI 0.46 to 2.62; very low quality evidence). Adverse experiences were reported but the data for people with diabetic foot infection could not be extracted.

See GRADE profiles: Table 9**.**

3.1.2.1.2 Piperacillin with tazobactam versus ampicillin with sulbactam

Harkless et al. (2005) assessed the efficacy and safety of piperacillin with tazobactam (IV) compared with ampicillin with sulbactam (IV) in people (mean age 61) with diabetes mellitus and open infected foot ulcers confirmed by clinical symptoms. People randomly received piperacillin with tazobactam 4 g/0.5 g every 8 hours (n=155) or ampicillin with sulbactam 2 g/1 g every 6 hours (n=159) for between 4 and 14 days (which could be extended to a maximum 21 days). People receiving ampicillin with sulbactam who had MRSA or methicillin-resistant Staphylococcus epidermidis (MRSE) were also given vancomycin (IV) 1 g every 2 hours. All people received standard wound care, including off-loading, debridement, moist dressings and one-time use of a topical antiseptic after surgery or debridement. People were followed up at day 4, day 7, the end of treatment visit, and at the test-of-cure visit (within 14 to 21 days of treatment completion).

Overall, there was no significant difference between piperacillin with tazobactam and ampicillin with sulbactam for cure or improvement at 14 to 21 day follow-up (n=289, 71.2% versus 66.7%, RR 1.07, 95% CI 0.92 to 1.25, moderate quality evidence). There were also no significant differences between treatments in people having at least 1 treatment-related adverse effect (n=314, 18.7% versus 13.2%, RR 1.42, 95% CI 0.85 to 2.37, low quality evidence) or withdrawal due to treatment-related adverse

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effects (n=314, 11.6% versus 8.2%, RR 1.42 95% CI 0.72 to 2.80, very low quality evidence).

See GRADE profiles: Table 10

3.1.3 Glycycline versus Carbapenem

3.1.3.1.1 Tigecycline versus ertapenem with or without vancomycin

Lauf et al. (2014) compared tigecycline (IV) to ertapenem (IV) with or without vancomycin (IV) for clinical response in hospitalised men and women aged 18 years or older (mean age 59) with diabetes mellitus and a foot infection that did not extend above the knee confirmed by clinical assessment (PEDIS infection grade 2-4; perfusion grade 1-2). Adults (n=944) randomly received tigecycline 150 mg once daily with or without adjunctive placebo (n=477) or ertapenem 1 g once daily with or without vancomycin (n=467) at the investigators discretion for coverage against MRSA, coagulase-negative staphylococci, or enterococci for up to 28 days (or 42 days in people with osteomyelitis). People were followed up at 12 to 92 days after the last dose for those without osteomyelitis and at 25 to 27 weeks for those with osteomyelitis.

There was no significant difference between tigecycline and ertapenem with or without vancomycin for clinical cure for people without osteomyelitis (n=813, 77.5% versus 82.5%, RR 0.94, 95% CI 0.88 to 1.01, moderate quality evidence [NICE analysis]) or for people with osteomyelitis (n=62, 31.6% versus 54.2%, RR 0.68, 95%CI 0.35 to 1.32, very low quality evidence, very low quality evidence [NICE analysis]) at 12 to 92 days follow-up. There were significant differences in adverse events and study withdrawal due to adverse events, with those prescribed tigecycline having significantly more adverse events (n=944, 71.1% versus 57%, RR 1.25 95% CI 1.13 to 1.38, low quality evidence) and study withdrawals (n=944, 2.1% versus 0.43%, RR 4.90, 95% CI 1.08 to 22.22, low quality evidence) than those prescribed ertapenem with or without vancomycin. There was no significant difference between treatments for drug discontinuation due to adverse events (n=944, 8.8%, versus 5.8% RR 1.52, 95% CI 0.96 to 2.43, low quality evidence).

See GRADE profiles: Table 11.

3.1.4 Carbapenem versus penicillin

3.1.4.1.1 Imipenem with cilastatin versus piperacillin-clindamycin

Bouter et al. (1996) assessed the efficacy and safety of imipenem with cilastatin (IV) compared with piperacillin-clindamycin (IV) in adults hospitalised with diabetic foot lesions (n=45) confirmed by clinical assessment (Wagner stages 2, 3 or 4; having an ankle/brachial index of ≤0.45). Adults randomly received imipenem with cilastatin 500 mg four times a day (n=21) or piperacillin 3000 mg four times a day in combination with clindamycin 600 mg three times a day (n=24) for at least 10 days. If people's clinical condition worsened after 72 hours, treatment was discontinued. In cases of chronic osteomyelitis, antibiotic treatment was continued with ciprofloxacin (500 mg twice a day) or ofloxacin (400 mg twice a day) and/or clindamycin (600 mg three times a day) depending on culture results. People were followed-up every 3 days and after treatment completion (at least 10 days).

Overall there was no significant difference between imipenem with cilastatin and piperacillin-clindamycin for clinical cure at 10 days follow-up (n=45, 19% versus 25%, RR 0.76, 95% CI 0.25 to 2.34, very low quality evidence). There was a significant

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difference in the number of people having treatment-related adverse effects, with people prescribed imipenem with cilastatin having significantly less adverse effects than those prescribed piperacillin-clindamycin (n=45, 14.3% versus 50%, RR 0.29 95%CI 0.09 to 0.88, low quality evidence).

See GRADE profiles: **Table** 12.

3.1.4.1.2 Imipenem with cilastatin versus ampicillin with sulbactam

Grayson et al. (1994) assessed the efficacy and safety of imipenem with cilastatin (IV) compared with ampicillin with sulbactam (IV) in adults aged 18 years and over (mean age 60) with diabetes and a limb-threatening infection involving the lower extremity who needed hospitalisation or had received antibiotic treatment which had not worked and had an eligible pathogen. People randomly received imipenem with cilastatin 500 mg every 6 hours (n=48) or ampicillin with sulbactam 3 g every 6 hours (n=48) for 5 days.

Overall there were no significant difference between imipenem with cilastatin and ampicillin with sulbactam for the number of infections cured at 6-day follow-up (n=96, 81.3% versus 85.4%, RR 0.95, 95% CI 0.80 to 1.14, moderate quality evidence). There was also no significant difference in adverse effects leading to withdrawal of study treatment (n=93, 15.2% versus 19.1%, RR 0.79, 95%CI 0.32 to 1.96, very low quality evidence).

See GRADE profiles: Table 13.

3.1.4.1.3 Ertapenem versus piperacillin with tazobactam

Lipsky et al. (2005a) assessed the efficacy and safety of ertapenem (IV) compared with piperacillin with tazobactam (IV) in adults (mean age 58) with diabetes and a foot infection that did not extend above the knee and was classified as moderate-to-severe and requiring intravenous antibiotics. Adults randomly received ertapenem 1 g once a day, followed by a saline placebo every 6 hours for 3 additional doses (n=295) or piperacillin with tazobactam 3.375 g every 6 hours (n=291) for a minimum of 5 days. People had wounds debrided at baseline or whenever necessary during the study. After 5 days people in either treatment group could be switched to oral co-amoxiclav 875/125 mg every 12 hours for up to 23 days. Vancomycin could also be given to people in either group to ensure adequate coverage for potentially resistant Enterococcus species and meticillin-resistant Staphylococcus aureus (MRSA). People were followed up at 5 days, at discontinuation of IV therapy or at the end of any subsequent oral therapy, and at 10 days after the last dose of IV or oral antibiotic.

Overall, there was no significant difference between ertapenem and piperacillin with tazobactam for the resolution of all signs and symptoms at 5-day follow-up (n=445, 92.2% versus 94.2%, RR 0.98, 95%CI 0.93 to 1.03, moderate quality evidence).

There were also no significant differences in the number of people having treatment-related adverse effects (n=586, 19.6% versus 14.9%, RR 1.31, 95% CI 0.92 to 1.88, low quality evidence) or for withdrawals due to treatment-related adverse effects (n=586, 2.1% versus 1%, RR 2.03, 95% CI 0.51 to 8.03, very low quality evidence).

See GRADE profiles: Table 14.

3.1.4.1.4 Piperacillin with tazobactam versus imipenem with cilastatin

Saltoglu et al. (2010) assessed the efficacy and safety of piperacillin with tazobactam (IV) compared with imipenem with cilastatin (IV) in hospitalised adults (mean age 58)

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with a clinical diagnosis of moderate to severe diabetic lower extremity infection (based on Wagner grades 2-4). Adults randomly received piperacillin with tazobactam 4.5 g three times a day (n=30) or imipenem with cilastatin 500 mg four times a day (n=32) for 14 days. All study participants were followed for 2 months after discharge.

Overall, there were no significant differences between piperacillin with tazobactam and imipenem with cilastatin for a successful clinical response at 5-day follow-up (n=58, 46.7% versus 32.1%, RR 1.66, 95% CI 0.84 to 3.25, low quality evidence). There were also no significant differences in the number of people needing amputations (n=62, 60% versus 68.8%, RR 0.87, 95% CI 0.60 to 1.27, very low quality evidence) or having adverse events (n=62, 30% versus 9.4%, RR 3.20, 95% CI 0.96 to 10.71, very low quality evidence).

See GRADE profiles: Table 15.

3.1.4.1.5 Ertapenem versus piperacillin with tazobactam

Zhang-Rong et al. (2016) compared ertapenem (IV) to piperacillin with tazobactam (IV) in adults with diabetes who had a diabetic foot infection confirmed by screening in a clinic or inpatient department. Adults randomly received daily ertapenem 1.0 g followed by 2 doses of placebo every 8 hours (n=275) or piperacillin with tazobactam 4.5 g every 8 hours (n=275) for 5 to 28 days. Participants were assessed on day 5 of treatment, at discontinuation of IV antibiotics and 10 days after the last dose of antibiotic. Following IV treatment, participants could switch to oral co-amoxiclav 625 mg twice daily. Vancomycin was prescribed at the investigators discretion to cover resistant species if suspected or isolated. The study stratified participants by severity (moderate and severe) using the University of Texas Diabetic Classification System. The study undertook an intention to treat analysis alongside a per protocol analysis, both of which are reported.

Overall, there was no significant difference between treatments for clinical resolution of diabetic foot infection at discontinuation of antibiotic treatment in adults with moderate to severe infections (n=533, 88.8% versus 90.6%, RR 0.98, 95% CI 0.90 to 1.04, high quality evidence).

Additional sub-group analyses were undertaken which found no significant differences between treatments for clinical resolution of diabetic foot infection at discontinuation of antibiotic treatment in adults with moderate infection (n=201, 93.3% versus 90.7%, RR 1.03, 95%CI 0.95 to 1.12, high quality evidence) or severe infection (n=332, 85.9% versus 90.5%, RR 0.95, 95% CI 0.88 to 1.03, high quality evidence). There were no significant differences between treatments for the resolution of signs and symptoms of diabetic foot infection at 5-day follow-up (n=533, 84.3% versus 87.2%, RR 0.97, 95% CI 0.90 to 1.04, high quality evidence) or for the need for more antibiotics at 10-day follow-up after the last dose (n=533, 76.8% versus 76.3%, RR 1.01, 95% CI 0.92 to 1.11).

There were no significant differences between treatments for serious adverse events (n=550, 6.2% versus 4.4%, RR 1.42, 95% CI 0.69 to 2.91, low quality evidence) or any drug-related serious adverse events (n=550, 0.4% versus 1.1%, RR 0.33, 95% CI 0.03 to 3.18, low quality evidence). However there were a total of 8 deaths, and 6 amputations of lower extremities.

See GRADE profiles: Table 16.

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3.1.5 Cephalosporin versus cephalosporin

3.1.5.1.1 Cefoxitin versus ceftizoxime

Hughes et al. (1987) assessed the efficacy and safety of cefoxitin (IV) compared with ceftizoxime (IV) in adults with a history of peripheral arterial insufficiency or diabetes mellitus and either biologically or empirically confirmed infection. Adults randomly received cefoxitin up to 2 g every 4 hours (n=25) or ceftizoxime up to 4 g every 8 hours (n=28) for a minimum of 5 days. All participants were followed up at 3 days, with subsequent follow-up evaluations at 3, 6, 9, and 12 months.

Overall, there was no significant difference between cefoxitin and ceftizoxime for satisfactory clinical response (n=54, 65.4%, versus 82.1% RR 0.83 95% CI 0.60 to 1.14, low quality evidence). The follow-up periods varied in the study and the analysis is based on the number of participants with a satisfactory clinical response. There was also no significant difference between treatments in the number of people having treatment-related adverse effects (n=63, 63.3%, versus 48.5% RR 1.31, 95% CI 0.84 to 2.04, low quality evidence).

See GRADE profiles: Table 17.

3.1.5.1.2 Ceftriaxone versus cefazolin

Bradsher et al. (1984) assessed the efficacy and safety of ceftriaxone (IV or IM) compared with cefazolin (IV) in hospitalised adults (mean age 56) with skin and soft tissue infections. Adults randomly received ceftriaxone 1 g once a day (n=42) or cefazolin 1 g every 6 hours or every 8 hours depending on treatment site (n=42) and were followed up at 7 days. Of those included in the study (n=84), 20 participants had a diabetic foot infection (n=10 received or every 8 hours depending on treatment site; n=10 received ceftriaxone 1g (IV or IM) once a day or cefazolin 1 g (IV) every 6 hours).

Overall, there was no significant difference between ceftriaxone and cefazolin for cure defined as the resolution of signs and symptoms of infection (n=84, 50% versus 59.5%, RR 0.84, 95% CI 0.57 to 1.24; very low quality evidence), for treatment-related adverse effects (n=84, 28.6% versus 31%, RR 0.92, 95% CI 0.48 to 1.78, very low quality evidence), or for the number of surgical procedures (n=84, 35.7% versus 28.6%, RR 1.25, 95% CI 0.67 to 2.34, very low quality evidence) at 7 days follow-up.

See GRADE profiles: Table 18.

3.1.6 Cephalosporin versus penicillin

3.1.6.1.1 Cefoxitin versus ampicillin with sulbactam

Erstad et al. (1997) assessed the efficacy and safety of cefoxitin (IV) compared with ampicillin with sulbactam (IV) in adults (mean age 59) with at least a grade 1 foot infection. Adults randomly received cefoxitin 2 g every 6 hours (n=18) or ampicillin with sulbactam 3 g every 6 hours (n=18) for at least 5 days, but the maximum duration was left to the discretion of the attending surgeon. Participants were followed up daily until treatment was stopped.

Overall, there was no significant difference between cefoxitin and ampicillin with sulbactam for cure defined as the disappearance of all signs and symptoms associated with active infection at 5-day follow-up (n=36, 38.9% versus 5.6%, RR 7.00, 95% CI 0.95 to 51.25, low quality evidence) or for length of hospital stay (n=36,

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12.1 days [range 4 to 39] versus 21.1 days [range 6 to 58], p=0.06, low quality evidence). There was no significant difference in the number of patients who had a treatment-related adverse effect (n=36, 33.3% versus 38.9%, RR 0.86, 95%CI 0.36 to 2.05, very low quality evidence).

See GRADE profiles: Table 19.

3.1.7 Fluoroquinolone versus penicillin with beta-lactamase inhibitor

3.1.7.1.1 Moxifloxacin versus piperacillin with tazobactam then co-amoxiclav

Schaper et al. (2012) assessed the efficacy and safety of moxifloxacin (IV or oral) compared with piperacillin with tazobactam (IV) then co-amoxiclav (oral) in adults (mean age 59) with a diagnosed diabetic foot infection. Adults randomly received moxifloxacin 400 mg IV or oral once a day (n=110) or piperacillin with tazobactam 4 g/0.5 g IV three times a day then oral co-amoxiclav 875/125mg twice a day (n=96) for a minimum of 7 days up to a maximum of 21 days. Outcomes were assessed during treatment (days 3 to 5), at the end of treatment (7 to 21 days after inclusion) and at test of cure (14 to 21 days after the end of treatment).

Overall, there was no significant difference between moxifloxacin and piperacillin with tazobactam then co-amoxiclav for cure defined as the disappearance of all signs and symptoms associated with active infection (n=206, 76.4% versus 78.1%, RR 0.98, 95%CI 0.84 to 1.13, moderate quality evidence) at 6-day follow-up. There were also no significant differences in additional surgeries requiring amputation (n=206, 20.9% versus 25%, RR 0.84, 95% CI 0.51 to 1.38, very low quality evidence) or the number of people having significant adverse effects (n=233, 30.9% versus 31.8%, RR 0.97 95% CI 0.66 to 1.42, very low quality evidence).

See GRADE profiles: Table 20.

3.1.7.1.2 Clinafloxacin versus piperacillin with tazobactam then co-amoxiclav

Siami et al 2001 assessed the efficacy and safety of clinafloxacin (IV then oral) compared with piperacillin with tazobactam (IV) then co-amoxiclav (oral) in hospitalised adults (median age 52 and 54 respectively) with complicated skin and skin structure infections of which 19% (n=76) had a diagnosed diabetic foot infection. Adults with diabetic foot infection randomly received clinafloxacin 200 mg (IV) every 12 hours for 3 days, then switched to oral clinafloxacin 200 mg every 12 hours (n=42) or piperacillin with tazobactam 3.375 g (IV) every 6 hours for 3 days, then switched to oral co-amoxiclav 500 mg every 8 hours (n=34). Treatment was given for no longer than 14 days. Vancomycin was added to the piperacillin with tazobactam regimen if MRSA was suspected (number not provided in study). Participants were followed up at test for cure (6 to 14 days post treatment) and at 21 to 35 days post treatment.

Overall, there was no significant difference between clinafloxacin and piperacillin with tazobactam then co-amoxiclav for cure or improvement defined as the remission of signs and symptoms of baseline infection (n=54, 51.7% versus 48%, RR 1.07, 95%CI 0.63 to 1.85, very low quality evidence) at 14 days follow-up.

See GRADE profiles: Table 21.

3.1.7.1.3 Ofloxacin versus ampicillin with sulbactam then co-amoxiclav

Lipsky et al. (1997) assessed the efficacy and safety of ofloxacin (IV then oral) compared with ampicillin with sulbactam (IV) then co-amoxiclav (oral) in adults with diabetes and a foot infection (mean age 62). Adults randomly received ofloxacin

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400 mg (IV then oral) every 12 hours (n=47) or ampicillin with sulbactam 1-2 g/0.5-1 g (IV) every 6 hours then co-amoxiclav 500/125 mg (oral) every 8 hours. Metronidazole was added to the ofloxacin regimen to improve coverage of anaerobic bacteria, and gentamicin, co-trimoxazole, or another agent was added to the amino-penicillin regimen for broader coverage of Gram-negative bacilli if participants did not improve. Participants were followed up at 3 to 7 days or until treatment was completed (14 to 28 days).

Overall, there was no significant difference between ofloxacin and ampicillin with sulbactam then co-amoxiclav for cure defined as the disappearance of all signs and symptoms associated with active infection (n=88, 85.1% versus 82.9%, RR 1.03, 95% CI 0.85 to 1.23, moderate quality evidence) at 7 days follow-up. There was no significant difference between treatments for the number of participants having a treatment-related adverse event (n=88, 36.2% versus 22%, RR 1.65, 95% CI 0.83 to 3.29, low quality evidence).

See GRADE profiles: Table 22.

3.1.7.1.4 Moxifloxacin versus co-amoxiclav

Vick-Fragoso et al. (2009) assessed the efficacy and safety of moxifloxacin (IV then oral) compared with co-amoxiclav (IV then oral) in adults (mean age 52) with complicated skin and skin structure infections (n=804). The study undertook a per protocol analysis to assess the clinical efficacy of treatments (n=622) and an intention to treat analysis which assessed the microbiological efficacy of treatments (n=339). People with diabetic foot infection made up 16% of the study (n=134). Adults randomly received moxifloxacin 400 mg (IV) once daily for 3 days followed by oral moxifloxacin 400 mg once daily (n=406) or co-amoxiclav 1000 mg/200 mg (IV) three times a day for at least 3 days followed by oral co-amoxiclav 500/125 mg three 3 times a day (n=397) for 7 to 21 days. Participants were followed-up at 14 to 28 days.

Overall, there were no significant differences between moxifloxacin and co-amoxiclav for cure defined as the disappearance of all signs and symptoms associated with active infection (n=632, 80.6% versus 84.5%, RR 0.95, 95% CI 0.88 to 1.02, low quality evidence) at 14 to 28-day follow-up. There were no significant differences in the mean duration of treatment (13.5 days versus 14.1 days, MD -0.60 days, 95% CI -1.62 to 0.42, very low quality evidence), adverse effects (n=803, 52.0% versus 47.9%, RR 1.09, 95% CI 0.95 to 1.25, very low quality evidence) or serious adverse events (n=803, 14% versus 11.3%, RR 1.24, 95% CI 0.86 to 1.79, very low quality evidence) between treatments at 14 to 28-day follow-up. Sensitivity analysis was undertaken on the population of the study with diabetic foot infection and there was no significant difference between treatments for cure (n=112, 51% versus 66.7%, RR 0.77, 95% CI 0.55 to 1.06, low quality evidence).

See GRADE profiles: Table 23.

3.1.7.1.5 Moxifloxacin versus piperacillin with tazobactam then co-amoxiclav

Lipsky et al. (2007) assessed the efficacy and safety of moxifloxacin (IV then oral) compared with piperacillin with tazobactam (IV) then co-amoxiclav (oral) in adults (mean age 56) with complicated skin and skin structure infections, confirmed by at least 1 sign or symptom of wound infection, that required hospitalisation and IV antibiotics (n=607). Of the total population, 21% (n=127) had a diabetic foot infection. Adults with diabetic foot infections (n=127) randomly received moxifloxacin 400 mg/day (IV then oral) (n=63) or piperacillin with tazobactam 3.0 g/0.375 g every 6 hours (IV) then oral co-amoxiclav suspension 800 mg every 12 hours (n=64). IV

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treatment was given for a minimum of 3 days, then continued or switched to oral treatment with a total treatment duration of 7 to 14 days. Participants were followed up at 10 to 42 days after completing antibiotic treatment.

