Review

Short- versus long-course antibiotics in osteomyelitis: A systematic review and meta-analysis

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ABSTRACT

Current practice of long-term antibiotic use in patients with osteomyelitis is controversial. Recent studies showed short-term antibiotic use to be non-inferior to long-term use, but the results of these studies have been inconsistent. In this review, the PubMed and Embase databases were searched from inception through to June 2018 for randomised controlled trials (RCTs), cohort studies or case–control studies comparing two different durations of antibiotic use. Short antibiotic courses were defined as antibiotics administered for a shorter period than the recommended 4–6 weeks. A random-effects model was used to calculate summary odds ratios (ORs) of treatment failure in patients treated with short-course antibiotics compared with long-course antibiotics. A total of 15 articles (5 RCTs and 10 observational studies) and 3598 patients were included. The overall OR of treatment failure in patients receiving short-course antibiotics was 1.50 [95% confidence interval (CI) 0.97–2.34]. Subgroup analysis revealed that a short course of antibiotic treatment was associated with an increased treatment failure rate in vertebral osteomyelitis (OR = 2.06, 95% CI 1.18–3.57) while having a similar rate to a long antibiotic course in acute osteomyelitis of childhood (OR = 1.86, 95% CI 0.75–4.64). Meta-regression found a higher proportion of *Staphylococcus aureus* infection was related to a higher risk of treatment failure in patients with vertebral osteomyelitis (Coef. = 4.996; *P* = 0.032). Short-course antibiotics are safe and effective in children with acute osteomyelitis. Long-course antibiotics may still be preferred in vertebral osteomyelitis, especially in patients with *S. aureus* infection.

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1. Introduction

Osteomyelitis is an infection of the bone commonly caused by pyogenic bacteria, mycobacteria and fungi [1]. Infection routes include haematogenous spread and contiguous contamination. Haematogenous osteomyelitis is most commonly caused by *Staphylococcus aureus* and is usually monomicrobial. Contiguous osteomyelitis commonly occurs following open trauma or surgery and is usually polymicrobial [2]. Osteomyelitis tends to occur at different sites in different groups of patients. In adults, the vertebrae are the most common site of infection, whilst in children the long bones, especially the femur and tibia, are the predominant sites [3,4]. In diabetic patients, osteomyelitis of the lower extremities is often seen owing to vascular and neurological insufficiency [1]. Osteomyelitis can also be acute or chronic, although currently there is no consistent definition [5–7]. The presence of necrotic bones is one of the key features of chronic osteomyelitis [8].

Osteomyelitis is a deadly disease and its incidence has substantially increased in recent years. A recent Japanese study found that the incidence of vertebral osteomyelitis increased from 5.3/100 000 population per year in 2007 to 7.4/100 000 in 2010 [9]. Similar results reported in the USA showed that the incidence of vertebral osteomyelitis rose from 2.9/100 000 in 1998 to 5.4/100 000 in 2013 [10]. In children, the incidence of acute osteomyelitis and septic arthritis was estimated to be 8/100 000 children per year [11].

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The mortality rate of osteomyelitis has remained high. In vertebral osteomyelitis, mortality ranges from 3–6% in developed countries [9,12].

Treatment of osteomyelitis generally includes surgical debridement and antibiotic therapy. Current guidelines recommend that most patients with vertebral osteomyelitis are treated with 6 weeks of parenteral or highly bioavailable oral antimicrobial therapy [13]. For chronic osteomyelitis of the long bones, the current practice is a 4–6-week course of parenteral antibiotics, followed by oral therapy ranging from weeks to months [14,15]. For diabetic foot osteomyelitis, $\geq$3 months of antibiotic therapy is recommended for non-surgically treated patients [16]. Studies supporting current practice were mostly low-quality evidence, including observational studies and uncontrolled case series. However, prolonged antibiotic therapy may lead to increased antimicrobial resistance, unnecessary health expenditure and patient discomfort. Recent systematic reviews and meta-analyses on the duration of antibiotic courses for the treatment of acute bacterial sinusitis, acute pyelonephritis and community-acquired pneumonia revealed that there was no difference in the outcome between a short and long antibiotic course [17–19].

A systematic review in 2013 suggested that early transition from intravenous (i.v.) to oral therapy may be as effective as longer courses for acute osteomyelitis of childhood [20]. Therefore, the aim of this review was to summarise the available evidence and to analyse the comparative effectiveness and safety of a long versus short duration of antibiotic therapy for osteomyelitis.