Overall, there were no significant differences between moxifloxacin and piperacillin with tazobactam then co-amoxiclav for cure defined as the resolution of all signs and symptoms or sufficient improvement such that additional antibiotics were not required (n=127, 44.4% versus 39.1%, RR 1.14, 95% CI 0.75 to 1.72, moderate quality evidence) at 10 to 42 days follow-up. There was no significant difference between treatments for withdrawals due to treatment-related adverse events (n=127, 23.8% versus 23.4%, RR 1.02, 95%CI 0.54 to 1.90, low quality evidence) but there was a significant difference in the number of people who had treatment-related adverse effects at 10 to 42 days follow-up, with people prescribed moxifloxacin having significantly more adverse effects at 10 to 42 days follow-up than those prescribed piperacillin with tazobactam then co-amoxiclav (n=127, 31.7% vs 12.5%, RR 2.54, 95% CI1.21 to 5.34, moderate quality evidence).

See GRADE profiles: Table 24.

3.1.8 Other antibiotic comparisons

3.1.8.1.1 Clindamycin versus cefalexin

Lipsky et al. (1990), assessed the efficacy and safety of oral clindamycin compared with oral cefalexin in adults (mean age 61) with diabetes who had non-limb threatening lower extremity infections confirmed by clinically infected lesions (n=56). Adults randomly received clindamycin 300 mg (n=27) or cefalexin 500 mg (n=29) four times a day for 2 weeks. Participants were followed up at 2 weeks.

Overall, there were no significant differences between clindamycin and cefalexin for complete lesion healing (n=52, 40% versus 33.3%, RR 1.20, 95% CI 0.59 to 2.46, very low quality evidence) or for adverse events (n=52, 4% versus 7.4%, RR 0.54, 95% CI 0.005 to 5.59, very low quality evidence).

See GRADE profiles: Table 25.

3.1.8.1.2 Linezolid versus ampicillin with sulbactam or co-amoxiclav

Lipsky et al. (2004) assessed the efficacy and safety of linezolid (IV or oral) compared with ampicillin with sulbactam (IV) or co-amoxiclav (oral) in adults (mean age 63) with diabetes and a foot infection defined as cellulitis, paronychia, infected ulcer, deep soft-tissue infection, septic arthritis, abscess, or osteomyelitis. Participants with osteomyelitis were enrolled if a 4-week antibiotic regimen was considered to be sufficient for treatment. Adults randomly received linezolid 600 mg (IV or oral) every 12 hours (n=203) or ampicillin with sulbactam 1.5-3 g (IV) every 6 hours or co-amoxiclav 500-875 mg (oral) every 8 to 12 hours (n=108). Participants also received twice-daily dressing changes and periodic debridement as needed throughout the study. Participants were followed up at 15-21 days.

Overall, there were no significant differences between linezolid and ampicillin with sulbactam or co-amoxiclav for cure defined as the resolution of all signs and symptoms (n=311, 81.3% versus 71.3%, RR 1.14, 95% CI 0.99 to 1.31, low quality evidence) at 15 to 21 days follow-up.

There was no significant difference between treatments for withdrawals due to treatment-related adverse events (n=361, 7.5% versus 3.3%, RR 2.24, 95% CI 0.78 to 6.47, low quality evidence) but there was a significant difference in the number of

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people who had treatment-related adverse effects, with people prescribed linezolid having significantly more than those prescribed ampicillin with sulbactam or co-amoxiclav (n=361, 26.6% vs 10%, RR 2.66, 95% CI 1.49 to 4.73, moderate quality evidence).

See GRADE profiles: **Table** 26.

3.1.8.1.3 Daptomycin versus a semi-synthetic penicillin

Lipsky et al. (2005b) assessed the efficacy and safety of daptomycin (IV) compared with a semi-synthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin at the investigators choice) (IV) in adults (mean age 62) with diabetes requiring hospitalisation for an infected ulcer that was known or suspected to be caused by a Gram-positive organism, based on a Gram-stained smear (n=133). Adults randomly received daptomycin 4 mg/kg every 24 hours or a semi-synthetic penicillin given in equally divided doses totalling 4-12 g per day for 7 to 14 days. For suspected or proven polymicrobial infection, aztreonam to cover Gram-negative bacteria or metronidazole to cover obligate anaerobic bacteria was added at the investigators' discretion. Wound care, including debridement and pressure off-loading was provided where appropriate. Participants were followed-up at the end of treatment (within 3 days of the last dose of study drug), at 'test-of-cure' (within 6–20 days after completing treatment) and at 'post-study' (within 20–28 days after completing treatment).

Overall, there was no significant difference between daptomycin and a semi-synthetic penicillin for cure defined as resolution of all signs and symptoms (n=52, 64% versus 70.4%, RR 0.91, 95%CI 0.62 to 1.33, very low quality evidence).

See GRADE profiles: **Table** 27.

3.1.8.1.4 Daptomycin versus vancomycin

Lipsky et al. (2005b) assessed the efficacy and safety of daptomycin (IV) compared with vancomycin (IV) in adults (mean age 62) with diabetes requiring hospitalisation for an infected ulcer that was known or suspected to be caused by a Gram-positive organism, based on a Gram-stained smear (n=133). Adults randomly received daptomycin 4 mg/kg every 24 hours or vancomycin 1 g every 12 hours for 7 to 14 days. For suspected or proven polymicrobial infection, aztreonam to cover Gram-negative bacteria or metronidazole to cover obligate anaerobic bacteria was added at the investigators discretion. Wound care, including debridement and pressure off-loading was provided where appropriate. Participants were followed up at the end of treatment (within 3 days of the last dose of study drug), at 'test-of-cure' (within 6–20 days after completing treatment) and at 'post-study' (within 20–28 days after completing treatment).

Overall, there was no significant difference between daptomycin and vancomycin for cure defined as resolution of all signs and symptoms (n=43, 71.4% versus 69.0%, RR 1.04, 95%CI 0.69 to 1.56, very low quality evidence) at 6 to 20 days follow-up.

See GRADE profiles: **Table** 28.

3.1.9 Antibiotic dual treatment in adults

3.1.9.1.1 Metronidazole plus ceftriaxone versus ticarcillin with clavulanic acid

Clay et al. (2004) assessed the efficacy and safety of metronidazole plus ceftriaxone (IV) compared with ticarcillin with clavulanic acid (IV) in hospitalised adults (mean

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age 64) with a diagnosis of diabetes and a clinical diagnosis of a diabetic lower-extremity infection confirmed by physical signs of infection (n=70). Adults randomly received metronidazole 1 g plus ceftriaxone 1 g once a day (n=36) or ticarcillin with clavulanic acid 3.1 g every 6 hours (n=34), with treatment duration varying and participants followed up at 4 days.

Overall, there were no significant differences between metronidazole plus ceftriaxone compared with ticarcillin with clavulanic acid for cure defined as disappearance of all signs and symptoms associated with active infection (n=70, 86% versus 82%, RR 1.05, 95% CI 0.85 to 1.28, low quality evidence) at 4 days follow-up or for mean duration of treatment (n=70, 6.7 days versus 6.1 days, MD -0.60, 95%CI -1.20 to 2.40, low quality evidence).

See GRADE profiles: Table 29.

3.1.9.1.2 Amdinocillin plus cefoxitin versus cefoxitin

File et al. (1983) assessed the efficacy and safety of amdinocillin plus cefoxitin (IV) compared with cefoxitin (IV) in hospitalised adults (mean age 56) with clinical evidence of bacterial soft tissue infection (n=45); most participants had diabetes mellitus (n=25) and an infection localised to the lower extremities (n=37). Adults randomly received amdinocillin 10mg/kg every 6 hours plus cefoxitin 1-2 g every 4 to 6 hours or cefoxitin 1-2 g every 4 to 6 hours, with treatment duration varying and participants followed up at 6 to 20 days.

Overall, there were no significant differences between amdinocillin plus cefoxitin and cefoxitin for satisfactory clinical response defined as cure or improvement of presenting signs and symptoms (n=41, 90% versus 71.4%, RR 1.26, 95% CI 0.93 to 1.70, very low quality evidence) or for the number of patients requiring amputation (n=41, 10% versus 19%, RR 0.53, 95% CI 0.11 to 2.56, very low quality evidence) at 6 to 20 days follow-up.

See GRADE profiles: **Table** 30.

3.1.10 Antibiotic dose frequency

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.11 Antibiotic course length

The evidence for antibiotic course length in people with diabetic foot infections comes from 1 newly identified randomised control trial in adults (Tone et al. 2015), with no studies identified in NICE Clinical Guideline19: Diabetic foot problems - Prevention and management (NICE 2015). The following comparison was included:

- Short-course (6 weeks) empirical antibiotic (IV or oral) versus long-course (12 weeks) empirical antibiotic (IV or oral).

3.1.11.1.1 Short-course versus long-course antibiotics

Tone et al. (2015) compared the effectiveness and tolerance of a 6-week (n=20) versus a 12-week (n=20) course of antibiotics. The antibiotics used included rifampicin (n=27), levofloxacin or ciprofloxacin (n=28), or a combination of rifampicin and a fluoroquinolone (n=19) as first-line antibiotics in adults (mean age 64) with non-surgically treated diabetic foot osteomyelitis (n=53). All participants received standardised debridement and wound care as appropriate.

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Overall, there were no significant differences between 6 weeks and 12 weeks duration of antibiotic treatment for overall remission (n=40, 60% versus 70%, RR 0.86, 95%CI 0.54 to 1.36, very low quality evidence), complete healing sustained for at least 4 consecutive weeks (n=40, 90% versus 80%, RR 1.13, 95%CI 0.86 to 1.46, low quality evidence), major amputation (n=40, 10% versus 10%, RR 1.00, 95%CI 0.16 to 6.42, very low quality evidence) or for antibiotic-related gastrointestinal adverse events (n=40, 15% versus 45%, RR 0.33, 95%CI 0.11 to 1.05, low quality evidence).

See Grade profiles: **Table 31**.

3.1.12 Antibiotic route of administration in adults

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.13 Children and young people

No systematic reviews or randomised controlled trials met the inclusion criteria

3.1.14 Prevention

No systematic reviews or randomised controlled trials met the inclusion criteria

3.1.15 The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the outcomes that mattered most were any that indicated cure, improvement or resolution of diabetic foot infection and any adverse events associated with treatment.

The quality of the evidence

The quality of evidence for antibiotics compared to other antibiotics ranged from very low to high.

The quality of evidence for duration of treatment was very low to low.

There was no evidence for antibiotic dose, frequency or route of administration.

There was no evidence of antibiotic use in children and young people.

There was no evidence for the use of antibiotics to prevent diabetic foot infection.

Benefits and harms

Efficacy of antibiotics versus other antibiotics

Overall, there were no differences in the clinical effectiveness of the following antibiotic comparisons in adults with diabetic foot infection, with or without osteomyelitis:

- Oral clindamycin compared with oral cefalexin (Lipsky et al. 1990)
- IV or oral fluoroquinolone (moxifloxacin; clinafloxacin; ofloxacin) compared with IV or oral penicillin with a beta-lactamase inhibitor (piperacillin with tazobactam then

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co-amoxiclav [vancomycin was added if MRSA was suspected], ampicillin with sulbactam then co-amoxiclav [gentamicin, co-trimoxazole, or another antibiotic was added for broader coverage of gram-negative bacteria if required] or co-amoxiclav) (Schaper et al. 2013; Siami et al 2001; Lipsky et al. 1997; Vick-Fragoso et al. 2009; Lipsky et al. 2007)

- IV or oral linezolid compared with IV ampicillin with sulbactam or oral co-amoxiclav (Lipsky et al. 2004)
- IV penicillin with a beta-lactamase inhibitor (piperacillin with tazobactam) compared with IV penicillin with a beta-lactamase inhibitor (ticarcillin with clavulanic acid or ampicillin with sulbactam) (Tan et al. 1993; Harkless et al. 2005)
- IV glycycline (tigecycline) compared with IV carbapenem (ertapenem, with or without vancomycin) (Lauf et al. 2014)
- IV carbapenem (imipenem with cilastatin or ertapenem) compared with IV penicillin (piperacillin with clindamycin, ampicillin with sulbactam or piperacillin with tazobactam) (Paul-Bouter et al. 1996; Grayson et al. 1994; Lipsky et al. 2005a; Saltoglu et al. 2010; Zhang-Rong et al. 2016)
- IV cephalosporin (cefoxitin or ceftriaxone) compared with IV cephalosporin (ceftizoxime or cefazolin) (Hughes et al. 1987; Bradsher et al. 1984)
- IV cephalosporin (cefoxitin) compared with IV penicillin with a beta-lactamase inhibitor (ampicillin with sulbactam) (Erstad et al 1997)
- IV daptomycin compared with IV semi-synthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin (Lipsky et al. 2005b)
- IV daptomycin compared with IV vancomycin (Lipsky et al. 2005b)
- IV metronidazole plus IV ceftriaxone compared with IV ticarcillin with clavulanic acid (Clay et al. 2004)
- IV amdinocillin plus IV cefoxitin compared with IV cefoxitin (File et al. 1983).

Based on 21 RCTs.

Safety of antibiotics

Overall, in the studies, there were no differences between antibiotics in most comparisons in people with diabetic foot infection, with or without osteomyelitis. Some differences were seen for the following comparisons:

- IV tigecycline had a significantly higher number of adverse events (71.1% versus 57%) and study withdrawals due to adverse events (2.1% versus 0.43%) compared with IV ertapenem with or without vancomycin (Lauf et al 2014)
- IV imipenem with cilastatin had a significantly lower number of adverse events compared with IV piperacillin-clindamycin (14.3% versus 50%; Bouter et al. 1996)
- IV then oral moxifloxacin had a significantly higher number of adverse events compared with IV piperacillin with tazobactam then oral co-amoxiclav (31.7% vs 12.5%; Lipsky et al. 2007)
- IV linezolid had a significantly higher number of adverse events compared with IV ampicillin with sulbactam or oral co-amoxiclav (26.6% vs 10%; Lipsky et al. 2004).

Antibiotic course length

Short-course antibiotics (6 weeks) were not significantly different to long-course antibiotics (12 weeks) for overall remission, complete healing, major amputation, or antibiotic-related gastrointestinal adverse events in adults with non-surgically treated diabetic foot osteomyelitis (1 RCT; Tone et al 2015).

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Cost effectiveness and resource use

The committee discussed the resource implications for the recommendations made and agreed that there would not be any resource use implications for this guidance.

It was agreed that the cost of the majority of antibiotics recommended is relatively low. In cases where more expensive antibiotics may be used for more severe infections, the cost of the antibiotic and any associated monitoring would be minimal compared to the costs and consequences of possible complications resulting from inappropriate or delayed treatment.

Other factors the committee took into account

Treatment

The committee agreed that all foot wounds in people with diabetes are likely to be colonised with bacteria, but a diabetic foot infection is characterised by the presence of at least 2 of the classic findings of infection (local swelling or induration, erythema, local tenderness or pain, local warmth, or purulent discharge). The committee agreed with the Infectious Diseases Society of America definitions of mild, moderate and severe infection, which are referred to in the NICE guideline on diabetic foot problems. However, they acknowledged that the populations within the studies did not always differentiate between severities of diabetic foot infection.

The committee agreed with the recommendation from the NICE guideline on diabetic foot problems, that antibiotics should be started as soon as possible for people with a suspected diabetic foot infection because prompt treatment is required to prevent complications. They also agreed that cultures and samples should be taken for microbiological testing before, or as close as possible to, the start of antibiotic treatment, to enable empirical antibiotic treatment to be amended as appropriate when results are available.

Choice of treatment

The committee discussed the evidence for the effectiveness of different antibiotics for treating diabetic foot infections. It was noted that no evidence was identified for children or young people. The committee agreed that this reflects their clinical experience that a diabetic foot infection in a child or young person is unlikely and they did not make recommendations on antibiotic choice for children and young people.

The committee noted that most antibiotics compared with another antibiotic showed no difference in clinical outcomes. However, the committee discussed that the antibiotics in the evidence review were not wholly representative of UK practice, with some not being available in the UK and others not widely used.

The committee noted that there were no differences in adverse events between many antibiotic comparisons. However, they noted that there were differences in adverse events between some antibiotic classes, with lower rates generally being seen for beta-lactam antibiotics compared with other classes.

The committee agreed, based on evidence and their experience, that the choice of antibiotic should be based on severity of infection (mild, moderate or severe) and the risk of developing complications, whilst minimising side effects and the risk of developing antibiotic resistance (using narrow spectrum antibiotics first, where possible). When available, microbiological results should be used to guide treatment. Patient preference is also important to consider when choosing antibiotics, particularly relating to the need for inpatient treatment, or prolonged treatment.

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Diabetes is a chronic condition and people may have had previous foot infections, with previous courses of antibiotics, that will influence their preferences.

Antibiotic dose frequency and route of administration

The committee acknowledged that there was no evidence identified for antibiotic dose frequency or route of administration. However, they discussed that a person with a diabetic foot infection may already be on a number of other medications, and this should be taken into account.

In line with the NICE guideline on antimicrobial stewardship and Public Health England's Start smart – then focus, the committee agreed that oral antibiotics should be used in preference to intravenous antibiotics where possible. Intravenous antibiotics should only be used for people who are severely ill, unable to tolerate oral treatment, or where oral treatment would not provide adequate coverage or tissue penetration. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and any microbiological results) and switched to oral treatment where possible.

Antibiotic course length

The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of side effects.

The committee discussed the limited evidence on course length, which compared 6 weeks with 12 weeks of antibiotic treatment in adults with non-surgically treated diabetic foot osteomyelitis.

Based on limited evidence and their experience, the committee agreed that a shorter course of antibiotics was generally as effective as a longer course of antibiotics for adults with a mild diabetic foot infection, and a 7-day course was sufficient for most people. The committee discussed that a longer course (up to a further 7 days) may be needed for some people based on a clinical assessment of their symptoms and history.

For people with a moderate or severe diabetic foot infection (which includes osteomyelitis), course length will vary based on a clinical assessment of their response to treatment. The committee discussed that a 7-day course would be a minimum, with antibiotic treatment for up to 6 weeks if people have osteomyelitis. Where prolonged antibiotic treatment is given, for example in osteomyelitis, they discussed the importance of reviewing the need for continued antibiotics regularly.

Advice

The committee made the recommendations by consensus and based on recommendations in the NICE guideline on antimicrobial stewardship (NG15). The committee agreed by consensus that if symptoms worsened rapidly or significantly at any time, or did not improve within 2 to 3 days then people with diabetic foot infection should be advised to seek medical help.

Safety

The committee considered the following information about the safety of various drugs was important:

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- Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).
- About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta lactam antibiotics (BNF, May 2019). See the NICE guideline on drug allergy: diagnosis and management (2014) for more information.
- Cholestatic jaundice and hepatitis can occur with flucloxacillin up to 2 months after stopping treatment, with risk factors being increasing age and use for more than 14 days (BNF, May 2019). Cholestatic jaundice can also occur with co-amoxiclav, and is more common in people over 65 years and in men; treatment should not usually exceed 14 days (BNF, May 2019).
- Macrolides, including clarithromycin and erythromycin, should be used with caution in people with a predisposition to QT interval prolongation. Common side effects, such as nausea, vomiting, abdominal discomfort, and diarrhoea, are less frequent with clarithromycin than with erythromycin (BNF, May 2019).
- Tetracyclines, including doxycycline, can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to pregnant or breast-feeding women, and use in children under 12 years is either contraindicated or cautioned for use in severe or life-threatening infections where there are no alternatives (BNF, May 2019).
- Co-trimoxazole is associated with rare but serious side effects including blood disorders and Stevens-Johnson syndrome. It is cautioned for use in older people because there is an increased risk of serious side effects, and in those with a predisposition to hyperkalaemia because this is a very common side effect. Monitoring of blood counts is recommended with prolonged treatment (BNF, May 2019).
- Fluoroquinolones, including ciprofloxacin, have restrictions and precautions around their use because of rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems (MHRA Drug Safety Update, March 2019). They may also be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people (MHRA Drug Safety Update, November 2018).
- Aminoglycoside (for example gentamicin) doses are based on body weight and renal function. Ototoxicity and nephrotoxicity are important side effects to consider, and whenever possible treatment should not exceed 7 days (BNF, May 2019).
- Clindamycin has been associated with antibiotic-associated colitis and diarrhoea. Although this can occur with most antibiotics, it is more frequent with clindamycin. Monitoring of liver and renal function is recommended if treatment exceeds 10 days, and in infants (BNF, May 2019).
- Glycopeptide (for example vancomycin and teicoplanin) doses are based on body weight. Therapeutic drug monitoring and monitoring of various patient parameters including blood count, urinalysis, auditory function, hepatic function and renal function is recommended depending on the particular glycopeptide (BNF, May 2019).
- Severe optic neuropathy can occur with linezolid, particularly if used for longer than 28 days. Blood disorders have also been reported and weekly full blood counts are recommended (BNF, May 2019).

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Reassessment

The committee made the recommendations by consensus, that where microbiological results are available, they should be used to guide antibiotic choice. The committee also discussed factors that would indicate that a person with diabetic foot infection would need to be reassessed: theses included a diabetic foot infection that is rapidly or significantly worsening or not improving, other diagnoses, symptoms suggesting a more serious illness or condition and previous antibiotic use.

Prevention

The committee agreed with the recommendation from the NICE guideline on diabetic foot problems, that antibiotics should not be given to prevent diabetic foot infections. No evidence was identified for antibiotic prophylaxis, and the committee discussed that antibiotic prophylaxis is not appropriate because of concerns around antimicrobial resistance. The committee discussed that people should be advised to seek medical help if symptoms of a diabetic foot infection develop.

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4 Terms used in the guideline

Diabetic foot infection

A diabetic foot infection is defined as any type of skin, soft tissue or bone infection affecting tissues below the ankle in people with diabetes and can include cellulitis, paronychia abscesses, myositis tendonitis, necrotising fasciitis, osteomyelitis and septic arthritis (Selva Olid et al 2015, Lipsky 2004). It is defined clinically by the presence of systemic signs of infection related to a foot lesion (usually an ulcer), purulent secretions, or at least 2 signs of inflammation including redness, warmth, pain or tenderness, and tissue hardening (Selva Olid et al 2015).

The Infectious Diseases Society of America guideline on diabetic foot infection [2012]) classify infection severity as:

- Mild: local infection involving only the skin and subcutaneous tissue; if erythema, must be 0.5 to less than 2cm around the ulcer (exclude other causes of inflammatory response, such as trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis and venous stasis).
- Moderate: local infection with erythema more than 2 cm around the ulcer or involving structures deeper than skin and subcutaneous tissues (such as abscess, osteomyelitis, septic arthritis or fasciitis), and no systemic inflammatory response signs.
- Severe: local infection with signs of systemic inflammatory response (such as temperature >38°C or <36°C, increased heart rate or increased respiratory rate).

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Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• Diabetes UK [online] • Diabetic foot problems: prevention and management - NICE guideline [NG19] – NICE 2016 • Kerr 2017 • Selva Olid et al 2015 • Lipsky 2004 • Lipsky et al 2016 • Nelson et al 2017
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2018)

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Key area	Key question(s)	Evidence sources
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving people in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) February 2019 • Summary of product characteristics

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Appendix B: Review protocol

Review question	What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for foot infection (with or without osteomyelitis) in people with diabetes?
Types of review question	Intervention
Objective of the review	To determine the most effective antibiotic regimens and antimicrobial therapies for foot infection in people with diabetes. In line with the major goals of antimicrobial stewardship which includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Children (aged 72 hours and older), young people and adults with type 1 or type 2 diabetes and foot ulcer with soft tissue infection (with or without osteomyelitis or gangrene)
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Any antibiotic regimen or antimicrobial therapy licensed for use in the UK[1]. For the treatment or prevention of diabetic foot infection in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).

1 Antibiotic regimens or antimicrobial therapies include: antibiotics, which includes back-up prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, systemic or topical; and antiseptics

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Eligibility criteria – comparator(s)/ control or reference (gold) standard	• Standard care. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions
Outcomes and prioritisation	• Cure rates of foot infection in people with diabetes • Rates and extent of amputation (major or minor) • Adverse events (treatment failure, healthcare associated infections, side effects of antibiotics, mortality, sepsis) • Length of stay • Health-related quality of life The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).
Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs
Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further inclusions specific to this guideline include: • Studies in which people with diabetes are a subset of the people with foot infection and data is presented separately. Further exclusions specific to this guideline include: • Studies on antibiotic regimens and antimicrobial therapies for people with diabetes and infection in a site other than the foot.

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	• Studies in which people with foot infection is not a subset of the population or where data is not presented separately. • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • non-antimicrobial and non-pharmacological interventions • general management of diabetic foot, for example with offloading, control of ischaemia, wound debridement, wound dressings (including antiseptic or antibacterial wound dressings), electrical stimulation therapy, autologous platelet‑rich plasma gel, regenerative wound matrices, dalteparin, growth factors, or hyperbaric oxygen therapy. • Interventions or comparators not specified in the research protocol for NG19, including surgery
Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). The search may identify studies in populations with or without osteomyelitis. These will be analysed within these categories to enable the production of management recommendations.
Selection process – duplicate screening/ selection/ analysis	The references identified and used in the development of NG19 - Diabetic foot problems: prevention and management (n=21 RCTs) will be taken forward and considered for inclusion in this APG – diabetic foot. Based on committee expertise, studies no longer deemed to be relevant to clinical practice will be excluded with a clear rationale provided. The database searches used for NG19 will be re-run from February 2014 to present All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved.

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	If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes. The committee will consider all final includes from both remaining relevant studies from NG19 and any newly identified studies in the development of the APG – diabetic foot
Data management (software)	Existing GRADE tables from NG19 will be utilised where appropriate and updated depending on the outputs from the re-run searches for the purposes of this APG – diabetic foot Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy database, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process (including Daily Update and Epub Ahead of Print) via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. A summary of the proposed search strategy is given in the appendix below. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries

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	• conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from February 2014 to the present day The results will be downloaded in the following mutually exclusive sets: • Systematic reviews and meta-analysis • Randomised controlled trials Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	Due to the pre-existing clinical guideline NG19 which has antibiotic prescribing recommendations for diabetic foot, this APG on diabetic foot will update the antibiotic recommendations in NG19. On discussion with NICE quality assurance colleagues it was decided that the most efficient way to do this was to consider the outcomes from NG19. All other process will follow those outlined in the interim process guide (2017) - for details please see the interim process guide (2017).
Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.

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Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).
Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).
Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).
Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).
Rationale/ context – Current management	For details please see the interim process guide (2017).
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.

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Sources of funding/support	Developed and funded by NICE.
Name of sponsor	Developed and funded by NICE.
Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.

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Appendix C: Literature search strategy

1 exp Diabetes Mellitus/

2 Diabet*.tw.

3 or/1-2

4 Foot Diseases/

5 Ulcer/

6 Gangrene/

7 Osteomyelitis/ 1

8 soft tissue infections/ or wound infection/ 2

9 ((Foot* or feet* or toe* or tissue* or wound*) adj4 (infect* or disease*)).tw.

10 or/4-9

11 3 and 10

12 Diabetic Foot/

13 (Diabe* adj4 (foot* or feet* or toe* or ulcer* or gangrene* or osteomyelit*)).tw.

14 or/11-13

15 Animals/ not Humans/

16 14 not 15

17 limit 16 to english language

18 Meta-Analysis.pt.

19 Meta-Analysis as Topic/

20 Review.pt.

21 exp Review Literature as Topic/

22 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.

23 (review$ or overview$).ti.

24 (systematic$ adj4 (review$ or overview$)).tw.

25 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.

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26 ((studies or trial$) adj1 (review$ or overview$)).tw.

27 (integrat$ adj2 (research or review$ or literature)).tw.

28 (pool$ adj1 (analy$ or data)).tw.

29 (handsearch$ or (hand adj2 search$)).tw.

30 (manual$ adj2 search$).tw.

31 or/18-30

32 animals/ not humans/

33 31 not 32

34 Randomized Controlled Trial.pt.

35 Controlled Clinical Trial.pt.

36 Clinical Trial.pt.

37 exp Clinical Trials as Topic/

38 Placebos/

39 Random Allocation/

40 Double-Blind Method/

41 Single-Blind Method/

42 Cross-Over Studies/

43 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.

44 (random$ adj2 allocat$).tw.

45 placebo$.tw.

46 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

47 (crossover$ or (cross adj over$)).tw.

48 or/34-47

49 animals/ not humans/

50 48 not 49

51 Epidemiologic Studies/

52 exp Case-Control Studies/

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53 exp Cohort Studies/
54 Cross-Sectional Studies/
55 Comparative Study.pt.
56 case control$.tw.
57 case series.tw.
58 (cohort adj (study or studies)).tw.
59 cohort analy$.tw.
60 (follow up adj (study or studies)).tw.
61 (observational adj (study or studies)).tw.
62 longitudinal.tw.
63 prospective.tw.
64 retrospective.tw.
65 cross sectional.tw.
66 or/51-65
67 animals/ not humans/
68 66 not 67
69 33 or 50 or 68
70 17 and 69
71 17 not 70

Key to search operators in above table

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)

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adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other
?	Wildcard operator – used to retrieve alternate spellings with a single letter variation. For example: *c?t* would retrieve the words *cat*, *cot* and *cut*, and also the acronym *CBT.*

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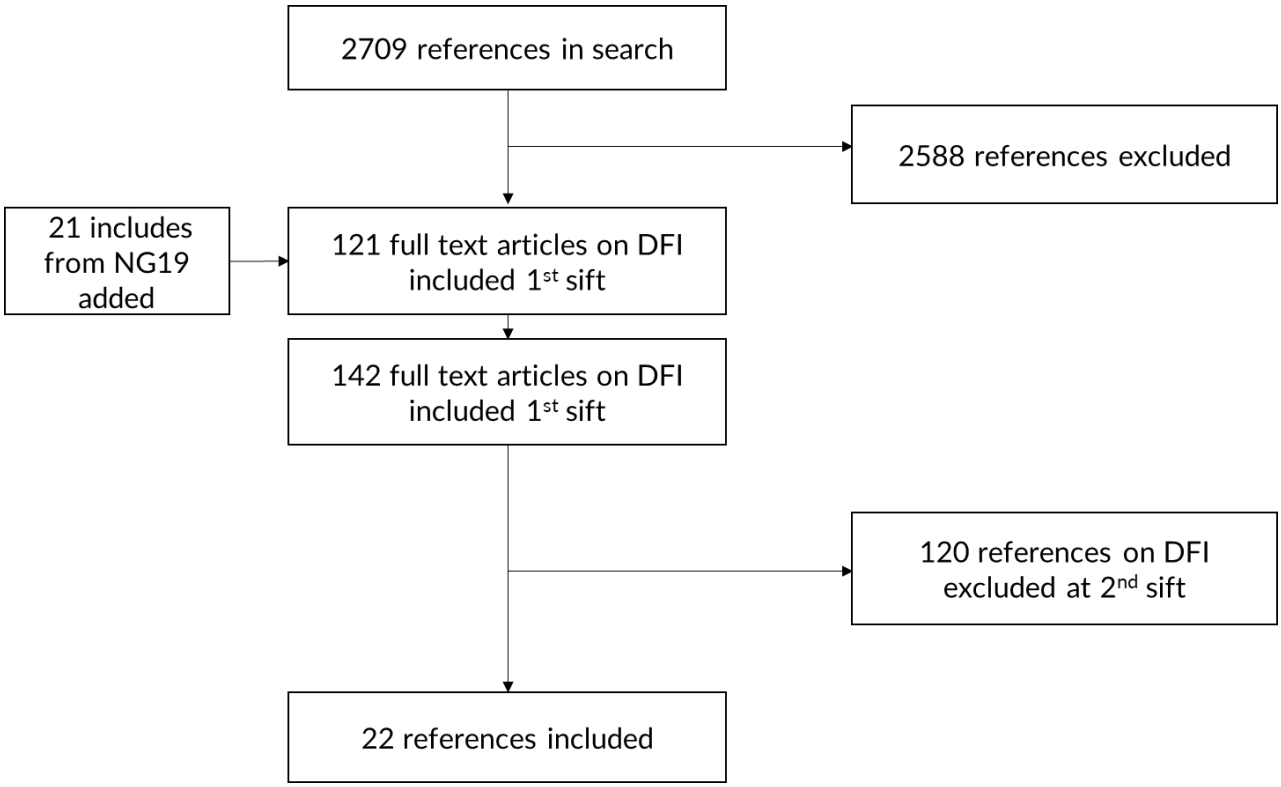
Appendix D: Study flow diagram



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Appendix E: Evidence tables

Short Title	Title	Study Characteristics	Risk of Bias
Bouter et al. (1996)	Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy	**Study type:** RCT **Study details** Study location - Amersfoort, The Netherlands. Study setting - Bosch McdiCentre, Den Bosch and the Eemland Hospital Study dates – not reported Duration of follow-up – Every 3 days and after completion of treatment (at least 10 days) Sources of funding – not reported **Inclusion criteria** Diabetic foot lesions, Wagner Stages II, III or IV, and have an ankle/brachial index (AB1) of at least 0.45. **Exclusion criteria** Patients known to be hypersensitive to any of the study drugs or who had received antimicrobial therapy known or presumed effective against the infecting pathogens within 48 h preceding initiation of treatment were excluded from the study. Patients with a high probability of death within 48 h were also excluded from the study as were patients known to be infected with Xan-thomonas maltophilia other microorganisms known or presumed resistant to the study drugs. **Sample characteristics** The two study populations were similar with regard to age, sex, type of diabetes mellitus and associated conditions. The two study groups	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *No – concealment unclear* **Blinding of outcome assessment** *No – concealment unclear* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		were comparable in terms of baseline severity. **Intervention** Piperacillin 3000 mg QID in combination with clindamycin 600 mg (P/CL)- TID Dosages reduced in patients with renal or liver function impairment. **Control** Imipenem/cilastatin (I/C)- 500 mg QID. Dosages reduced in patients with renal or liver function impairment. **Outcome measure(s)** Clinical response to treatment categorised as: cured, improved, failed and died **Primary outcomes**: Cure (resolution of signs and symptoms at 10 days follow-up): no significant difference between imipenem with cilastatin and piperacillin-clindamycin for clinical cure at 10 days follow-up (n=45, 19% versus 25%, RR 0.76, 95% CI 0.25 to 2.34, very low quality evidence). Treatment related adverse events: significant difference in the number of people having treatment-related adverse effects, with people prescribed imipenem with cilastatin having significantly less adverse effects than those prescribed piperacillin-clindamycin (n=45, 14.3% versus 50%, RR 0.29 95%CI 0.09 to 0.88, low quality evidence).	
Bradsher et al (1984)	Ceftriaxone treatment of skin and soft tissue infections in a once daily regimen	**Study type** *randomised trial*	**Random sequence generation** *Yes* **Allocation concealment** *No - lack of allocation concealment*

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Short Title	Title	Study Characteristics	Risk of Bias
		Study details Study location - USA Study setting - 2 hospitals Study dates – not reported Duration of follow-up - Follow up 7 days Sources of funding – not reported **Inclusion criteria** Eligible participants were hospitalised adults with a suspected serious bacterial infection of the skin and soft tissue. **Exclusion criteria** Patients who had received antibiotics in the previous 72 hours or patients with renal failure, pregnancy, lactation, neutropenia or significant penicillin hypersensitivity. **Sample characteristics** The two treatment groups were comparable with respect to race and sex and there were no major differences in terms of underlying illnesses. The table below shows the baseline demographics for participants in each treatment group **Intervention** 1g every 6 hours or 1g every 8 hours (depending on treatment site) l IV or IM cefazolin **Control** 1g ceftriaxone (IV or IM) once a day **Outcome measure(s)** Cure - Patients were considered cured if there was resolution of signs and symptoms of infection. Toxicity - Patients were monitored daily for signs of toxicity.	**Blinding of participants and personnel** *No - lack of allocation concealment* **Blinding of outcome assessment** *No - lack of allocation concealment* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Primary outcomes Cure (resolution of signs and symptoms of infection) (at 7 days follow-up): No significant difference between ceftriaxone and cefazolin (n=84, 50% versus 59.5%, RR 0.84, 95% CI 0.57 to 1.24; very low quality evidence) Treatment-related adverse effects (at 7 days follow-up): No significant difference between ceftriaxone and cefazolin (n=84, 28.6% versus 31%, RR 0.92, 95% CI 0.48 to 1.78, very low quality evidence), or for Number of surgical procedures (at 7 days follow-up): No significant difference between ceftriaxone and cefazolin the (n=84, 35.7% versus 28.6%, RR 1.25, 95% CI 0.67 to 2.34, very low quality evidence)	
Clay et al. (2004)	Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males,	**Study type** Prospective, open label, randomised controlled trial (RCT) **Study details** Study location - USA Study setting - veterans affairs medical centre Study dates – not outlined Duration of follow-up - After 96 hours of treatment with IV therapy Sources of funding - Roche pharmaceuticals **Inclusion criteria** Eligible participants were adult hospitalised males aged 18 years or over with a diagnosis of type1 or type 2 diabetes and a clinical diagnosis of a diabetic lower-extremity infection (based on physical signs of infection).	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *No - allocation concealment unclear, extracted subgroup data* **Blinding of outcome assessment** *No - allocation concealment unclear, extracted subgroup data* **Incomplete outcome data** *No*

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Short Title	Title	Study Characteristics	Risk of Bias
		Exclusion criteria Exclusion criteria included: bone involvement, hypersensitivity to any of the study medications, receipt of an intravenous (IV) antibiotic for more than 24 hours before study enrolment, presence of neutropenia or thrombocytopenia. **Sample characteristics** All participant baseline demographics in both the MTZ/CTX and T/C groups were generally well matched. The following table shows baseline characteristics of the treatment group **Intervention** Participants in group 1 received 1g IV metronidazole plus 1g IV ceftriaxone once a day. **Control** Participants in group 2 received 3.1g of IV ticarcillin/clavulanate every 6 hours. **Outcome measure(s)** Treatment success - defined as at least 1 of the following measures of clinical stability or improvement at 96 hours: body temperature less than 100.6 F, normalisation of finger stick blood sugar concentration; improvement in wound staging; white blood cell count of less than 10,000/mm3 Patients completing less than 96 hours - patients completing less therapy due to transfer to oral therapy were considered successful if it was noted on patient's chart. Treatment failure at 96 hours - defined as worsening of initial signs and symptoms after receiving 1 dose of study medication; The change or addition of at least 1 more antibiotic to assigned regimen; Occurrence of an adverse event that required discontinuation of study drug.	**Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - open label trial* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Primary outcome Cure at 4 days follow-up (disappearance of all signs and symptoms associated with active infection): No significant differences between metronidazole plus ceftriaxone compared with ticarcillin with clavulanic acid (n=70, 86% versus 82%, RR 1.05, 95% CI 0.85 to 1.28, low quality evidence) Mean duration of treatment: No significant differences between metronidazole plus ceftriaxone compared with ticarcillin with clavulanic acid (n=70, 6.7 days versus 6.1 days, MD -0.60, 95%CI -1.20 to 2.40, low quality evidence).	
Erstad et al (1997)	Prospective, Randomized Comparison of Ampicillin/Sulbactam and Cefoxitin for Diabetic Foot Infections.	**Study type** *Prospective randomised controlled trial (RCT)* **Study details** Study location - Southern Arizona, USA Study setting - University medical centre Study dates – not reported Duration of follow-up - Daily until therapy was stopped Sources of funding – not reported **Inclusion criteria** At least Grade 1 foot infection and had not received successful antimicrobial therapy within the previous four-day period, as noted by clinical improvement. **Exclusion criteria** Known hypersensitivity to penicillins or cephalosporins, a calculated creatinine clearance less than 15 mL/minute, a recent history of drug or alcohol abuse, or a concomitant infection at a site other than the foot that required additional antimicrobials. Patients were also excluded if they were terminally ill, neutropenic (neutrophil count <1500/m3),	**Random sequence generation** *Yes* **Allocation concealment** *No - lack of allocation concealment* **Blinding of participants and personnel** *No - lack of allocation concealment* **Blinding of outcome assessment** *No - lack of allocation concealment* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias**

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Short Title	Title	Study Characteristics	Risk of Bias
		pregnant, or breastfeeding. **Sample characteristics** There were no significant differences in the baseline characteristics of the patients in the two groups on study entry **Intervention** Cefoxitin-2 g every six hours - therapy was given for at least 5 days **Control** Ampicillin/sulbactam — 3 g every six hours - therapy was given for at least 5 days but maximum duration was left to discretion of attending surgeon. **Outcome measure(s)** Cure - complete alleviation of signs and symptoms of infection Improvement - partial alleviation of signs and symptoms of infection Failure - no improvement Bacteriologic evaluation - radication of the causative organisms Adverse events **Primary outcome** Cure at 5-day follow-up (disappearance of all signs and symptoms associated with active infection): No significant difference between cefoxitin and ampicillin with sulbactam (n=36, 38.9% versus 5.6%, RR 7.00, 95% CI 0.95 to 51.25, low quality evidence) Length of hospital stay: No significant difference between cefoxitin and ampicillin with sulbactam (n=36, 12.1 days [range 4 to 39] versus 21.1 days [range 6 to 58], p=0.06, low quality evidence).	*No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Number of patients who had a treatment-related adverse effect: No significant difference between cefoxitin and ampicillin with sulbactam (n=36, 33.3% versus 38.9%, RR 0.86, 95%CI 0.36 to 2.05, very low quality evidence).	
File et al (1983)	Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections)	**Study type** *Single-blind randomised comparative design* **Study details** Study location - Ohio, USA Study setting - city hospital Study dates – not reported Duration of follow-up – varied with monitoring on day 3 of therapy, and periodically during therapy and at end of treatment Sources of funding – not reported **Inclusion criteria** Eligible participants were hospitalised adult patients with clinical evidence of bacterial soft tissue infection. Most patients had diabetes mellitus and for the majority of patients infection was localised to the lower extremities. **Exclusion criteria** Patients were excluded if they were allergic to penicillins or cephalosporins, or if they required other antibiotics during the stud period. **Sample characteristics** Patient in each group were similar in terms of sex age and diagnosis. A total of 32/41 study participants had diabetes or osteomyelitis **Intervention** Participants in the combined group received 1-2g g IV cefoxitin every 4	**Random sequence generation** *Yes* **Allocation concealment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Blinding of participants and personnel** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Blinding of outcome assessment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias**

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Short Title	Title	Study Characteristics	Risk of Bias
		to 6 hours plus 10mg/kg IV amdinocillin every 6 hours. **Control** Participants in the comparator group received 1-2g g IV cefoxitin every 4 to 6 hours. **Outcome measure(s)** Satisfactory symptomatic response - defined as cure (disappearance of all presenting signs and symptoms Secondary outcome measures: Satisfactory bacteriological response – defined as the eradication of a pathogen at end of therapy Unsatisfactory clinical response - defined as no appreciable change or worsening of symptoms at end of therapy. Bacterial persistence - defined as continued presence of pathogen at end of therapy. **Primary outcomes:** Satisfactory clinical response (cure or improvement of presenting signs and symptoms): No significant differences between amdinocillin plus cefoxitin and cefoxitin (n=41, 90% versus 71.4%, RR 1.26, 95% CI 0.93 to 1.70, very low quality evidence) Number of patients requiring amputation at 6 to 20 days follow-up: No significant differences between amdinocillin plus cefoxitin and cefoxitin (n=41, 10% versus 19%, RR 0.53, 95% CI 0.11 to 2.56, very low quality evidence).	*No* **Overall risk of bias** *Serious - lack of allocation concealment* **Directness** *Directly related*
Grayson et al (1994)	Use of Ampicillin/Sulbactam Versus Imipenem/Cilastatin in the Treatment of Limb-Threatening	**Study type** *Randomised Control Trial (RCT)* **Study details** Study location – not reported	**Random sequence generation** *Yes* **Allocation concealment** *No - allocation concealment unclear, extracted subgroup data*

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Short Title	Title	Study Characteristics	Risk of Bias
	Foot Infections in Diabetic Patient	Study setting – not reported Study dates – not reported Duration of follow-up - Daily for first 6 days and then regularly until therapy was completed Sources of funding – not reported **Inclusion criteria** Requirement for hospitalization, age of ≥18 years, and presence of diabetes mellitus and limb- threatening infection involving the lower extremity (limb-threatening infection was defined by at least the presence of cellulitis, with or without ulceration or purulent discharge). Also included were patients who had recently received antibiotic therapy but had failed to demonstrate clinical improvement and whose cultures revealed one or more pathogens were eligible **Exclusion criteria** Known hypersensitivity to β-lactam antibiotics; requirement for other concomitant antibiotic treatment; serum creatinine level of ≥3.5 mg/dL; pregnancy; illness so severe that the patient was likely to die within 48 hours; severe underlying disease that might interfere with evaluation of the therapeutic response; immune depression by virtue of underlying disease, prior organ trans-plantation, or immunosuppressive drug therapy; and current involvement in a clinical study of an investigational drug. **Sample characteristics** Patient in each group were similar in terms of age and duration of diabetes. Patients in the treatment groups were similar in regard to severity of diabetes and presence of peripheral vascular disease, sensory neuropathy, and renal impairment. The sites and severity of infection, including the frequency of osteomyelitis, were similar for both treatment groups.	**Blinding of participants and personnel** *No - allocation concealment unclear, extracted subgroup data* **Blinding of outcome assessment** *No - allocation concealment unclear, extracted subgroup data* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Intervention Imipenem/cilastatin (I/C; 500 mg-IV every 6 hours) - doses were adjusted in patients with impaired renal function. **Control** Ampicillin/sulbactam (A/S; 3 g-IV every 6 hours) - doses were adjusted in patients with impaired renal function. **Outcome measure(s)** Clinical cure, improvement or failure Microbiological outcomes – eradication, partial eradication, persistence, super infection, indeterminate Recurrence Adverse events – significant (severe reaction necessitating withdrawal of the study agent or specific treatment), moderate (a reaction that did not necessitate withdrawal of the study agent or specific treatment), mild (an event uncertainly associated with the study drug) **Primary outcomes:** Number of infections cured at 6-day follow-up: No significant difference between imipenem with cilastatin and ampicillin with sulbactam (n=96, 81.3% versus 85.4%, RR 0.95, 95% CI 0.80 to 1.14, moderate quality evidence). Adverse effects leading to withdrawal of study treatment: No significant difference between imipenem with cilastatin and ampicillin with sulbactam (n=93, 15.2% versus 19.1%, RR 0.79, 95%CI 0.32 to 1.96, very low quality evidence).	
Harkless et al (2005)	An Open-Label, Randomized Study Comparing Efficacy and Safety of Intravenous Piperacillin/Tazobac	**Study type** *Randomised Control Trial (RCT)* **Study details** Study location - Regional areas in United States	**Random sequence generation** *Yes* **Allocation concealment** *Yes*

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Short Title	Title	Study Characteristics	Risk of Bias
	tam and Ampicillin/Sulbactam for Infected Diabetic Foot Ulcers.	Study setting - not reported Study dates – not reported Duration of follow-up - Day 4, day 7, at the end of treatment visit, and at the test-of-cure visit (occurred within 14-21 days of completion of therapy) Sources of funding - **Inclusion criteria** Adult patients with diabetes mellitus and open infected foot ulcers that met the University of Texas Grade IB, ID, IIB, or IID classification of foot ulcers , have at least one full- or partial-thick-ness infected ulcer at or below the ankle. Patients were also required to have purulent drainage or two of the following: Erythema, local edema, fluctuance, induration, increased local warmth, or fever. **Exclusion criteria** Pregnancy or lactation; anticipated amputation of the infected area within two months; conditions requiring concurrent topical antibiotics to the ulcer site or any other systemic antibacterials during the study period; creatinine clearance less than 40 mL/min; conditions requiring immunosuppressive drug treatments; gangrene or severely impaired arterial supply to any portion of the affected foot; hypersensitivity to penicillins, /S-lactamase inhibitors, or vancomycin; presence of organisms known or suspected to be resistant to either study drug; renal insufficiency requiring renal replacement therapy; osteomyelitis; or thrombocytopenia. A patient could be withdrawn from the study for noncompliance, adverse events, investigator belief that withdrawal was in the best interest of the patient, patient choice, lack of efficacy, patient loss to follow-up, or death. Additionally, patients who had infections caused by organisms resistant to randomized treatment were withdrawn from the study.	**Blinding of participants and personnel** *Yes* **Blinding of outcome assessment** *Yes* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - open-labelled trial, no blinding* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Sample characteristics Patients' demographic characteristics, baseline diagnoses, wound classes and ulcer locations, and concomitant diseases were similarly distributed in the two **Intervention** I.V. piperacillin /tazobactam (P/T) (4 g/0.5 g q8h) - doses adjusted in patients with renal function in both groups. **Control** I.V. ampicillin/ sulbactam (A/S-2 g/1 g q6h) - Patients with MRSA or methicillin-resistant Staphylococcus epidermidis (MRSE) present as part of a polymicrobial infection were also given vancomycin at 1 g ql2h **Outcome measure(s)** Rates of clinical success - (defined as cure or improvement for the patient-level clinical response) Eradication of Gram Positive and Negative organisms Adverse events **Primary outcomes:** Cure or improvement at 14 to 21 day follow-up: No significant difference between piperacillin with tazobactam and ampicillin with sulbactam (n=289, 71.2% versus 66.7%, RR 1.07, 95% CI 0.92 to 1.25, moderate quality evidence). People having at least 1 treatment-related adverse effect: No significant differences between piperacillin with tazobactam and ampicillin with sulbactam (n=314, 18.7% versus 13.2%, RR 1.42, 95% CI 0.85 to 2.37, low quality evidence) or Withdrawal due to treatment-related adverse effects:	

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant difference between piperacillin with tazobactam and ampicillin with sulbactam (n=314, 11.6% versus 8.2%, RR 1.42 95% CI 0.72 to 2.80, very low quality evidence).	
Hughes et al (1987)	Treatment and Long-Term Follow-Up of Foot Infections in Patients with Diabetes or Ischemia: A Randomized, Prospective, Double-Blind Comparison of Cefoxitin and Ceftizoxime	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - USA Study setting - 2 Veterans Administration medical centers (VAMC) Study dates – not reported Duration of follow-up - Every 3 days. Subsequent follow-up evaluations were made after 3, 6, 9, and 12 months. Sources of funding – not reported **Inclusion criteria** a history or clinical evidence of peripheral arterial insufficiency or diabetes mellitus; isolation of bacterial organisms from wound, soft tissue, or bone; two or more signs of infection, including local heat, drainage, erythema, or temperature greater than 38 °C. **Exclusion criteria** Excluded for previous penicillin or cephalosporin allergy, rapidly progressive underlying disease, concomitant infection, or antibiotic therapy effective against the bacterial isolates within three days preceding initiation of-the study. **Sample characteristics** Evaluable patients were similar with regard to age, sex, duration of therapy, and associated conditions. **Intervention** Ceftizoxime, up to 4 gm IV every eight hours. Dosages of study medication were reduced for patients with renal dysfunction. Placebo	**Random sequence generation** *Yes* **Allocation concealment** *No - allocation concealment unclear* **Blinding of participants and personnel** *No - blinding unclear* **Blinding of outcome assessment** *No - blinding unclear* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear, blinding unclear.* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		infusions were given at appropriate intervals to patients in the ceftizoxime group to maintain double-blind conditions. **Control** Cefoxitin, up to2 gm IV every four hours. Dosages of study medication were reduced for patients with renal dysfunction. **Outcome measure(s)** Clinical responses at 3 days, 3, 6, 9 and 12 months Adverse events **Primary outcomes:** Satisfactory clinical response: No significant difference between cefoxitin and ceftizoxime (n=54, 65.4%, versus 82.1% RR 0.83 95% CI 0.60 to 1.14, low quality evidence). Treatment-related adverse effects: No significant difference between cefoxitin and ceftizoxime (n=63, 63.3%, versus 48.5% RR 1.31, 95% CI 0.84 to 2.04, low quality evidence).	
Lauf et al (2014)	Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagnostic microbiology and infectious disease,	Study type *Randomised controlled trial (RCT)* Study details Study location - 119 investigational sites in 30 countries Study setting – not reported Study dates – not reported Duration of follow-up - Follow up was at the test of cure assessment: (12 to 92 days after the last dose for those without osteomyelitis) (25-27 weeks for subjects in the sub study arm with osteomyelitis).	**Random sequence generation** *Yes* **Allocation concealment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Blinding of participants and personnel** *No - unclear allocation concealment, participants were taken from many different sites internationally*

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Short Title	Title	Study Characteristics	Risk of Bias
		Sources of funding - Wyeth research, Pfizer Inc Inclusion criteria Hospitalised men and women aged 18 years or older with diabetes mellitus who had a foot infection that did not extend above the knee. PEDIS infection grade from 2 to 4 and a perfusion grade from 1 to 2. In addition the infection had to be of acute onset or a worsening within 14 days prior to the screening visit. Exclusion criteria Patients who had received more than 48 hours of prior antibiotic unless considered a prior treatment failure. Infections categorised as necrotising fasciitis, crepitant cellulitis, wet gangrene, gas gangrene, ecthyma gangrenosum or which involved implanted prosthetic material or devices that were not to be removed, or infection known or suspected to be caused by a pathogen known to be resistant to either study drug. Severely impaired arterial supply to any portion of the affected foot or requiring anticipated complete resection or amputation of the infected anatomical site within 1 month were also excluded along with patients: undergoing haemodialysis, hemofiltration, peritoneal dialysis or plasmapheresis; contraindication or hypersensitivity to any of the study treatments, were neutropenic or receiving immunosuppressive therapy, creatinine clearance of less than 30 mL/min, any significant hepatic disease, a known or suspected infection other than diabetic foot which would require treatment with a systemic antibacterial agent, and pregnant or lactating women. Sample characteristics The two treatment groups were comparable with respect to age, weight and sex and there were no major differences in terms of underlying illnesses. The table below shows the baseline demographics for participants in each treatment group	*and unclear if standard of care was similar for all participants* **Blinding of outcome assessment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Intervention 150 mg once-daily, parenteral intravenous [IV] tigecycline Control 1 g once-daily intravenous [IV] ertapenem ± vancomycin Outcome measure(s) Cure – defined as resolution of signs and symptoms of infection such that no further antibiotic therapy was required. Safety assessment - included a physical examination and 12 lead ECG at baseline, day 3, last day of study medication and at the test of cure assessment. Clinical response - non-inferiority of tigecycline to ertapenem ± vancomycin was evaluated using the lower limit of a 2-sided 95% confidence interval that must be not less than 10% for non-inferiority. Primary outcomes: Clinical cure for people without osteomyelitis at 12 to 92 days follow-up: No significant difference between tigecycline and ertapenem with or without vancomycin (n=813, 77.5% versus 82.5%, RR 0.94, 95% CI 0.88 to 1.01, moderate quality evidence [NICE analysis]) Clinical cure for people with osteomyelitis at 12 to 92 days follow-up: No significant difference between tigecycline and ertapenem with or without vancomycin (n=62, 31.6% versus 54.2%, RR 0.68, 95%CI 0.35 to 1.32, very low quality evidence, very low quality evidence [NICE analysis] Adverse events: Those prescribed tigecycline having significantly more adverse events than those prescribed ertapenem with or without vancomycin (n=944, 71.1% versus 57%, RR 1.25 95% CI 1.13 to 1.38, low quality evidence)	

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Short Title	Title	Study Characteristics	Risk of Bias
		Study withdrawal due to adverse events: Those prescribed tigecycline having significantly more study withdrawals than those prescribed ertapenem with or without vancomycin (n=944, 2.1% versus 0.43%, RR 4.90, 95% CI 1.08 to 22.22, low quality evidence) Drug discontinuation due to adverse events: No significant difference between treatments for drug discontinuation due to adverse events (n=944, 8.8%, versus 5.8% RR 1.52, 95% CI 0.96 to 2.43, low quality evidence).	
Lipsky et al (2005b)	Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections.	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - United States, Europe. South Africa, Australia, and Israel Study setting - 134 sites further details not specified Study dates – not reported Duration of follow-up - Patients were assessed at 'end-of-therapy' (i.e. within 3 days of the last dose of study drug); 'test-of-cure' (i.e. within 6-20 days after completing the study drug); and 'post-study' (i.e. within 20-28 days after completing the study drug). Sources of funding – not reported **Inclusion criteria** Eligible patients were those with diabetes between the ages of 18 and 85 years who required hospitalization for an infected ulcer that was known or suspected (based on a Gram-stained smear) to be caused by a Gram-positive organism. **Exclusion criteria** Patients with minor or superficial skin infections, uncomplicated cellulitis, myositis, multiple infected ulcers at distant sites, infected	**Random sequence generation** *Yes* **Allocation concealment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Blinding of participants and personnel** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Blinding of outcome assessment** *No - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants* **Incomplete outcome data** *No*

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Short Title	Title	Study Characteristics	Risk of Bias
		third-degree burn wounds, osteomyelitis, known bacteraemia shock, hypotension, or any disorder that could interfere with the treatment evaluation were excluded. Other exclusions were pregnancy, infection due to an organism known to be resistant lo any study drug before study entry, body weight less than 40kg, history of hypersensitivity reaction lo any study drug, need for haemodialysis or peritoneal dialysis, impaired renal function (creatinine clearance less than 30ml7min). immunosuppression, serum creatine phosphokinase (CPK) more than 50% above the upper limit of normal, or the use of any 3-hydroxy-3-metlwlghitaryl coenzyme reductase inhibitor (statin) drugs. Patients were also excluded if they had received more than 24h of systemic antibiotic therapy for the infected ulcer within the previous 48 h. **Sample characteristics** Patients in the daptomycin and comparator groups were statistically equivalent with respect to all noted baseline variables, including mean age (60 and 63 years), sex (54% and 54% male) and race (80% and 78% white), respectively. **Intervention** Daptomycin [4mg/kg every 24h intravenously (iv) over 30min] **Control** Vancomycin 1 g every 12h iv over 60min or a semi-synthetic penicillin (nafcillin. oxacillin, cloxacillin or flucloxacillin, per the investigator's choice) given in equally divided doses totalling 4-12g/day iv]. **Outcome measure(s)** Clinical success rates Adverse events **Primary outcome:** Cure (resolution of all signs and symptoms) at 6 to 20 days follow-up.	**Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment not clear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant difference between daptomycin and vancomycin (n=43, 71.4% versus 69.0%, RR 1.04, 95%CI 0.69 to 1.56, very low quality evidence)	
Lipsky (1997)	A double- Antibiotic Therapy for Diabetic Foot Infections: Comparison of Two Parenteral-to-Oral Regimens.	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - USA Study setting - 12 centres no further detail provided Study dates – not reported Duration of follow-up - third to seventh day or until therapy was completed Sources of funding – not reported **Inclusion criteria** Patients who had diabetes mellitus and a foot infection that required antibiotic therapy, as evidenced by purulent drainage, erythema, and swelling, and who were 18 years of age or older. **Exclusion criteria** Patients who had evidence of osteomyelitis, usually suspected because of clinical, laboratory, and plain radiograph findings, or who had an infection known to be caused by a microorganism resistant to any of the study drugs, were allergic to any of the study drugs or related compounds, were grossly underweight, had a seizure or major psychiatric disorder, were pregnant or nursing, were undergoing renal dialysis, or were likely to die during the study. Patients who had received potentially effective antimicrobial therapy within 48 hours before presentation. Those patients who required a second systemic antimicrobial for any reason other than as defined below or who were receiving a topical antimicrobial at the site of infection **Sample characteristics** There were no statistically significant differences in the demographic	**Random sequence generation** *Yes* **Allocation concealment** *No - open label trial* **Blinding of participants and personnel** *No - open label trial* **Blinding of outcome assessment** *No - open label trial* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		characteristics of the patients randomized to receive the two therapeutic arms. The severity of infections was, on average, nearly identical in the two treatment groups. **Intervention** Ofloxacin—400 mg of ofloxacin intravenously that was changed when appropriate to 400 mg of ofloxacin orally every 12 hours. Metronidazole was added if patient not improving(for improved coverage of anaerobic bacteria) to the ofloxacin regimen. **Control** Aminopenicillin— 1-2 g of ampicillin/0.5-1 g of sulbactam intravenously every 6 hours that was changed when appropriate to 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours. Gentamicin, trimethoprim sulfamethoxazole, or another agent (for broader coverage of gram-negative bacilli) to the aminopenicillin regimen. **Outcome measure(s)** Clinical cure – defined as either Cure (the disappearance of all signs and symptoms associated with active infection) Improved (incomplete abatement of the signs or symptoms) or Failed (no improvement during therapy) Microbiological outcomes – defined as either Cured (eradication of the original pathogens); Partially cured (eradication of some but not all of the original pathogens), or Failed (persistence of the original pathogens). Adverse events **Primary outcomes:** Cure defined as the disappearance of all signs and symptoms associated with active infection at 7 days follow-up:	

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant difference between ofloxacin and ampicillin with sulbactam then co-amoxiclav (n=88, 85.1% versus 82.9%, RR 1.03, 95% CI 0.85 to 1.23, moderate quality evidence). Treatment-related adverse event: No significant difference between ofloxacin and ampicillin with sulbactam then co-amoxiclav (n=88, 36.2% versus 22%, RR 1.65, 95% CI 0.83 to 3.29, low quality evidence).	
Lipsky et al (2007)	Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-Clavulanate.	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - 6 countries no further details reported Study setting - 68 centres no further details reported Study dates – not reported Duration of follow-up – Sources of funding - not reported **Inclusion criteria** At least 18 years of age, with a cSSSI (complicated skin and skin structure infections). Each enrolled patient had to have al least three of the following signs or symptoms of wound infection: drainage or discharge, erythema, fluctuance, localized heat or warmth, pain or tenderness, swelling or induration, fever, Leucocytosis or >15% immature neutrophils on peripheral blood smear. The investigators only enrolled patients with an infection of sufficient severity to require hospitalization and iv antimicrobial therapy. **Exclusion criteria** Excluded patients who had received antibiotic therapy for >24h within 3 days prior to study enrolment or those who needed concomitant systemic antibiotic therapy for treatment of other infections. We also	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *Yes* **Blinding of outcome assessment** *Yes* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *No serious risk of bias*

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Short Title	Title	Study Characteristics	Risk of Bias
		excluded patients with a DFI who had suspected or **Sample characteristics** There were no statistically significant differences between patients in the two treatment groups in their demographic or clinical characteristics at baseline for all variables **Intervention** IV therapy for at least 3 days with moxifloxacin (400 mg/day). Then switched to oral therapy with moxifloxacin 400 mg/day **Control** Piperacillin-tazobactam (P/T) (3.0 g/0.375 g every 6 h) for at least 3 days. Then switched to amoxicillin-clavulanate (A/C) suspension 800 mg every 12 h **Outcome measure(s)** Clinical cure rates at the TOC (test-of cure) visit (10-42 days post-therapy) Bacteriologic eradication rates for the microbiologically-valid population at TOC Adverse events **Primary outcomes:** Cure (resolution of all signs and symptoms or sufficient improvement such that additional antibiotics were not required) at 10 to 42 days follow-up: No significant differences between moxifloxacin and piperacillin with tazobactam then co-amoxiclav (n=127, 44.4% versus 39.1%, RR 1.14, 95% CI 0.75 to 1.72, moderate quality evidence). Withdrawals due to treatment-related adverse events at 10 to 42 follow-up:	**Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant difference between moxifloxacin and piperacillin with tazobactam then co-amoxiclav (n=127, 23.8% versus 23.4%, RR 1.02, 95%CI 0.54 to 1.90, low quality evidence) Number of people who had treatment-related adverse effects at 10 to 42 days follow-up: People prescribed moxifloxacin have significantly more adverse effects than those prescribed piperacillin with tazobactam then co-amoxiclav (n=127, 31.7% vs 12.5%, RR 2.54, 95% CI1.21 to 5.34, moderate quality evidence).	
Lipsky et al (2004)	Treating Foot Infections in Diabetic Patients: A Randomized, Multicentre, Open-Label Trial of Linezolid versus Ampicillin-Sulbactam/ Amoxicillin-Clavulanate	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - 8 countries. Study setting - 45 sites Study dates – not reported Duration of follow-up - The test-of-cure evaluation was conducted 15-21 days after treatment was completed Sources of funding – not reported **Inclusion criteria** Men and women (age, ≥18 years) with diabetes mellitus, a foot infection (cellulitis, paronychia, infected ulcer, deep soft-tissue infection, septic arthritis, abscess, or osteomyelitis) were potentially eligible. **Exclusion criteria** If they had critical ischemia of the affected limb, if they had a wound with prosthetic materials or devices; if they had an infection requiring >28 days of antibiotic treatment; or if they had a wound with extensive gangrene. Patients were also excluded if they had received potentially	**Random sequence generation** *Yes* **Allocation concealment** *No – allocation concealment unclear, extracted subgroup data* **Blinding of participants and personnel** *No - allocation concealment unclear, extracted subgroup data* **Blinding of outcome assessment** *No - allocation concealment unclear, extracted subgroup data* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No*

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Short Title	Title	Study Characteristics	Risk of Bias
		effective antibiotic therapy for >72 h in the week before enrolment, if they needed additional treatment with antibiotics not tested in our study, if they had an absolute neutrophil count of <500 cells/mm3, if they were pregnant or lactating, or if they had a history of hypersensitivity to linezolid, penicillin, or vancomycin. **Sample characteristics** There were no significant differences between the 2 treatment groups at baseline with respect to demographic characteristics, medical histories, findings of physical examination, and results of laboratory tests. **Intervention** Linezolid (600 mg ql2 h either iv or per oral) **Control** ampicillin-sulbactam (A/S, 1.5-3 g q6h iv}, or amoxicillin-clavulanate (A/C, 500-875 mg every 8-12 h per oral). **Outcome measure(s)** Clinical cure Adverse events **Primary output** Cure (defined as the resolution of all signs and symptoms) at 15 to 21 days follow-up: No significant differences between linezolid and ampicillin with sulbactam or co-amoxiclav (n=311, 81.3% versus 71.3%, RR 1.14, 95% CI 0.99 to 1.31, low quality evidence). Withdrawals due to treatment-related adverse events: No significant difference between linezolid and ampicillin with sulbactam or co-amoxiclav (n=361, 7.5% versus 3.3%, RR 2.24, 95% CI 0.78 to 6.47, low quality evidence)	**Overall risk of bias** *Serious - open-labelled study, no blinding* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Number of people who had treatment-related adverse effects: People prescribed linezolid had significantly more treatment-related adverse effects than those prescribed ampicillin with sulbactam or co-amoxiclav (n=361, 26.6% vs 10%, RR 2.66, 95% CI 1.49 to 4.73, moderate quality evidence).	
Lipsky et al (1990)	Outpatient management of uncomplicated lower-extremity infections in diabetic patients.	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - Washington, USA Study setting - Veterans Affairs Medical Centre Study dates – not reported Duration of follow-up – not reported Sources of funding – not reported **Inclusion criteria** non-limb threatening; lower extremity infections; Clinically infected lesions were defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, induration, fluctuance, drainage **Exclusion criteria** Systemic or topical antimicrobial therapy within the preceding 2 weeks, presence of systemic toxicity, an infection that was immediately threatening to life or limb, patient unable to perform daily wound care, history of nonadherence with outpatient treatment, unwilling to return for outpatient visits, allergy to study drugs. **Sample characteristics** No differences at baseline for mean age of the participants or patients with an ulcer	**Random sequence generation** *Yes* **Allocation concealment** *No – open-labelled trial, no blinding* **Blinding of participants and personnel** *No - open-labelled trial, no blinding* **Blinding of outcome assessment** *No - open-labelled trial, no blinding* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - blinding and allocation concealment unclear.* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Intervention Clindamycin 300 mg orally, four times daily for 2 weeks. **Control** Cephalexin 500 mg orally, four times daily for 2 weeks **Outcome measure(s)** Complete healing (at 2 weeks) Improved lesions (at 2 weeks) Lesions not improved (at 2 weeks) Adverse effects (at 2 weeks) **Primary outcomes:** Complete lesion healing: No significant differences between clindamycin and cefalexin (n=52, 40% versus 33.3%, RR 1.20, 95% CI 0.59 to 2.46, very low quality evidence) Adverse events No significant differences between clindamycin and cefalexin (n=52, 4% versus 7.4%, RR 0.54, 95% CI 0.005 to 5.59, very low quality evidence).	
Lipsky et al (2005a)	Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - USA Study setting – not reported Study dates – not reported Duration of follow-up - Day 5 of intravenous therapy, at the time of discontinuation of intravenous therapy (DCIV), at the time of discontinuation of any subsequent oral antibiotic therapy, and at the	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *Yes (participants) – No (personnel – open label)*

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Short Title	Title	Study Characteristics	Risk of Bias
		follow-up assessment (FUA) 10 days after the last dose of study antibiotic therapy (intravenous or oral). Sources of funding – not reported **Inclusion criteria** Patients with diabetes mellitus (type 1 or type 2, controlled by diet or medications) and a foot infection that did not extend above the knee and required intravenous antibiotics. All patients had purulent drainage or at least three other indicators of infection. **Exclusion criteria** Patients who had infections that were: mild and did not require parenteral antibiotic therapy; known at entry to be caused by pathogens resistant to either study drug; predominantly caused by thermal bums; categorised as necrotising fasciitis; known or suspected to be associated with underlying osteomyelitis, complicated by indwelling foreign or prosthetic material; or associated with gangrenous tissue that could not be adequately removed by surgical debridement. Women who were pregnant, nursing, or fertile and not using contraception, as well as patients with: a history of a serious reaction to any β lactam antibiotic; Patients with a need for any additional concomitant systemic antibacterial agent other than the study drug(s) or vancomycin; Patients with diabetes or impaired glucose tolerance that was secondary; arterial perfusion insufficiency of the affected limb, requiring a revascularisation procedure; any rapidly progressive or terminal illness; a requirement for dialysis; immunosuppression of any cause; or receiving corticosteroid therapy {2=40 mg prednisone daily or its equivalent). Presence in patients of the following laboratory variables: markedly abnormal liver function tests; haematocrit of less than 25%, haemoglobin of less than 8 g/L, platelet count of less than 75	**Blinding of outcome assessment** *No – open label trial* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment not clear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		OOO/mm1; or coagulation test results more than 1.5 times the upper limit of normal (unless on anticoagulant therapy). Patients who had been treated for more than 24 h with systemic antibiotic therapy likely to be effective for their infection within the 72 h before study screening, unless there was clinical evidence of treatment failure with an associated deep-tissue culture that yielded pathogen(s). **Sample characteristics** The baseline characteristics—including details of peripheral neuropathy, palpable pedal pulses, and wound severity—of those randomized, which were similar between groups. **Intervention** Intravenous ertapenem (1 g bolus, followed by a saline placebo every 6 h for three additional **Control** Intravenous piperacillin/tazobactam (P/T-3-375 g every 6 h). **Outcome measure(s)** Clinical cure Microbiological outcomes Adverse events **Primary outcome** Resolution of all signs and symptoms at 5-day follow-up: No significant difference between ertapenem and piperacillin with tazobactam (n=445, 92.2% versus 94.2%, RR 0.98, 95%CI 0.93 to 1.03, moderate quality evidence). Number of people having treatment-related adverse effects:	

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant differences between ertapenem and piperacillin with tazobactam (n=586, 19.6% versus 14.9%, RR 1.31, 95% CI 0.92 to 1.88, low quality evidence) Withdrawals due to treatment-related adverse effects: No significant differences between ertapenem and piperacillin with tazobactam (n=586, 2.1% versus 1%, RR 2.03, 95% CI 0.51 to 8.03, very low quality evidence).	
Saltoglu et al (2010)	Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital,	**Study type** *Randomised controlled trial (RCT)* **Study details** Study location - Turkey Study setting – University hospital Study dates – not reported Duration of follow-up - On days 1, 7, 14 and 28 of treatment patients were followed with haematological, biochemical, erythrocyte sedimentation rate and C-reactive protein values. Microbiological responses were assessed by obtaining cultures at days 4-7 and at end of therapy. Sources of funding – not reported **Inclusion criteria** Hospitalised adults aged 18 years or over with a clinical diagnosis of moderate to severe diabetic lower extremity infection (based on Wagner grades 2-4) **Exclusion criteria** Treatment with any potentially effective antibiotic in the previous 48hours; hypersensitivity to any study medications; epilepsy; psychiatric illness; pregnancy or lactation	**Random sequence generation** *Yes* **Allocation concealment** *No – open-labelled trial, no blinding* **Blinding of participants and personnel** *No - open-labelled trial, no blinding* **Blinding of outcome assessment** *No - open-labelled trial, no blinding* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - open label trial*

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Short Title	Title	Study Characteristics	Risk of Bias
		Sample characteristics Baseline characteristics were comparable in terms of age, sex, duration of diabetes, size of ulcer, and other clinical findings. The table below shows the demographic and clinical characteristics of patients. **Intervention** 4.5g IV Piperacillin/Tazobactam 3 times a day **Control** 500mg IV imipenem/ Cilastatin 4 times a day **Outcome measure(s)** Clinical response to the antibiotics being tested - cure was recorded as the complete regression of signs and symptoms such as purulent discharge, erythema, or induration that were present before treatment commenced. Relapse rate at the end of 2 months **Primary outcome** Successful clinical response at 5-day follow-up: No significant differences between piperacillin with tazobactam and imipenem with cilastatin (n=58, 46.7% versus 32.1%, RR 1.66, 95% CI 0.84 to 3.25, low quality evidence). Number of people needing amputations: No significant differences between piperacillin with tazobactam and imipenem with cilastatin (n=62, 60% versus 68.8%, RR 0.87, 95% CI 0.60 to 1.27, very low quality evidence) or Adverse events: No significant differences between piperacillin with tazobactam and imipenem with cilastatin (n=62, 30% versus 9.4%, RR 3.20, 95% CI 0.96 to 10.71, very low quality evidence).	**Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
Schaper et al (2012)	Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study,	**Study type** *Randomised controlled trials (RCT)* **Study details** Study location - Multinational (Netherlands, UK, France, Germany, Belgium, USA) Study setting – not reported Study dates – not reported Duration of follow-up - treated for a minimum of 7 days and maximum of 21 days Sources of funding – not reported **Inclusion criteria** Eligible participants were men and women aged 18 years or over with a diagnosis of a complicated bacterial skin & skin structure infection of less than 21 days duration, requiring hospitalisation and parenteral antibiotic treatment of 48 hours or more. The data subset required all patients had to have a DFI of moderate to severe infection intensity (based on PEDIS grade 2-4). **Exclusion criteria** Patients who had received therapy with a topical or systemic antimicrobial for more than 24 hours in the previous 7 days were excluded **Sample characteristics** A subset of patients with diabetic foot infections (DFI) included in the RELIEF trial (n=233) and are considered in this evidence review. There were no significant differences between the patient demographics in either treatment group. **Intervention** 400mg sequential IV / oral moxifloxacin (MOX) plus matching placebo	**Random sequence generation** *Yes* **Allocation concealment** *No – lack of allocation concealment* **Blinding of participants and personnel** *No - lack of allocation concealment* **Blinding of outcome assessment** *No - lack of allocation concealment* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - allocation concealment unclear.* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		3 times a day **Control** 875/125mg IV Piperacillin/Tazobactam 3 times a day followed by oral amoxicillin/ clavulanate (PIP/TAZ/AMC) 2 times a day **Outcome measure(s)** Primary efficacy variable was response at TOC - photographs of lesions were taken at each assessment. Safety assessment was based on physical examination, vital signs, ECG, adverse events, and standard laboratory tests throughout study. Clinical cures or successes were patients considered to be cured at TOC. **Primary outcomes** Cure (disappearance of all signs and symptoms associated with active infection) at 6-day follow-up: No significant difference between moxifloxacin and piperacillin with tazobactam then co-amoxiclav (n=206, 76.4% versus 78.1%, RR 0.98, 95%CI 0.84 to 1.13, moderate quality evidence). Additional surgeries requiring amputation: No significant difference between moxifloxacin and piperacillin with tazobactam then co-amoxiclav (n=206, 20.9% versus 25%, RR 0.84, 95% CI 0.51 to 1.38, very low quality evidence) Number of people having significant adverse effects No significant difference between moxifloxacin and piperacillin with tazobactam then co-amoxiclav (n=233, 30.9% versus 31.8%, RR 0.97 95% CI 0.66 to 1.42, very low quality evidence).	
Siami et al (2001)	Clinafloxacin versus piperacillin-tazobactam in	**Study type** *Randomised controlled trial (RCT)*	**Random sequence generation** *Yes*

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Short Title	Title	Study Characteristics	Risk of Bias
	treatment of patients with severe skin and soft tissue infections	**Study details** Study location – not reported Study setting – not reported Study dates – not reported Duration of follow-up - TOC 6 to14 days post therapy; Long term follow up 21 to 35 days post therapy Sources of funding – not reported **Inclusion criteria** Eligible participants were adult patients with severe or limb-threatening SSTIs serious enough to require hospitalisation. Patients with an aetiology and diagnosis of spontaneous infection or a diabetic foot infection were included **Exclusion criteria** Pregnancy or breast-feeding, significant hepatobiliary or renal dysfunction, immunodeficiency conditions, risk of convulsive disorders, hypersensitivity to study medications, septic shock, infected burns or decubitus ulcers, osteomyelitis and major amputation. Patients were not allowed to have been treated with more than a single dose of antibacterial therapy for the current SSTI or had the infected site treated with a topical antibiotic within 24 hours prior to baseline collection of culture. Patients were not allowed to have had any other investigational drug in the 7 days prior to entry in the study or received treatment with any other investigational drug in the 4 weeks prior to randomisation. Patients were excluded if taking corticosteroids, requiring concomitant topical antimicrobial therapy for an SSTI and patients known to have SSTI pathogens resistant to study medication. **Sample characteristics** No differences at baseline for gender, age or race	**Allocation concealment** *No – lack of allocation concealment* **Blinding of participants and personnel** *No - lack of allocation concealment* **Blinding of outcome assessment** *No - lack of allocation concealment* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - location concealment unclear* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Intervention Clindamycin 200mg IV every 12 hours plus placebo infusions every 12 hours switched to 200mg oral clinafloxacin every q12 hours after 3 days **Control** 3.375g IV Piperacillin/Tazobactam every 6 hours plus vancomycin (only if MRSA suspected) switched to 500mg oral amoxicillin/clavulanate every 8 hours **Outcome measure(s)** Clinical cure rate and by-pathogen microbiological eradication rates (determined at TOC) Clinical cure rate and by-pathogen microbiological eradication rates (determined at long term follow up). Development of resistance, amputation rate and survival rate Cure - defined as remission of signs and symptoms of baseline infection; failure was defined as absence of remission. **Primary outcome:** Cure or improvement (remission of signs and symptoms of baseline infection) at 14 days follow-up: No significant difference between clinafloxacin and piperacillin with tazobactam then co-amoxiclav (n=54, 51.7% versus 48%, RR 1.07, 95%CI 0.63 to 1.85, very low quality evidence).	
Tan et al (1993)	Treatment of hospitalised patients with complicated skin and structure infections: double-blind, randomised, multicentre study of piperacillin-tazobactam versus	**Study type** *Randomised controlled trail (RCT)* **Study details** Study location – not reported Study setting - 20 centres no further detail reported Study dates – not reported Duration of follow-up - Patients were evaluated for their clinical	**Random sequence generation** *Yes* **Allocation concealment** *No - allocation concealment unclear, extracted subgroup data* **Blinding of participants and personnel** *No - allocation concealment unclear, extracted*

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Short Title	Title	Study Characteristics	Risk of Bias
	ticarcillin-clavulanate	responses to therapy daily for the duration of treatment in the hospital, at 24 to 72 h after the completion of therapy (early follow-up), and at 10 to 14 days after the completion of therapy (late follow-up). Sources of funding – not reported **Inclusion criteria** Patients 16 years of age and older with complicated skin or skin structure infections like ischemic or diabetic foot infections, present with purulent drainage or collection and at least three of the following: temperature greater than 38°C, peripheral leukocyte count greater than 10,000/mm3 with greater than 5% immature neutrophils, local erythema, local swelling, tenderness, pain, or fluctuance. **Exclusion criteria** Known or suspected hypersensitivity to beta-lactam antibiotics or {3-lactamasc inhibitors; moderate to severe renal dysfunction; evidence of active liver disease; peripheral granulocyte counts of <l,000/mm3 or platelet counts of <50,000/mm3; receipt of more than two doses of another antibacterial agent within 72 h prior to enrolment; receipt of another investigational drug within 1 month prior to enrolment; active or treated leukaemia; AIDS; the need for haemodialysis, peritoneal dialysis, plasmapheresis, or hemoperfusion; osteomyelitis contiguous with a skin or skin structure infection; potential requirement for amputation of the infected area; pressure ulcer infections of greater than 2 weeks' duration {because of the. known difficulty in eradicating organisms from chronic decubitus ulcers); and a concomitant infection other than the skin and skin structure infection. **Sample characteristics** The distribution of patients by race and sex was comparable between the two treatment arms and the mean ages among all treated patients were similar. Differences in the distributions of clinical diagnoses were not significant between the two treatment arms.	*subgroup data* **Blinding of outcome assessment** *No - allocation concealment unclear, extracted subgroup data* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious – due to allocation concealment unclear, extracted subgroup data* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Intervention Dosed every 6 h with piperacillin-tazobactam (P/T), 3 g and 375 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms. **Control** Dosed every 6 h with ticarcillin-clavulanate (T/C), 3 g and 100 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms. **Outcome measure(s)** Clinical response – cure/improved or unfavourable Adverse events **Primary outcome** Clinical response at 10 to 14 days after the completion of treatment: No significant difference between piperacillin with tazobactam and ticarcillin with clavulanic acid in (n=35, 38.9% versus 35.3%, RR 1.10, 95% CI 0.46 to 2.62; very low quality evidence). Adverse experiences Findings reported but the data for people with diabetic foot infection could not be extracted.	
Tone et al (2015)	Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study	**Study type** *Randomised controlled trail (RCT)* **Study details** Study location - France Study setting – not reported Study dates – not reported Duration of follow-up – end of treatment (6 weeks or 12 weeks respectively	**Random sequence generation** *Yes* **Allocation concealment** *No - Blinding inappropriate for the study design* **Blinding of participants and personnel** *No - Blinding inappropriate for the study design*

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Short Title	Title	Study Characteristics	Risk of Bias
		Sources of funding – not reported **Inclusion criteria** Diabetic patients treated non-surgically (i.e., without amputation or resection of the infected bone) for osteomyelitis of the foot complicating a neuropathic foot without peripheral arterial disease that was assessed by clinical examination and complementary investigations. **Exclusion criteria** Patients were excluded in case of absence of both anterior and posterior pedal pulses with Doppler arterial examination showing significant stenosis or occlusions. In case of persisting doubt, transcutaneous oxygen pressure examination was used to assess the existence of a critical ischemia (,30 mmHg). Patients 18 years old or over were included if they had type 2 diabetes and osteomyelitis of the foot (i.e., below the ankle). Patients who had gangrene and who required bone resection because of bone and/or joint destruction or amputation due to severe peri-osteoarticular damage were not included. **Sample characteristics** Overall no statistical differences between intervention and control groups at baseline for all characteristics which included sex, age, diabetes related complications and location of infection **Intervention** Short-course (6 weeks) empirical antibiotic (IV or oral): Gram-positive cocci infections: rifampin was used in combination with levofloxacin, co-ceazole, doxycycline, linezolid, or any other antimicrobial agent active against bone pathogens for the entire duration of treatment; for Gram-negative bacilli infections: levofloxacin or ciprofloxacin was used in combination with cefotaxime, ceftriaxone, or cefepime for the first 2 weeks of treatment and then continued for the rest of the treatment as monotherapy	**Blinding of outcome assessment** *No* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious – processes for blinding are unclear* **Directness** *Directly relevant*

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Short Title	Title	Study Characteristics	Risk of Bias
		Control Long-course (12 weeks) empirical antibiotic (IV or oral): Gram-positive cocci infections: rifampin was used in combination with levofloxacin, co-ceazole, doxycycline, linezolid, or any other antimicrobial agent active against bone pathogens for the entire duration of treatment; for Gram-negative bacilli infections: levofloxacin or ciprofloxacin was used in combination with cefotaxime, ceftriaxone, or cefepime for the first 2 weeks of treatment and then continued for the rest of the treatment as monotherapy **Outcome measure(s)** Remission of diabetic foot osteomyelitis Complete healing sustained for at least 4 consecutive weeks Major amputation Antibiotic-related gastrointestinal adverse events **Primary outcome** Overall remission: No significant differences between 6 weeks and 12 weeks duration of antibiotic treatment (n=40, 60% versus 70%, RR 0.86, 95%CI 0.54 to 1.36, very low quality evidence), Complete healing sustained for at least 4 consecutive weeks: No significant differences between 6 weeks and 12 weeks duration of antibiotic treatment (n=40, 90% versus 80%, RR 1.13, 95%CI 0.86 to 1.46, low quality evidence), Major amputation: No significant differences between 6 weeks and 12 weeks duration of antibiotic treatment (n=40, 10% versus 10%, RR 1.00, 95%CI 0.16 to 6.42, very low quality evidence)	

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Short Title	Title	Study Characteristics	Risk of Bias
		Antibiotic-related gastrointestinal adverse events: No significant differences between 6 weeks and 12 weeks duration of antibiotic treatment (n=40, 15% versus 45%, RR 0.33, 95%CI 0.11 to 1.05, low quality evidence).	
Vick-Fragoso et al (2009)	Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections,	**Study type** *Randomised controlled trail (RCT)* **Study details** Study location - Worldwide Study setting – not specified Study dates – not specified Duration of follow-up - Patients had to receive the study drug for at least 3 days (if clinical failure) or at least 5 days (to be classed a success). Sources of funding - Bray **Inclusion criteria** Patients aged 18 years or over with a CSSSI at 1 site only were eligible for enrolment. If they required systemic antimicrobial therapy. CSSSIs were prospectively defined as diabetic foot infections, necrotising fasciitis, post-surgical wound infection, complicated cellulitis, complicated erysipelas, major abscess of the skin, infection of traumatic lesion and infected ulcer. **Exclusion criteria** Patients with a diagnosis of mild to moderate SSSIs, secondary infected burns, atopic dermatitis or eczema were excluded. Also excluded were pregnant or nursing women with severe life-threatening diseases, people with a life expectancy of less than 2 months, end stage liver cirrhosis, severe renal impairment requiring dialysis and septic shock. Other exclusions were patients with neutropenia or at AIDS stage 1 or 2. Patients with known congenital or sporadic syndromes of QTc prolongation or taking concomitant medication.	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *No - open label trial* **Blinding of outcome assessment** *No - open label trial* **Incomplete outcome data** *No* **Selective reporting** *No* **Other sources of bias** *No* **Overall risk of bias** *Serious - open label trial* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		Patients with hypersensitivity to fluoroquinolones and beta-lactams **Sample characteristics** Overall, the baseline demographic characteristics for the PP population were comparable between treatment groups, although there were significantly more men in the amoxicillin/clavulanate group (p=0.05). The table below shows baseline and demographic characteristics **Intervention** Moxifloxacin (IV then oral) for 7 to 21 days **Control** Co-amoxiclav (IV then oral) for 7 to 21 days **Outcome measure(s)** Cure rates at test for cure Adverse events Withdrawals due to adverse event **Primary outcome** Cure (disappearance of all signs and symptoms associated with active infection) at 14 to 28-day follow-up: No significant differences between moxifloxacin and co-amoxiclav for (n=632, 80.6% versus 84.5%, RR 0.95, 95% CI 0.88 to 1.02, low quality evidence). Mean duration of treatment No significant differences between moxifloxacin and co-amoxiclav (13.5 days versus 14.1 days, MD -0.60 days, 95% CI -1.62 to 0.42, very low quality evidence) Adverse effects at 14 to 28-day follow-up	

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant differences between moxifloxacin and co-amoxiclav (n=803, 52.0% versus 47.9%, RR 1.09, 95% CI 0.95 to 1.25, very low quality evidence) Serious adverse events at 14 to 28-day follow-up No significant differences between moxifloxacin and co-amoxiclav (n=803, 14% versus 11.3%, RR 1.24, 95% CI 0.86 to 1.79, very low quality evidence) Treatments for cure (sensitivity analysis - population of the study with diabetic foot infection only) at 14 to 28-day follow-up: No significant difference between moxifloxacin and co-amoxiclav (n=112, 51% versus 66.7%, RR 0.77, 95% CI 0.55 to 1.06, low quality evidence).	
Zhang-Rong et al (2016)	A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial) Hormone-sensitive metastatic prostate cancer	**Study type** *Randomised controlled trail (RCT)* **Study details** Study location - China Study setting - clinic or inpatient department Study dates – not reported Duration of follow-up - Participants were assessed on day 5 of treatment, at discontinuation of IV antibiotics and 10 days after the last dose of antibiotic Sources of funding - Merck **Inclusion criteria** Chinese diabetic adults between 18 and 80 years of age and had DFIs below the knee with purulent drainage and/ or three or more of the following: fever (temperature ≥38.58C); elevated white blood cell count (.10000/mm3) with .5% band neutrophils; peri wound oedema, erythema, tenderness or pain; fluctuance, warmth or induration; or lymphangitis with a skin lesion.	**Random sequence generation** *Yes* **Allocation concealment** *Yes* **Blinding of participants and personnel** *Yes* **Blinding of outcome assessment** *Yes* **Incomplete outcome data** *No* **Selective reporting** *No*

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Short Title	Title	Study Characteristics	Risk of Bias
		Females were eligible if they had no potential for reproduction or agreed to remain abstinent or use an acceptable birth control at enrolment and throughout the study **Exclusion criteria** Patients were excluded if they: had mild infections and did not require parenteral antibiotics; had causative pathogens at screening with known resistance to either study drug; had lower extremity wounds caused by thermal burns or categorized as necrotizing fasciitis, or associated with unremovable gangrenous tissue, or with underlying osteomyelitis (unless all infected bone was removed within 48 h of study antibiotic initiation); had or required a revascularization procedure; had any rapidly progressive or terminal illness; or had immunosuppression of any cause. Also excluded were patients who: received a systemic antibiotic for ≥24 h within 72 h before screening (unless treatment failure); were pregnant or planning to become pregnant within 1month of study completion; had a history of a serious reaction to any b-lactam antibiotic; or were unlikely to complete the study based on the investigator's judgement. **Sample characteristics** Participants had moderate diabetic foot infections (n=201) and severe diabetic foot infections (n=332) **Intervention** Ertapenem (IV) for 5-28 days - Investigators could administer vancomycin if Enterococcus spp and/or MRSA organisms were known or suspected; After 5 days of IV treatment (ertapenem or piperacillin with tazobactam) the investigator could switch adults to co-amoxiclav (oral) 875/125 mg every 12 hours **Control** Piperacillin with tazobactam (IV) 5-28 days investigators could administer vancomycin if Enterococcus spp and/or MRSA organisms were known or suspected; After 5 days of IV treatment (ertapenem or	**Other sources of bias** *No* **Overall risk of bias** *No serious risk of bias* **Directness** *Directly related*

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Short Title	Title	Study Characteristics	Risk of Bias
		piperacillin with tazobactam) the investigator could switch adults to co-amoxiclav (oral) 875/125 mg every 12 hours **Outcome measure(s)** Clinical response – resolution of most pre-therapy signs and symptoms of the infection at D5, no need for iv antibiotics at DCIV and no need for any more antibiotics at FUA Failure (or relapse) - defined as the presence of persistence or progression of most pre-therapy signs and symptoms (or worsened signs and symptoms with a previous favourable outcome). Microbiological response - defined as a favourable clinical response and documented eradication (at least one isolate) with no new pathogens isolated or presumptive eradication of all pathogens **Primary outcome** Clinical resolution of diabetic foot infection at discontinuation of antibiotic treatment: No significant difference between ertapenem and piperacillin with tazobactam in adults with moderate to severe infections (n=533, 88.8% versus 90.6%, RR 0.98, 95% CI 0.90 to 1.04, high quality evidence). Sub-group analyses: clinical resolution of diabetic foot infection at discontinuation of antibiotic treatment in adults with moderate infection: No significant difference between ertapenem and piperacillin with tazobactam (n=201, 93.3% versus 90.7%, RR 1.03, 95%CI 0.95 to 1.12, high quality evidence) or Sub-group analyses: clinical resolution of diabetic foot infection at discontinuation of antibiotic treatment in adults with severe infection:	

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Short Title	Title	Study Characteristics	Risk of Bias
		No significant difference between ertapenem and piperacillin with tazobactam (n=332, 85.9% versus 90.5%, RR 0.95, 95% CI 0.88 to 1.03, high quality evidence). T Resolution of signs and symptoms of diabetic foot infection at 5-day follow-up: No significant difference between ertapenem and piperacillin with tazobactam (n=533, 84.3% versus 87.2%, RR 0.97, 95% CI 0.90 to 1.04, high quality evidence) Need for more antibiotics at 10-day follow-up after the last dose: No significant difference between ertapenem and piperacillin with tazobactam (n=533, 76.8% versus 76.3%, RR 1.01, 95% CI 0.92 to 1.11). Serious adverse events: No significant difference between ertapenem and piperacillin with tazobactam (n=550, 6.2% versus 4.4%, RR 1.42, 95% CI 0.69 to 2.91, low quality evidence) Drug-related serious adverse events: No significant difference between ertapenem and piperacillin with tazobactam (n=550, 0.4% versus 1.1%, RR 0.33, 95% CI 0.03 to 3.18, low quality evidence). Deaths and amputations: There was a total of 8 deaths, and 6 amputations of lower extremities.	

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Appendix F: Included studies

Newly identified

Tone Alina, Nguyen Sophie, Devemy Fabrice, Topolinski Helene, Valette Michel, Cazaubiel Marie, Fayard Armelle, Beltrand Eric, Lemaire Christine, and Senneville Eric (2015) Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes care 38(2), 302-7

Xu Zhang-Rong, Ran Xing-Wu, Xian Yang, Yan Xiao-Dong, Yuan Guo-Yue, Mu Sheng-Mei, Shen Ju-Fang, Zhang Bo-Shao, Gan Wei-Jin, and Wang Jue (2016) Ertapenem versus piperacillin with tazobactam for diabetic foot infections in China: a Phase 3, multicentre, randomized, double-blind, active-controlled, non-inferiority trial. The Journal of antimicrobial chemotherapy 71(6), 1688-96

NICE clinical guideline 19: Diabetic foot problems: prevention and management

Bouter, KP, Visseren, FLJ, Van Loenhout, RMM, Bartelink, AKM, Erkelens, DW, Diepersloot, RJA Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. International Journal of Antimicrobial Agents 1996; 7: 143-47.

Bradsher, T and Snow, J.M. (1984) Ceftriaxone treatment of skin and soft tissue infections in a once daily regimen, American Journal of Medicine 77 (4) 63-67.

Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89

Erstad, BL, McIntyre, J Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. Vascular Surgery 1997; 31: 419-26.

File, Jr and Tan,J.S. (1983) Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections) American Journal of Medicine 75 (2 A) 100-105.

Grayson, ML, Gibbons, GW, Habershaw, GM, Freeman, DV, Pomposelli, FB, Rosenblum, BI, Levin, E, Karchmer, AW Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic people.[Erratum appears in Clin Infect Dis 1994 Oct;19(4):820]. Clinical Infectious Diseases 1994; 18: 683-93.

Harkless, L, Boghossian, J, Pollak, R, Caputo, W, Dana, A, Gray, S, Wu, D An open-label, randomized study comparing efficacy and safety of intravenous piperacillin with tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surgical Infections 2005; 6: 27-40.

Hughes, CE, Johnson, CC, Bamberger, DM, Reinhardt, JF, Peterson, LR, Mulligan, ME, Gerding, DN, George, WL, Finegold, SM Treatment and long-term follow-up of foot infections in people with diabetes or ischemia: a randomized, prospective, double-blind comparison of cefoxitin and ceftizoxime. Clinical Therapeutics 1987; 10: Suppl-49.

Lauf, L., Ozsvár, Z., Mitha, I., Regöly-Mérei, J., Embil, J. M., Cooper, A., & Maroko, R. (2014). Phase 3 study comparing tigecycline and ertapenem in people with diabetic foot infections with and without osteomyelitis. Diagnostic microbiology and infectious disease, 78(4), 469-480.

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Lipsky, BA, Armstrong, DG, Citron, DM, Tice, AD, Morgenstern, DE, Abramson, MA Ertapenem versus piperacillin with tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 2005; 366: 1695-703

Lipsky, BA, Baker, PD, Landon, GC, Fernau, R Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. Clinical Infectious Diseases 1997; 24: 643-48.

Lipsky, BA, Giordano, P, Choudhri, S, Song, J Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin with tazobactam/amoxicillin-clavulanate. Journal of Antimicrobial Chemotherapy 2007; 60: 370-376.

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Lipsky BA, Pecoraro RE, Larson SA et al. (1990) Outpatient management of uncomplicated lower-extremity infections in diabetic people. Archives of Internal Medicine 150: 790-7.

Lipsky, BA, Stoutenburgh, U Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. Journal of Antimicrobial Chemotherapy 2005; 55: 240-245.

Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin with tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.

Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin with tazobactam followed by PO co-amoxiclav in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.

Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin with tazobactam in treatment of people with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.

Tan, JS, Wishnow, RM, Talan, DA, Duncanson, FP, Norden, CW Treatment of hospitalized people with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin with tazobactam versus ticarcillin with clavulanic acid. The Piperacillin with tazobactam Skin and Skin Structure Study Group. Antimicrobial Agents & Chemotherapy 1993; 37: 1580-1586.

Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral co-amoxiclav for complicated skin and skin structure infections, Infection 37 (5) 407-17.

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Appendix G: GRADE profiles

G.1 Antibiotics compared with other antibiotics

G.1.1 Penicillins compared to penicillins

Table 4: GRADE profile – Piperacillin with tazobactam (IV) versus ticarcillin with clavulanic acid (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Empirical[1, 2]	Targeted treatment[1, 3]	Relative (95% CI)	Absolute		
Resolution of signs and symptoms - follow-up 10-14 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	7/18 (38.9%)	6/17 (35.3%)	RR 1.10 (0.46 to 2.62)	4 more per 100 (from 19 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL

[1] Tan et al. (1993)
[2] Downgraded 1 level - allocation concealment unclear, extracted subgroup data.
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 5: GRADE profile – Piperacillin with tazobactam (IV) versus ampicillin with sulbactam (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin with tazobactam (IV)	Ampicillin with sulbactam (IV)	Relative (95% CI)	Absolute		
Resolution of signs and symptoms - follow-up 14-21 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	99/139 (71.2%)	100/150 (66.7%)	RR 1.07 (0.92 to 1.25)	5 more per 100 (from 5 fewer to 17 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people experienced at least 1 treatment-related adverse effects - follow-up 14-21 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	29/155 (18.7%)	21/159 (13.2%)	RR 1.42 (0.85 to 2.37)	6 more per 100 (from 2 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Withdrawals due to treatment-related adverse effects (follow-up 14-21 days)												

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1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	18/155 (11.6%)	13/159 (8.2%)	RR 1.42 (0.72 to 2.80)	3 more per 100 (from 2 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL

[1] Harkless et al. 2005
[2] Downgraded 1 level - open-labelled trial, no blinding
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with piperacillin with tazobactam (IV)
[4] Downgraded 2 level - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

G.1.2 Glycycline vs carbapenem

Table 6: GRADE profile – Tigecycline (IV) versus ertapenem (IV) with or without vancomycin (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tigecycline (IV)**	**Ertapenem (IV) with or without vancomycin (IV)**	**Relative (95% CI)**	**Absolute**		
Clinical cure (follow-up 12-92 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none[3]	316/408 (77.5%)	334/405 (82.5%)	RR 0.94 (0.99 to 1.14)	49 fewer per 1000 (from 99 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (osteomyelitis) (follow-up 12-92 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none[3]	12/38 (31.6%)	13/24 (54.2%)	RR 0.68 (0.35 to 1.32)	173 fewer per 1000 (from 352 fewer to 173 more)	⊕OOO VERY LOW	CRITICAL
Any adverse events (follow-up 12-92 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none[3]	339/477 (71.1%)	266/467 (57%)	RR 1.25 (1.13 to 1.38)	142 more per 1000 (from 74 more to 216 more)	⊕⊕OO LOW	CRITICAL
Study withdrawal due to adverse events (follow-up 12-92 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none[3]	10/477 (2.1%)	2/467 (0.43%)	RR 4.90 (1.08 to 22.22)	17 more per 1000 (from 0 more to 91 more)	⊕⊕OO LOW	CRITICAL
Drug discontinuation due to adverse events (follow-up 12-92 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none[4]	42/477 (8.8%)	27/467 (5.8%)	RR 1.52 (0.96 to 2.43)	30 more per 1000 (from 2	⊕⊕OO LOW	CRITICAL

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										fewer to 83 more)		

[1] Lauf et al (2014)
[2] Downgraded 1 level - unclear allocation concealment, participants were taken from many different sites internationally and unclear if standard of care was similar for all participants
[3] Industry funded
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction, the effect estimate is consistent with no meaningful difference or appreciable benefit with tigecycline (IV)

G.1.3 Carbapenem versus penicillin

Table 7: GRADE profile - Imipenem/cilastatin (IV) versus piperacillin/clindamycin (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem/ Cilastatin (IV)	Piperacillin/ Clindamycin (IV)	Relative (95% CI)	Absolute		
Cured - resolution of signs and symptoms (follow-up 0-10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/21 (19%)	6/24 (25%)	RR 0.76 (0.25 to 2.34)	6 fewer per 100 (from 19 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Number of people experienced treatment-related adverse events (follow-up 0-10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	3/21 (14.3%)	12/24 (50%)	RR 0.29 (0.09 to 0.88)	36 fewer per 100 (from 6 fewer to 45 fewer)	⊕⊕OO LOW	CRITICAL

[1] Bouter et al 1996
[2] Downgraded 1 level - allocation concealment unclear
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Downgraded 1 levels - at a default minimal important difference of 25% relative risk reduction, the effect estimate is consistent with no meaningful difference or appreciable benefit with imipenem/cilastatin (IV)

Table 8: GRADE profile - Imipenem/cilastatin (IV) versus ampicillin/sulbactam (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem/ Cilastatin (IV)	Ampicillin/	Relative (95% CI)	Absolute		

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								Sulbactam (IV)				
Cured - resolution of soft-tissue infection (follow-up 0-6 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	39/41 (95.1%)	41/48 (85.4%)	RR 0.95 (0.80 to 1.14)	4 fewer per 100 (from 17 fewer to 12 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people who experienced an adverse effect - leading to a withdrawal of treatment (follow-up 0-6 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	7/46 (15.2%)	9/47 (19.1%)	RR 0.79 (0.32 to 1.96)	4 fewer per 100 (from 13 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL

[1] Grayson et al. 1994
[2] Downgraded 1 level - allocation concealment unclear
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 9: GRADE profile - Ertapenem (IV) versus piperacillin with tazobactam (IV)

Quality assessment							No of people		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ertapenem (IV) versus**	**Piperacillin with tazobactam (IV)**	**Relative (95% CI)**	**Absolute**		
Cured resolution of all signs and symptoms. (follow-up 0-5 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	202/219 (92.2%)	213/226 (94.2%)	RR 0.98 (0.93 to 1.03)	2 fewer per 100 (from 7 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people experienced treatment-related adverse events (follow-up 0-5 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	57/291 (19.6%)	44/295 (14.9%)	RR 1.31 (0.92 to 1.88)	5 more per 100 (from 1 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Withdrawals due to treatment-related adverse events (follow-up 0-5 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	6/291 (2.1%)	3/295 (1%)	RR 2.03 (0.51 to 8.03)	1 more per 100 (from 0 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL

[1] Lipsky et al. 2005a
[2] Open-labelled study, no blinding
[3] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with ertapenem (IV)
[4] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 10: GRADE profile - Piperacillin with tazobactam (IV) versus imipenem-cilastatin (IV)

Quality assessment	No of people	Effect	Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin with tazobactam (IV)	Imipenem-cilastatin (IV)	Relative (95% CI)	Absolute		
Successful clinical response (follow-up 0-5 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	14/30 (46.7%)	9/28 (32.1%)	RR 1.66 (0.84 to 3.25)	21 more per 100 (from 5 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Number of people requiring amputations												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	18/30 (60%)	22/32 (68.8%)	RR 0.87 (0.60 to 1.27)	9 fewer per 100 (from 27 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Number of patient adverse effects												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	9/30 (30%)	3/32 (9.4%)	RR 3.20 (0.96 to 10.71)	206 more per 1000 (from 4 fewer to 910 more)	⊕OOO VERY LOW	CRITICAL

[1] Saltoglu et al 2010
[2] Downgraded 1 level - open label trial
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with piperacillin with tazobactam (IV)
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 11: GRADE profile – Ertapenem (IV) versus Piperacillin with tazobactam (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ertapenem (IV)**	**Piperacillin with tazobactam (IV)**	**Relative (95% CI)**	**Absolute**		
Resolution of most signs and symptoms of infection (follow-up 5 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[3]	225/267 (84.3%)	232/266 (87.2%)	RR 0.97 (0.90 to 1.04)	3 fewer per 100 (from 9 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation of IV antibiotics (follow-up 5 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[3]	237/267 (88.8%)	241/266 (90.6%)	RR 0.98 (0.92 to 1.04)	2 fewer per 100 (from 7 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation of IV antibiotics - moderate infection (follow-up 5 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[3]	97/104 (93.3%)	88/97 (90.7%)	RR 1.03, (0.95 to 1.12)	27 more per 1000 (from 73 fewer to 36 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation of IV antibiotics - severe infection (follow-up 5 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[3]	140/163 (85.9%)	153/169 (90.5%)	RR 0.95 (0.88 to 1.03)	45 fewer per 1000 (from 45 fewer to 109 more)	⊕⊕⊕⊕ HIGH	CRITICAL
No need for any more antibiotics - 10 days after the last dose of antibiotic												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[3]	205/267 (76.8%)	203/266 (76.3%)	RR 1.01 (0.92 to 1.11)	8 more per 1000 (from 61 fewer to 84 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events - death or loss of limb												

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1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none[3]	17/275 (6.2%)	12/275 (4.4%)	RR 1.42 (0.69 to 2.91)	18 more per 1000 (from 14 fewer to 83 more)	⊕⊕OO LOW	CRITICAL
Drug related serious adverse events – death or loss of limb												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none[3]	1/275 (0.36%)	3/275 (1.1%)	RR 0.33 (0.03 to 3.18)	7 fewer per 1000 (from 11 fewer to 24 more)	⊕⊕OO LOW	CRITICAL

[1] Zhang-Rong et al. 2016 - Duration of study treatment was no longer than 28 days.
[2] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[3] Industry funded

Table 12: GRADE profile - Cefoxitin (IV) vs ceftizoxime (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cefoxitin (IV)**	**Ceftizoxime (IV)**	**Relative (95% CI)**	**Absolute**		
Cured or improvement												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	17/26 (65.4%)	23/28 (82.1%)	RR 0.83 (0.60 to 1.14)	14 fewer per 100 (from 33 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Treatment-related adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	19/30 (63.3%)	16/33 (48.5%)	RR 1.31 (0.84 to 2.04)	15 more per 100 (from 8 fewer to 50 more)	⊕⊕OO LOW	CRITICAL

[1] Hughes et al. 1987
[2] Downgraded 1 levels - Allocation concealment unclear, blinding unclear.
[3] Downgraded 1 levels - At a default minimal important difference of 25% relative risk reduction, the effect estimate is consistent with no meaningful difference or appreciable benefit with cefoxitin (IV)

Table 13: GRADE profile - Ceftriaxone (IV) versus cefazolin (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftriaxone (IV)**	**Cefazolin (IV)**	**Relative (95% CI)**	**Absolute**		
Cured - follow-up 7 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	21/42 (50%)	25/42 (59.5%)	RR 0.84 (0.57 to 1.24)	10 fewer per 100 (from 26 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Treatment-related adverse events - follow-up 7 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	12/42 (28.6%)	13/42 (31%)	RR 0.92 (0.48 to 1.78)	2 fewer per 100 (from 16 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL

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Number of surgical procedures												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	15/42 (35.7%)	12/42 (28.6%)	RR 1.25 (0.67 to 2.34)	71 more per 1000 (from 94 fewer to 383 more)	⊕OOO VERY LOW	CRITICAL

[1] Bradsher et al. (1984)
[2] Downgraded 1 level - lack of allocation concealment;
[3] Downgraded 1 level - only 20/82 participants had a confirmed diabetic foot infection
[4] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 14: GRADE profile - Cefoxitin (IV) versus ampicillin with sulbactam (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cefoxitin (IV)**	**Ampicillin with sulbactam (IV)**	**Relative (95% CI)**	**Absolute**		
Cured - follow-up 0-5 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	7/18 (38.9%)	1/18 (5.6%)	RR 7.00 (0.95 to 51.25)	33 more per 100 (from 0 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Length of hospital stay - days (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious [4]	none	mean: 12.1 days (range 4 to 39)	mean: 21.1 days (range 6 to 58)	not estimated (study reported p=0.06)		⊕⊕OO LOW	CRITICAL
Treatment-related adverse events - follow-up 0-5 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	6/18 (33.3%)	7/18 (38.9%)	RR 0.86 (0.36 to 2.05)	5 fewer per 100 (from 25 fewer to 41 more)	⊕OOO VERY LOW	CRITICAL

[1] Erstad et al. (1997)
[2] Downgraded 1 level - allocation concealment unclear
[3] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with cefoxitin (IV)
[4] Downgrade 1 level - no explanation was provided
[5] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 15: GRADE profile - Moxifloxacin (IV then oral) plus placebo (oral) vs Piperacillin with tazobactam (IV) then co-amoxiclav (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moxifloxacin (IV then oral) plus placebo (oral)**	**Piperacillin with tazobactam (IV) then co-amoxiclav(oral)**	**Relative (95% CI)**	**Absolute**		

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Cured - follow-up 6 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	84/110 (76.4%)	75/96 (78.1%)	RR 0.98 (0.84 to 1.13)	2 fewer per 100 (from 13 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Surgery requiring amputation												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	23/110 (20.9%)	24/96 (25%)	RR 0.84 (0.51 to 1.38)	4 fewer per 100 (from 12 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Significant adverse effects - follow-up 6 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	38/123 (30.9%)	35/110 (31.8%)	RR 0.97 (0.66 to 1.42)	1 fewer per 100 (from 11 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL

[1] Schaper et al. (2012)
[2] Downgraded 1 level - allocation concealment unclear.
[3] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 16: GRADE profile - Clinafloxacin (IV then oral) versus piperacillin with tazobactam (IV) then co-amoxiclav (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clinafloxacin (IV then oral)**	**Piperacillin with tazobactam (IV) then co-amoxiclav(oral)**	**Relative (95% CI)**	**Absolute**		
Cured or improvement - follow-up 14 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	15/29 (51.7%)	12/25 (48%)	RR 1.07 (0.63 to 1.85)	34 more per 1000 (from 178 fewer to 408 more)	⊕OOO VERY LOW	CRITICAL

[1] Siami et al. (2001)
[2] Downgraded 1 level - location concealment unclear
[3] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 17: GRADE profile - Ofloxacin (IV and oral) versus ampicillin/sulbactam (IV) then co-amoxiclav (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ofloxacin (IV and oral)**	**Ampicillin/sulbactam (IV) then co-amoxiclav(oral)**	**Relative (95% CI)**	**Absolute**		
Cured - follow-up 7 days												

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1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	40/47 (85.1%)	34/41 (82.9%)	RR 1.03 (0.85 to 1.23)	25 more per 1000 (from 124 fewer to 191 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of patients experienced treatment-related adverse events - follow-up 7 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	17/47 (36.2%)	9/41 (22%)	RR 1.65 (0.83 to 3.29)	14 more per 100 (from 4 fewer to 50 more)	⊕⊕OO LOW	CRITICAL

[1] Lipsky et al. 1997
[2] Downgraded 1 level - allocation concealment unclear
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with ofloxacin (IV and oral)

Table 18: GRADE profile - Moxifloxacin (IV and oral) versus co-amoxiclav (IV and oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moxifloxacin (IV and oral)**	**Amoxicillin/ Clavulanate (IV and oral)**	**Relative (95% CI)**	**Absolute**		
Cured (follow-up 14-28 days)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	254/315 (80.6%)	268/317 (84.5%)	RR 0.95 (0.88 to 1.02)	4 fewer per 100 (from 10 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Mean duration of treatment – days (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	13.5 days (SD+/- 4.8)	14.1 days (SD +/- 4.8)	Mean difference (days) = -0.60 (95%CI: -1.62 to 0.42)		⊕OOO VERY LOW	CRITICAL
People experiencing significant adverse effects - follow-up 14-28 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[5]	none	211/406 (52%)	190/397 (47.9%)	RR 1.09 (0.95 to 1.25)	4 more per 100 (from 2 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[5]	none	57/406 (14%)	45/397 (11.3%)	RR 1.24 (0.86 to 1.79)	3 more per 100 (from 2 fewer to 9 more)	⊕⊕⊕O VERY LOW	CRITICAL
Cured – people with DFI only - follow-up 14-28 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	25/49 (51%)	42/63 (66.7%)	RR 0.77 (0.55 to 1.06)	15 fewer per 100 (from 30 fewer to 4 more)	⊕⊕OO LOW	CRITICAL

[1] Vick-Fragoso et al. (2009)
[2] Downgraded 1 level - open label trial
[3] Downgrade 1 level - population includes all patients with complicated skin and skin structure infections, people with diabetic foot infection were 16% (n=134) of the sample
[4] Downgrade 1 level - no explanation was provided
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with moxifloxacin (IV and oral)

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Table 19: GRADE profile - Moxifloxacin (IV and oral) versus piperacillin with tazobactam (IV) and co-amoxiclav (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin (IV and oral)	Piperacillin with tazobactam (IV) and co-amoxiclav(oral)	Relative (95% CI)	Absolute		
Cured (follow-up 10-42 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness[2]	serious[3]	none	28/63 (44.4%)	25/64 (39.1%)	RR 1.14 (0.75 to 1.72)	5 more per 100 (from 10 fewer to 28 more)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals due to treatment-related adverse events - follow-up 10-42 days												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness[2]	very serious[4]	none	15/63 (23.8%)	15/64 (23.4%)	RR 1.02 (0.54 to 1.90)	0 more per 100 (from 11 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Adults experienced treatment-related adverse effects - follow-up 10-42 days												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness[2]	serious[3]	none	20/63 (31.7%)	8/64 (12.5%)	RR 2.54 (1.21 to 5.34)	19 more per 100 (from 3 more to 54 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Lipsky et al. 2007
[2] The analysis undertaken considered only those with diabetic foot infection
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with moxifloxacin (IV and oral)

Table 20: GRADE profile - Clindamycin Hydrochloride (oral) vs Cephalexin (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin Hydrochloride (oral)	Cephalexin (oral)	Relative (95% CI)	Absolute		
complete healing - follow-up 2 weeks												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	10/25 (40%)	9/27 (33.3%)	RR 1.20 (0.59 to 2.46)	7 more per 100 (from 14 fewer to 49 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	1/25 (4%)	2/27 (7.4%)	RR 0.54 (0.05 to 5.59)	3 fewer per 100 (from 7 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL

[1] Lipsky et al. 1990

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[2] Downgraded 1 level - blinding and allocation concealment unclear.
[3] Downgraded 2 levels - At a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 21: GRADE profile - Linezolid (IV or oral) vs ampicillin/sulbactam (IV) or co-amoxiclav (oral)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linezolid (IV or oral)	Ampicillin/Sulbactam (IV) or Co-amoxiclav(oral)	Relative (95% CI)	Absolute		
cured (follow-up 15-21 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	165/203 (81.3%)	77/108 (71.3%)	RR 1.14 (0.99 to 1.31)	10 more per 100 (from 1 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Withdrawals due to treatment-related adverse effects (follow-up 15-21 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	18/241 (7.5%)	4/120 (3.3%)	RR 2.24 (0.78 to 6.47)	4 more per 100 (from 1 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Participants experiencing treatment-related adverse effects (follow-up 15-21 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	64/241 (26.6%)	12/120 (10%)	RR 2.66 (1.49 to 4.73)	17 more per 100 (from 5 more to 37 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Lipsky et al. 2004 – findings for the ampicillin/sulbactam (IV) or co-amoxiclav (oral) arm of the trial were combined in the trials analysis
[2] Downgraded 1 level - open-labelled study, no blinding
[3] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with Linezolid (IV or oral)

Table 22: GRADE profile - Daptomycin (IV) vs Semi-synthetic penicillin (nafcillin or oxacillin or cloxacillin or flucloxacillin) (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daptomycin (IV)	Nafcillin or oxacillin or cloxacillin or flucloxacillin (IV)	Relative (95% CI)	Absolute		
Cured - follow-up 6-20 days												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[3]	none	16/25 (64%)	19/27 (70.4%)	RR 0.91 (0.62 to 1.33)	6 fewer per 100 (from 27 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL

[1] Lipsky et al. 2005b

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[2] Downgraded 1 level - allocation concealment not clear.
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

Table 23: GRADE profile - Daptomycin (IV) vs Vancomycin (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daptomycin (IV)	Vancomycin (IV)	Relative (95% CI)	Absolute		
Cured (follow-up 6-20 days)												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[3]	none	10/14 (71.4%)	20/29 (69%)	RR 1.04 (0.69 to 1.56)	3 more per 100 (from 21 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL

[1] Lipsky et al. 2005b
[2] Downgraded 1 level - allocation concealment not clear.
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

G.2 Antibiotic dual treatment

Table 24: GRADE profile – Metronidazole plus ceftriaxone (IV) vs ticarcillin with clavulanic acid (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metronidazole plus Ceftriaxone (IV)	Ticarcillin with clavulanic acid (IV)	Relative (95% CI)	Absolute		
Cured - follow-up 4 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	31/36 (86.1%)	28/34 (82.4%)	RR 1.05 (0.85 to 1.28)	3 more per 100 (from 12 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Mean duration of treatment – days (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	6.7 (SD +/- 3.3) days	6.1 (SD +/- 4.3) days	MD -0.60 lower (1.20 lower to 2.40 higher)		⊕⊕OO LOW	CRITICAL

[1] Clay et al. 2004
[2] Downgraded 1 level - open label trial
[3] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with metronidazole plus Ceftriaxone (IV)
[4] No explanation was provided

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Table 25: GRADE profile - Amdinocillin and cefoxitin (IV) vs cefoxitin (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amdinocillin and cefoxitin (IV)	Cefoxitin (IV)	Relative (95% CI)	Absolute		
Satisfactory clinical response - follow-up 6-20 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	18/20 (90%)	15/21 (71.4%)	RR 1.26 (0.93 to 1.70)	19 more per 100 (from 5 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Number of patients requiring amputation - follow-up 6-20 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[5]	none	2/20 (10%)	4/21 (19%)	RR 0.53 (0.11 to 2.56)	9 fewer per 100 (from 17 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL

[1] File et al. (1983)
[2] Downgraded 1 level - lack of allocation concealment
[3] Downgrade 1 level - analysis includes all patients with a bacterial soft tissue infection (n=45) with 55.5% (n=25) of participants having diabetes mellitus and 82.2% (n=37) having an infection localised to the lower extremities
[4] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with cefoxitin (IV)
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

G.3 Antibiotic dose in population

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.4 Antibiotic dose frequency

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.5 Antibiotic course length

Table 26: GRADE profile –Short-course (6 weeks) versus long-course (12 weeks) antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 weeks antibiotics	12 weeks antibiotics	Relative (95% CI)	Absolute		

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Overall remission												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	12/20 (60%)	14/20 (70%)	RR 0.86 (0.54 to 1.36)	10 fewer per 100 (from 32 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Complete healing												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	18/20 (90%)	16/20 (80%)	RR 1.13 (0.86 to 1.46)	10 more per 100 (from 11 fewer to 37 more)	⊕⊕OO LOW	CRITICAL
Major amputation												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	2/20 (10%)	2/20 (10%)	RR 1.00 (0.16 to 6.42)	0 fewer per 100 (from 8 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Antibiotic-related gastrointestinal adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	3/20 (15%)	9/20 (45%)	RR 0.33 (0.11 to 1.05)	30 fewer per 100 (from 40 fewer to 2 more)	⊕⊕OO LOW	CRITICAL

[1] Tone et al. 2015
[2] Downgraded 1 level - processes for blinding are unclear
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable harm with a 6 week course
[5] Downgraded 1 level - At a default minimal important difference of 25% relative risk increase, the effect estimate is consistent with no meaningful difference or appreciable benefit with a 6 week course

G.6 Children and young people

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.7 Prevention

No systematic reviews or randomised controlled trials met the inclusion criteria.

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Appendix H: Excluded studies

Excluded at full text from update search (2013 – 2018)

Study reference	Reason
Afkhamizadeh Mozhgan, Aboutorabi Robab, Ravari Hassan, Fathi Najafi, Mohsen , Ataei Azimi, Sajad , Javadian Langaroodi, Adineh , Yaghoubi Mohammad Ali, and Sahebkar Amirhossein (2018) Topical propolis improves wound healing in patients with diabetic foot ulcer: a randomized controlled trial. Natural product research 32(17), 2096-2099	Excluded intervention: No assessment of the efficacy of antimicrobials in the treatment of diabetic foot infections
Agarwal K, Mistry M, Shah S, and Nelapatla R (2015) The effectiveness of statins in improving wound healing in experimental diabetes. European surgical research. 55, 117	Excluded on intervention: the use of statins as treatment is outside scope
Ahmed A, and Ahmed M I (2014) A comparison of efficacy of topical use of phenytoin and vaseline gauze dressing with vaseline gauze dressing alone in healing of diabetic foot ulcers. Journal of Postgraduate Medical Institute 28(3), 297-302	Excluded on intervention: dressings are out of scope
Ahmed Marwa, Reffat Sherif A, Hassan Amany, and Eskander Fikry (2017) Platelet-Rich Plasma for the Treatment of Clean Diabetic Foot Ulcers. Annals of vascular surgery 38, 206-211	Excluded on intervention: the use Platelet-Rich Plasma is outside of scope
Andrews Karen L, Houdek Matthew T, and Kiemele Lester J (2015) Wound management of chronic diabetic foot ulcers: from the basics to regenerative medicine. Prosthetics and orthotics international 39(1), 29-39	Excluded on intervention: treatment out of scope
Anonymous (2015) Corrigenda to The Effect of PDRN, an adenosine receptor A2A agonist, on the healing of chronic diabetic foot ulcers: Results of a clinical trial, [J of Clin Endocrinol Metab, 99, 5 (2014) E746-E753, DOI:10.1210/jc.2013-3569]. Translational Endocrinology and Metabolism 100(2), 763	Excluded on study type: not an RCT or SR
Antunes-Ricardo Marilena, Gutierrez-Uribe Janet, and Serna-Saldivar Sergio O (2015) Anti-inflammatory glycosylated flavonoids as therapeutic agents for treatment of diabetes-impaired wounds. Current topics in medicinal chemistry 15(23), 2456-63	Excluded on study type: not an RCT or SR
Armenio Andrea, Cutrignelli Daniela Anna, Nardulli Maria Luisa, Maggio Giulio, Memeo Giuseppe, De Santis , Valerio , Giudice Giuseppe, and Ressa Cosmo Maurizio (2017) Bio-Engineering tissue and V.A.C. therapy: A new method for the treatment of extensive necrotizing infection in the diabetic foot. Annali italiani di chirurgia 88, 268-274	Excluded on study type: not an RCT or SR
Bakker K, Apelqvist J, Lipsky B A, Van Netten , J, International Working Group on the Diabetic, and Foot (2016) The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes/metabolism research and reviews 32 Suppl 1, 2-6	Excluded on study type: not an RCT or SR
Bassetti Matteo, Pecori Davide, Cojutti Piergiorgio, Righi Elda, and Pea Federico (2017) Clinical and pharmacokinetic drug evaluation of delafloxacin for the treatment of acute bacterial skin and skin structure infections. Expert opinion on drug metabolism & toxicology 13(11), 1193-1200	Excluded on study type: not an RCT or SR

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Study reference	Reason
Bonner T, Foster M, and Spears-Lanoix E (2016) Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the united states: A systematic review of the literature. Diabetic Foot and Ankle 7, 29758	Excluded on intervention: diabetes-related foot care knowledge and foot self-care practice interventions is out of scope
Braun L, Kim P J, Margolis D, Peters E J, and Lavery L A (2014) What's new in the literature: An update of new research since the original WHS diabetic foot ulcer guidelines in 2006. Wound Repair and Regeneration 22(5), 594-604	Excluded on study type: not a RCT or SR
Braun Liza R, Fisk Whitney A, Lev-Tov Hadar, Kirsner Robert S, and Isseroff Roslyn R (2014) Diabetic foot ulcer: an evidence-based treatment update. American journal of clinical dermatology 15(3), 267-81	Excluded on study type: not a RCT or SR
Busch Ch, Aschermann I, Mnich Ch, and D (2017) Treatment of chronic ulcers: A critical short analysis. Phlebologie 46(1), 13-18	Excluded on study type: not a RCT or SR
Butranova O I, and Razdrogina T N (2015) Antibiotics for skin and soft tissues infections in type 2 diabetes mellitus. The International journal of risk & safety in medicine 27 Suppl 1, S57-8	Excluded on study type: not a RCT or SR
Bystritsky R, and Chambers H (2018) Cellulitis and soft tissue infections. Annals of Internal Medicine 168(3), ITC17-ITC31	Excluded on study type: not a RCT or SR
Cardona A F, and Wilson S E (2015) Skin and Soft-Tissue Infections: A Critical Review and the Role of Telavancin in Their Treatment. Clinical Infectious Diseases 61(Supplement 2), S69-S78	Excluded on study type: not a RCT or SR
Cawich Shamir O, Harnarayan Patrick, Budhooram Steve, Bobb Nahmorah J, Islam Shariful, and Naraynsingh Vijay (2014) Wonder of Life (kalanchoe pinnata) leaves to treat diabetic foot infections in Trinidad & Tobago: a case control study. Tropical doctor 44(4), 209-13	Excluded on study type: not a RCT or SR
Cawich Shamir O, Harnarayan Patrick, Islam Shariful, Budhooram Steve, Ramsewak Shivaa, and Naraynsingh Vijay (2014) Adverse events in diabetic foot infections: a case control study comparing early versus delayed medical treatment after home remedies. Risk management and healthcare policy 7, 239-43	Excluded on study type: not a RCT or SR
Charles Patrick G. P, Uckay Ilker, Kressmann Benjamin, Emonet Stephane, and Lipsky Benjamin A (2015) The role of anaerobes in diabetic foot infections. Anaerobe 34, 8-13	Excluded on study type: not a RCT or SR
Chen S, Ma J, Xu L, Niu T, Dong J, Liu W, and Han Q (2017) Safety and effectiveness of Traditional Chinese Medicinal herbs for diabetic foot: a systematic review and Meta-analysis. Journal of Traditional Chinese Medicine 37(6), 735-745	Excluded on study type: not a SR
Chu Yuejie, Wang Chao, Zhang Jinghang, Wang Penghua, Xu Jun, Ding Min, Li Xiwen, Hou Xiaoli, Feng Shuhong, and Li Xuemei (2015) Can We Stop Antibiotic Therapy When Signs and Symptoms Have Resolved in Diabetic Foot Infection Patients?. The international journal of lower extremity wounds 14(3), 277-83	Excluded on study type: not a RCT or SR
Clerici Giacomo, and Faglia Ezio (2014) Saving the limb in diabetic patients with ischemic foot lesions complicated by acute infection. The international journal of lower extremity wounds 13(4), 273-93	Excluded on study type: not a RCT or SR
Cruciani M, Lipsky B A, Mengoli C, de Lalla , and F (2013) Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database of Systematic Reviews 2013(8), CD006810	Excluded on intervention: Granulocyte-colony stimulating factors as adjunctive therapy is out of scope

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Study reference	Reason
Cruciani M, Lipsky B A, Mengoli C, de Lalla , and F (2013) Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database of Systematic Reviews 2013(8), CD006810	Excluded on study type: not a RCT or SR
Dale Adam P, and Saeed Kordo (2015) Novel negative pressure wound therapy with instillation and the management of diabetic foot infections. Current opinion in infectious diseases 28(2), 151-7	Excluded on study type: not a RCT or SR
Davern R, and Hatunic M (2018) An overview of the management of diabetic foot ulcers. Irish Medical Journal 111(4), 726	Excluded on study type: not a RCT or SR
Delgado-Enciso I, Madrigal-Perez V M, Lara-Esqueda A, Diaz-Sanchez M G, Guzman-Esquivel J, Rosas-Vizcaino L E, Virgen-Jimenez O, Kleiman-Trujillo J, Lagarda-Canales M R, Ceja-Espiritu G, Rangel-Salgado V, Lopez-Lemus U A, Delgado-Enciso J, Lara-Basulto A D, and Hernandez A D. S (2018) Topical 5% potassium permanganate solution acceleratesthe healing process in chronic diabetic foot ulcers. Biomedical Reports 8(2), 156-159	Excluded on study type: not a RCT or SR
Di Domenico , G , Leonardi G M, Vaccaro G, and Nocera C (2016) Combined use of chlortetracycline and platelet rich plasma for the treatment of infected diabetic foot ulcers. Vox sanguinis. Conference: 34th international congress of the international society of blood transfusion. United arab emirates. Conference start: 20160903. Conference end: 20160908 111, 296	Excluded on study type: not a RCT or SR
Dryden Matthew S (2014) Novel antibiotic treatment for skin and soft tissue infection. Current opinion in infectious diseases 27(2), 116-24	Excluded on study type: not a RCT or SR
Dumville Jo C, Lipsky Benjamin A, Hoey Christopher, Cruciani Mario, Fiscon Marta, and Xia Jun (2017) Topical antimicrobial agents for treating foot ulcers in people with diabetes. The Cochrane database of systematic reviews 6, CD011038	Excluded as all studies have already been considered in NG19
Dumville Jo C, Lipsky Benjamin A, Hoey Christopher, Cruciani Mario, Fiscon Marta, and Xia Jun (2017) Topical antimicrobial agents for treating foot ulcers in people with diabetes. The Cochrane database of systematic reviews 6, CD011038	Excluded as all studies have already been considered in NG19
Elraiyah Tarig, Tsapas Apostolos, Prutsky Gabriela, Domecq Juan Pablo, Hasan Rim, Firwana Belal, Nabhan Mohammed, Prokop Larry, Hingorani Anil, Claus Paul L, Steinkraus Lawrence W, and Murad Mohammad Hassan (2016) A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. Journal of vascular surgery 63(2 Suppl), 46S-2	Excluded on intervention: does not consider the efficacy of antimicrobial treatment
Eslam Roza Badr, Burian Angela, Vila Greisa, Sauermann Robert, Hammer Alexandra, Frenzel Dorothea, Minichmayr Iris K, Kloft Charlotte, Matzneller Peter, Oesterreicher Zoe, and Zeitlinger Markus (2014) Target site pharmacokinetics of linezolid after single and multiple doses in diabetic patients with soft tissue infection. Journal of clinical pharmacology 54(9), 1058-62	Excluded on study type: not a RCT or SR
Esposito S, Noviello S, De Caro , F , and Boccia G (2018) New insights into classification, epidemiology and microbiology of sstis, including diabetic foot infections. Infezioni in Medicina 26(1), 3-14	Excluded on study type: not a RCT or SR
Everett E, and Mathioudakis N (2018) Update on management of diabetic foot ulcers. Annals of the New York Academy of Sciences 1411(1), 153-165	Excluded on study type: not a RCT or SR
Everett E, and Mathioudakis N (2018) Update on management of diabetic foot ulcers. Annals of the New York Academy of Sciences 1411(1), 153-165	Excluded on study type: not a RCT or SR

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Study reference	Reason
Faraklas I, Yang D, Eggerstedt M, Zhai Y, Liebel P, Graves G, Dissanaike S, Mosier M, and Cochran A (2016) A Multi-Center Review of Care Patterns and Outcomes in Necrotizing Soft Tissue Infections. Surgical Infections 17(6), 773-778	Excluded on population: Does not consider diabetic foot infections specifically
Fejfarova Vladimira, Jirkovska Alexandra, Dubsky Michal, Game Frances, Vydlakova Jana, Sekerkova Alena, Franekova Jana, Kucerova Monika, Striz Ilja, Petkov Vladimir, Bem Robert, Woskova Veronika, Nemcova Andrea, and Skibova Jelena (2016) An Alteration of Lymphocytes Subpopulations and Immunoglobulins Levels in Patients with Diabetic Foot Ulcers Infected Particularly by Resistant Pathogens. Journal of diabetes research 2016, 2356870	Excluded on study type: not a RCT or SR
Frydrych L M, Fattahi F, He K, Ward P A, and Delano M J (2017) Diabetes and sepsis: Risk, recurrence, and ruination. Frontiers in Endocrinology 8(OCT), 271	Excluded on study type: not a RCT or SR
Game F L, Apelqvist J, Attinger C, Hartemann A, Hinchliffe R J, Londahl M, Price P E, Jeffcoate W J, International Working Group on the Diabetic, and Foot (2016) Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes/metabolism research and reviews 32 Suppl 1, 154-68	Excluded on study type: not a RCT or SR
Ghotaslou Reza, Memar Mohammad Yousef, and Alizadeh Naser (2018) Classification, microbiology and treatment of diabetic foot infections. Journal of wound care 27(7), 434-441	Excluded on study type: not a RCT or SR
Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, and Del C (2015) Common harms from amoxicillin: A systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ 187(1), E21-E31	Excluded on study type: not a RCT or SR
Giurato L, Meloni M, Izzo V, and Uccioli L (2017) Osteomyelitis in diabetic foot: A comprehensive overview. World Journal of Diabetes 8(4), 135-142	Excluded on study type: not a RCT or SR
Gore M R (2018) Odontogenic necrotizing fasciitis: A systematic review of the literature. BMC Ear, and Nose and Throat Disorders 18(1), 14	Excluded on study type: not a RCT or SR
Gorski A, Miedzybrodzki R, Weber-Dabrowska B, Fortuna W, Letkiewicz S, Rogoz P, Jonczyk-Matysiak E, Dabrowska K, Majewska J, and Borysowski J (2016) Phage therapy: Combating infections with potential for evolving from merely a treatment for complications to targeting diseases. Frontiers in Microbiology 7(SEP), 1515	Excluded on population: not focused on diabetic foot infections
Grigoropoulou Pinelopi, Eleftheriadou Ioanna, Jude Edward B, and Tentolouris Nikolaos (2017) Diabetic Foot Infections: an Update in Diagnosis and Management. Current diabetes reports 17(1), 3	Excluded on study type: not a RCT or SR
Gurusamy K S, Koti R, Toon C D, Wilson P, and Davidson B R (2013) Antibiotic therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) in non surgical wounds. Cochrane Database of Systematic Reviews 2013(11), CD010427	Excluded as all studies have already been considered in NG19
Gurusamy K S, Koti R, Toon C D, Wilson P, and Davidson B R (2013) Antibiotic therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) in non surgical wounds. Cochrane Database of Systematic Reviews 2013(11), CD010427	Excluded as all studies have already been considered in NG19

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Study reference	Reason
Hadi Syed Fazle, Khaliq Tanwir, Bilal Nighat, Sikandar Imran, Saaiq Muhammad, Zubair Muhammad, and Aurangzeb Sidra (2007) Treating infected diabetic wounds with superoxidized water as anti-septic agent : a preliminary experience. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 17(12), 740-3	Excluded on study type: not an RCT or SR
Hall Ronald G, 2nd , Smith Winter J, Putnam William C, and Pass Steven E (2018) An evaluation of tedizolid for the treatment of MRSA infections. Expert opinion on pharmacotherapy 19(13), 1489-1494	Excluded on study type: not an RCT or SR
Hassoun Lauren A, and Sivamani Raja K (2017) A systematic review of lactoferrin use in dermatology. Critical reviews in food science and nutrition 57(17), 3632-3639	Excluded on study type: not an RCT or SR
Huang Yun-Yu, Jiang Miao, Zhang Chi, Wang Zhong, He Dan, Guo Yu-Ming, Tian Jing-Ping, Yu Xiu-Chen, and Lu Ai-Ping (2015) Benefits of Chinese Medicine Among Patients with Diabetic Foot: An Expert Review from Clinical Studies. Current vascular pharmacology 13(4), 520-5	Excluded on study type: not an RCT or SR
Iacopi Elisabetta, Coppelli Alberto, Goretti Chiara, and Piaggesi Alberto (2015) Necrotizing Fasciitis and The Diabetic Foot. The international journal of lower extremity wounds 14(4), 316-27	Excluded on study type: not an RCT or SR
Johnson J E (2014) Antibiotic treatment and conservative surgery plus short-course antibiotics were similar for diabetic foot osteomyelitis. Journal of bone and joint surgery - american volume 96(22), 1923	Excluded on study type: not an RCT or SR
Karri V V. S. N. R (2014) Current perspective in the management of diabetic foot ulcers - an overview on the Indian scenario. International Journal of Pharmacy and Pharmaceutical Sciences 6(9), 1-2	Excluded on study type: not an RCT or SR
Karri Veera Venkata Satyanarayana Reddy, Kuppusamy Gowthamarajan, Talluri Siddhartha Venkata, Yamjala Karthik, Mannemala Sai Sandeep, and Malayandi Rajkumar (2016) Current and emerging therapies in the management of diabetic foot ulcers. Current medical research and opinion 32(3), 519-42	Excluded on study type: not an RCT or SR
Karri Veera Venkata Satyanarayana Reddy, Kuppusamy Gowthamarajan, Talluri Siddhartha Venkata, Yamjala Karthik, Mannemala Sai Sandeep, and Malayandi Rajkumar (2016) Current and emerging therapies in the management of diabetic foot ulcers. Current medical research and opinion 32(3), 519-42	Excluded on study type: not an RCT or SR
Kwon K T, and Armstrong D G (2018) Microbiology and antimicrobial therapy for diabetic foot infections. Infection and Chemotherapy 50(1), 11-20	Excluded on study type: not an RCT or SR
Labban L (2014) Honey as a promising treatment for diabetic foot ulcers (DFU). JMS - Journal of Medical Society 28(2), 64-68	Excluded on study type: not an RCT or SR
Labban L (2014) Honey as a promising treatment for diabetic foot ulcers (DFU). JMS - Journal of Medical Society 28(2), 64-68	Excluded on study type: not an RCT or SR
Lauf Laszlo, Ozsvar Zsofia, Mitha Ismael, Regoly-Merei Janos, Embil John M, Cooper Angel, Sabol Mary Beth, Castaing Nathalie, Dartois Nathalie, Yan Jean, Dukart Gary, and Maroko Robert (2014) Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagnostic microbiology and infectious disease 78(4), 469-80	Excluded as already considered in NG19
Lavigne J P, and Sotto A (2017) Microbial management of diabetic foot osteomyelitis. Future Microbiology 12(14), 1243-1246	Excluded on study type: not a RCT or SR

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Study reference	Reason
Lazaro-Martinez Jose Luis, Aragon-Sanchez Javier, and Garcia-Morales Esther (2014) Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes care 37(3), 789-95	Excluded on intervention: surgery is outside scope
Lazaro-Martinez Jose Luis, Aragon-Sanchez Javier, and Garcia-Morales Esther (2014) Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes care 37(3), 789-95	Excluded on intervention: surgery is outside scope
Li L (2015) 30 cases with diabetic foot treated with Chinese medicine foot bath and nursing intervention. Henan traditional chinese medicine [he nan zhong yi] 35(4), 925-927	Excluded on study type: not an RCT or SR
Lipsky B A (2015) Stopping Antibiotic Therapy for a Diabetic Foot Infection: Some Answers, but More Questions. International Journal of Lower Extremity Wounds 14(3), 307-308	Excluded on study type: not an RCT or SR
Lipsky B A, Aragon-Sanchez J, Diggle M, Embil J, Kono S, Lavery L, Senneville E, Urbancic-Rovan V, Van Asten , and S (2016) IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes/Metabolism Research and Reviews 32(Supplement 1), 45-74	Excluded on study type: not an RCT or SR
Lipsky B A, Cannon C M, Ramani A, Jandourek A, Calmaggi A, and Friedland H D (2015) Ceftaroline fosamil for treatment of diabetic foot infections: the CAPTURE study experience. Diabetes/metabolism research and reviews 31(4), 395-401	Excluded on intervention: not focused on antimicrobials
Lipsky B A, Silverman M H, and Joseph W S (2017) A proposed new classification of skin and soft tissue infections modeled on the subset of diabetic foot infection. Open Forum Infectious Diseases 4(1), ofw255	Excluded on study type: not a RCT or SR
Lipsky Benjamin A (2016) Diabetic foot infections: Current treatment and delaying the 'post-antibiotic era'. Diabetes/metabolism research and reviews 32 Suppl 1, 246-53	Excluded on study type: not a RCT or SR
Lipsky Benjamin, A , Hoey Christopher, Cruciani Mario, and Mengoli Carlo (2014) Topical antimicrobial agents for preventing and treating foot infections in people with diabetes.	Excluded on study type: not a RCT or SR
Malhotra R, Shu-Yi Chan, C , and Nather A (2014) Osteomyelitis in the diabetic foot. Diabetic Foot and Ankle 5, 24445	Excluded on study type: not a RCT or SR
Mannucci Edoardo, Genovese Stefano, Monami Matteo, Navalesi Giovanni, Dotta Francesco, Anichini Roberto, Romagnoli Fabio, and Gensini Gianfranco (2014) Photodynamic topical antimicrobial therapy for infected foot ulcers in patients with diabetes: a randomized, double-blind, placebo-controlled study--the D.A.N.T.E (Diabetic ulcer Antimicrobial New Topical treatment Evaluation) study. Acta diabetologica 51(3), 435-40	Excluded on interventions: the use of photodynamics in combination with antimicrobials is outside scope
Markakis K, Bowling F L, and Boulton A J. M (2016) The diabetic foot in 2015: an overview. Diabetes/metabolism research and reviews 32 Suppl 1, 169-78	Excluded on study type: not a RCT or SR
Markakis K, Bowling F L, and Boulton A J. M (2016) The diabetic foot in 2015: an overview. Diabetes/metabolism research and reviews 32 Suppl 1, 169-78	Excluded on study type: not a RCT or SR
Markakis K, Faris A R, Sharaf H, Faris B, Rees S, and Bowling F L (2018) Local Antibiotic Delivery Systems: Current and Future Applications for Diabetic Foot Infections. International Journal of Lower Extremity Wounds 17(1), 14-21	Excluded on study type: not a RCT or SR

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Study reference	Reason
Mohajeri Gholamreza, Safaee Masumeh, and Sanei Mohamad Hossein (2014) Effects of topical Kiwifruit on healing of neuropathic diabetic foot ulcer. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 19(6), 520-4	Excluded on intervention: no assessment of the efficacy of antimicrobials for diabetic foot infections
Monogue Marguerite L, Stainton Sean M, Baummer-Carr Arlinda, Shepard Ashley K, Nugent James F, Kuti Joseph L, and Nicolau David P (2017) Pharmacokinetics and Tissue Penetration of Ceftolozane-Tazobactam in Diabetic Patients with Lower Limb Infections and Healthy Adult Volunteers. Antimicrobial agents and chemotherapy 61(12),	Excluded on study type: not a RCT or SR
Nikoloudi M, Eleftheriadou I, Tentolouris A, Kosta O A, and Tentolouris N (2018) Diabetic Foot Infections: Update on Management. Current Infectious Disease Reports 20(10), 40	Excluded on study type: not a RCT or SR
Noor S, Khan R U, and Ahmad J (2017) Understanding Diabetic Foot Infection and its Management. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 11(2), 149-156	Excluded on study type: not a RCT or SR
Norman Gill, Dumville Jo C, Mohapatra Devi Prasad, Owens Gemma L, and Crosbie Emma J (2016) Antibiotics and antiseptics for surgical wounds healing by secondary intention. The Cochrane database of systematic reviews 3, CD011712	Excluded on population: not focused on diabetic foot infection
Panagopoulos Periklis, Drosos Georgios, Maltezos Efstratios, and Papanas Nikolaos (2015) Local antibiotic delivery systems in diabetic foot osteomyelitis: time for one step beyond?. The international journal of lower extremity wounds 14(1), 87-91	Excluded on study type: not a RCT or SR
Panagopoulos Periklis, Drosos Georgios, Maltezos Efstratios, and Papanas Nikolaos (2015) Local antibiotic delivery systems in diabetic foot osteomyelitis: time for one step beyond?. The international journal of lower extremity wounds 14(1), 87-91	Excluded on study type: not a RCT or SR
Paola L D, Carone A, Vasilache L, and Pattavina M (2015) Overview on diabetic foot: A dangerous, but still orphan, disease. European Heart Journal, and Supplement 17(Supplement_A), A64-A68	Excluded on study type: not a RCT or SR
Pea F (2016) Practical concept of pharmacokinetics/pharmacodynamics in the management of skin and soft tissue infections. Current Opinion in Infectious Diseases 29(2), 153-159	Excluded on study type: not a RCT or SR
Peters E J, Lipsky B A, Aragon-Sanchez J, Boyko E J, Diggle M, Embil J M, Kono S, Lavery L A, Senneville E, Urbancic-Rovan V, Van Asten , S A, Jeffcoate W J, International Working Group on the Diabetic, and Foot (2016) Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes/metabolism research and reviews 32 Suppl 1, 145-53	Excluded on study type: not a RCT or SR
Peters E J, Lipsky B A, Aragon-Sanchez J, Boyko E J, Diggle M, Embil J M, Kono S, Lavery L A, Senneville E, Urbancic-Rovan V, Van Asten , S A, Jeffcoate W J, International Working Group on the Diabetic, and Foot (2016) Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes/metabolism research and reviews 32 Suppl 1, 145-53	Excluded on study type: not a RCT or SR
Poole R M (2014) Nemonoxacin: First global approval. Drugs 74(12), 1445-1453	Excluded on intervention: not focused diabetic foot injury

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Study reference	Reason
Pulido-Cejudo A, Guzman-Gutierrez M, Jalife-Montano A, Ortiz-Covarrubias A, Martinez-Ordaz J L, Noyola-Villalobos H F, and Hurtado-Lopez L M (2017) Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. Therapeutic Advances in Infectious Disease 4(5), 143-161	Excluded on study type: not a RCT or SR
Puzniak Laura A, Quintana Alvaro, Wible Michele, Babinchak Tim, and McGovern Paul C (2014) Methicillin-resistant Staphylococcus aureus infection epidemiology and clinical response from tigecycline soft tissue infection trials. Diagnostic microbiology and infectious disease 79(2), 261-5	Excluded on study type: not a RCT or SR
Puzniak Laura A, Quintana Alvaro, Wible Michele, Babinchak Tim, and McGovern Paul C (2014) Methicillin-resistant Staphylococcus aureus infection epidemiology and clinical response from tigecycline soft tissue infection trials. Diagnostic microbiology and infectious disease 79(2), 261-5	Excluded on study type: not a RCT or SR
Ray Amanda, Malin Danielle, Nicolau David P, and Wiskirchen Dora E (2015) Antibiotic Tissue Penetration in Diabetic Foot Infections A Review of the Microdialysis Literature and Needs for Future Research. Journal of the American Podiatric Medical Association 105(6), 520-31	Excluded on study type: not a RCT or SR
Robineau O, Nguyen S, and Senneville E (2016) Optimising the quality and outcomes of treatments for diabetic foot infections. Expert review of anti-infective therapy 14(9), 817-27	Excluded on study type: not RCT or SR
Sagray Bryan A, Malhotra Sabina, and Steinberg John S (2014) Current therapies for diabetic foot infections and osteomyelitis. Clinics in podiatric medicine and surgery 31(1), 57-70	Excluded on study type: not RCT or SR
Schaper N C, Van Netten , J J, Apelqvist J, Lipsky B A, Bakker K, International Working Group on the Diabetic, and Foot (2017) Prevention and management of foot problems in diabetes: A Summary Guidance for Daily Practice 2015, based on the IWGDF guidance documents. Diabetes research and clinical practice 124, 84-92	Excluded on study type: not RCT or SR
Selva Olid, Anna , Sola Ivan, Barajas-Nava Leticia A, Gianneo Oscar D, Bonfill Cosp, Xavier , and Lipsky Benjamin A (2015) Systemic antibiotics for treating diabetic foot infections. The Cochrane database of systematic reviews (9), CD009061	Excluded as all studies have already been considered in NG19
Senneville E, and Robineau O (2017) Treatment options for diabetic foot osteomyelitis. Expert Opinion on Pharmacotherapy 18(8), 759-765	Excluded on study type: not RCT or SR
Senneville Eric, and Robineau Olivier (2017) Treatment options for diabetic foot osteomyelitis. Expert opinion on pharmacotherapy 18(8), 759-765	Excluded on study type: not RCT or SR
Sinwar Prabhu Dayal (2015) The diabetic foot management - recent advance. International journal of surgery (London, and England) 15, 27-30	Excluded on study type: not
Spichler Anne, Hurwitz Bonnie L, Armstrong David G, and Lipsky Benjamin A (2015) Microbiology of diabetic foot infections: from Louis Pasteur to 'crime scene investigation'. BMC medicine 13, 2	Excluded on study type: not RCT or SR
Strohal Robert, Mittlbock Martina, and Hammerle Gilbert (2018) The Management of Critically Colonized and Locally Infected Leg Ulcers with an Acid-Oxidizing Solution: A Pilot Study. Advances in skin & wound care 31(4), 163-171	Excluded on study type: not a RCT or SR

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Study reference	Reason
Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, Fayard A, Beltrand E, Lemaire C, and Senneville E (2015) Erratum: Six-Week Versus Twelve-Week Antibiotic Therapy for Nonsurgically Treated Diabetic Foot Osteomyelitis: A Multicenter Open-Label Controlled Randomized Study (Diabetes Care (2015) 38 (302-307)). Diabetes Care 38(4), 735	Excluded on study type: Linked to an included study but not an RCT or SR
Trujillo Valentin, Marin-Luevano Paulina, Gonzalez-Curiel Irma, Rodriguez-Carlos Adrian, Ramirez-Reyes Maira, Layseca-Espinosa Esther, Enciso-Moreno Jose A, Diaz Lorenza, and Rivas-Santiago Bruno (2017) Calcitriol promotes proangiogenic molecules in keratinocytes in a diabetic foot ulcer model. The Journal of steroid biochemistry and molecular biology 174, 303-311	Excluded on study type: not an RCT or SR
Tsang K K, Kwong E W. Y, Woo K Y, To T S. S, Chung J W. Y, and Wong T K. S (2015) The anti-inflammatory and antibacterial action of nanocrystalline silver and manuka honey on the molecular alternation of diabetic foot ulcer: A comprehensive literature review. Evidence-based Complementary and Alternative Medicine 2015, 218283	Excluded on study type: not a RCT or SR
Tucker H, Wible M, Gandhi A, and Quintana A (2017) Efficacy of intravenous tigecycline in patients with Acinetobacter complex infections: Results from 14 Phase III and Phase IV clinical trials. Infection and Drug Resistance 10, 401-417	Excluded on population: not focused on diabetic foot infection
Ubbink Dirk T, Santema Trientje B, and Stoekenbroek Robert M (2014) Systemic wound care: a meta-review of cochrane systematic reviews. Surgical technology international 24, 99-111	Excluded on population: not diabetic foot infections specifically
Uckay I, Jornayvaz F R, Lebowitz D, Gastaldi G, Gariani K, and Lipsky B A (2018) An overview on diabetic foot infections, including issues related to associated pain, hyperglycemia and limb ischemia. Current Pharmaceutical Design 24(12), 1243-1254	Excluded on study type: not an RCT or SR
Uckay I, Kressmann B, Malacarne S, Toumanova A, Jaafar J, Lew D, and Lipsky B A (2018) A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. BMC Infectious Diseases 18(1), 361	Excluded on intervention: dressings are outside scope
Uckay I, Von Dach , E , Kressmann B, Timurkaynak F, and Pittet D (2017) Less antibiotic use and remission in diabetic foot infections. Antimicrobial resistance and infection control. Conference: international conference on prevention and infection control, and ICPIC 2017. Switzerland 6(Supplement 3) (no pagination),	Excluded on study type: conference abstract
Uckay Ilker, Aragon-Sanchez Javier, Lew Daniel, and Lipsky Benjamin A (2015) Diabetic foot infections: what have we learned in the last 30 years?. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 40, 81-91	Excluded on study type: not RCT or SR
Uckay Ilker, Gariani Karim, Dubois-Ferriere Victor, Suva Domizio, and Lipsky Benjamin A (2016) Diabetic foot infections: recent literature and cornerstones of management. Current opinion in infectious diseases 29(2), 145-52	Excluded on study type: not RCT or SR
Ullal S, and Adhikari P (2014) Efficacy of honey in healing diabetic ulcers - a pilot study. Diabetes research and clinical practice 106(1 Suppl), S63-S64	Excluded on study type: not RCT or SR

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Study reference	Reason
Vas P, Panagopoulos P, and Papanas N (2016) "Ah, wherefore with infection should he live?": Microbial virulence factors in diabetic foot ulceration. Current Vascular Pharmacology 14(6), 498-501	Excluded on study type: Not RCT or SR
Vouillarmet Julien, Moret Myriam, Morelec Isabelle, Michon Paul, and Dubreuil Julien (2017) Application of white blood cell SPECT/CT to predict remission after a 6 or 12 week course of antibiotic treatment for diabetic foot osteomyelitis. Diabetologia 60(12), 2486-2494	Excluded on intervention: white blood cell SPECT/CT outside scope
Wen M (2015) Observation and nursing of the early diabetic foot with Chinese herbal medicinal bath therapy. Chinese medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu] 13(15), 110-112	Excluded on intervention: no assessment of the efficacy of antimicrobials
Xia X, Cheng L, Zhang S, Wang L, and Hu J (2018) The role of natural antimicrobial peptides during infection and chronic inflammation. Antonie van Leeuwenhoek, and International Journal of General and Molecular Microbiology 111(1), 5-26	Excluded on population: not focused on diabetic foot infections
Xu Dixon H, Zhu Ziwen, and Fang Yujiang (2017) The Effect of a Common Antibiotics Doxycycline on Non-Healing Chronic Wound. Current pharmaceutical biotechnology 18(5), 360-364	Excluded on population: not focused on diabetic foot infections
Yongabi K A, Novakovic M, Bukvicki D, Reeb C, and Asakawa Y (2016) Management of diabetic bacterial foot infections with organic extracts of liverwort marchantia debilis from Cameroon. Natural Product Communications 11(9), 1333-1336	Excluded on intervention: no assessment of the efficacy of antimicrobials

Study originally in NICE clinical guideline 19: Diabetic foot problems: prevention and management, but excluded from the update

Study reference	Reason for exclusion
Lipsky,B.A. Kuss,M. Edmonds,M. Reyzelman,A. Sigal,F. (2012) Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial.Journal of the American Podiatric Medical Association 102 (4) 323-32.	Excluded on intervention: dressings are outside scope

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