2. Methods

2.1. Search strategy

A systematic literature search was conducted in the PubMed and Embase databases for antibiotics, treatment duration and osteomyelitis from inception to June 2018. Three separate queries composed of Medical Subject Headings (MeSH) or Embase subject headings (Emtree) and title/abstract keywords for the three topics described above were combined, along with a query starting with 'NOT' to exclude unwanted article types (Supplementary Table S1). References cited in the retrieved articles were also screened to include studies not retrieved from the initial search. The search was not limited based on publication date, country or language. The database search was conducted independently by two authors (CYH and HTY).

2.2. Inclusion and exclusion criteria

Two reviewers (CYH and HTY) independently identified articles eligible for in-depth examination using the following inclusion and exclusion criteria. Studies were included if they enrolled patients with osteomyelitis who underwent an antibiotics regimen regardless of the presence of another intervention and compared outcomes between a longer and a shorter course of antibiotics. A shorter course of antibiotics was generally defined as antibiotics administered for a shorter period than the recommended 4–6 weeks. In acute osteomyelitis of childhood, the definition of short-course antibiotics was even shorter (i.e. 2–3 weeks). The outcomes could be recurrence rate, cure rate, mortality rate, complication rate or the requirement for a second treatment in the follow-up period. Randomised controlled trials (RCTs), cohort studies and case–control studies were included.

Studies were excluded if they enrolled patients with infections caused by *Mycobacterium, Brucella*, fungi or viruses. Studies with no definite outcome described separately for patients receiving different durations of antibiotics were also excluded. Moreover, case reports, case series, meta-analyses, guidelines, reviews and animal studies were also excluded. A study labelled as a case series could still be considered a cohort study if it described separate outcomes for different levels of exposure (i.e. different durations of antibiotics) [21]. For the two studies that reported the same cohort, only the study with more patients was included. Any discrepancy between reviewers as to which articles merited inclusion were resolved by consensus of three authors (CYH, HTY and CCL). The study selection process is summarised in Fig. 1.

2.3. Data extraction and outcome definition

Two reviewers independently extracted the following information: general study information (first author, year and country); study design; study population (size, age, type of osteomyelitis, diagnostic criteria and pathogen involved); antibiotic treatment (route, duration and type); and outcome (outcome definition and effect estimates). Different antibiotic durations of i.v. therapy or total antibiotic therapy (i.e. i.v. plus oral) were compared. The primary endpoint of the meta-analysis was 'treatment failure', including recurrence, persistent infection or the need for further unexpected intervention (either a second course of antibiotics or additional surgery). Persistent symptoms of infection leading to a prolonged course of antibiotics in patients who were originally scheduled to receive a short course of antibiotics was also counted as treatment failure. The odds ratio (OR) or the risk ratio was adopted as an effect estimate, defined as the odds (or risk) of treatment failure in patients receiving short-term antibiotics divided by the odds (or risk) of treatment failure in patients receiving long-term antibiotics.

2.4. Quality assessment

A modified Jadad scale was used for quality assessment of the RCTs. The double-blind criterion failed to discriminate between the quality of the studies, so it was changed to whether the people who assessed the outcomes (investigators) were blinded. When the investigators were blinded, one point was given to the study in the quality assessment.

The quality assessment for observational studies in this systematic review was adapted from the 'Newcastle–Ottawa Quality Assessment Form for Cohort Studies', and some of the statements in it were adjusted according to the current topic (Supplementary Table S2). For the diagnostic criteria, articles from the Infectious Diseases Society of America (IDSA) and other research were referred to [13,16,22]. The criterion for follow-up was determined to be 1 year following the study of Tice et al., which yielded the result that 95% of osteomyelitis recurrence occurs within 1 year [23].

When studies were determined to have pertinent data not included in the published article, attempts to contact the authors were made to procure the missing data. When the author did not respond, the article would be deemed as not having the full data.

2.5. Statistical analysis

Pooled ORs and 95% confidence intervals (CIs) were summarised with the DerSimonian and Laird method for random-effect models [24]. Heterogeneity was quantified with the I^2 statistic, which describes the variation in effect size that is attributable to heterogeneity across studies [24,25]. Galbraith plots were used to visualise the impact of individual studies on the overall homogeneity test statistic [26]. Meta-regression was used to evaluate whether effect size estimates were significantly different by specific study characteristics and quality factors. In addition to meta-regression, effect size was re-estimated stratified on the same study characteristics and quality factors, so that they are available as separate estimates. Even when the meta-regression
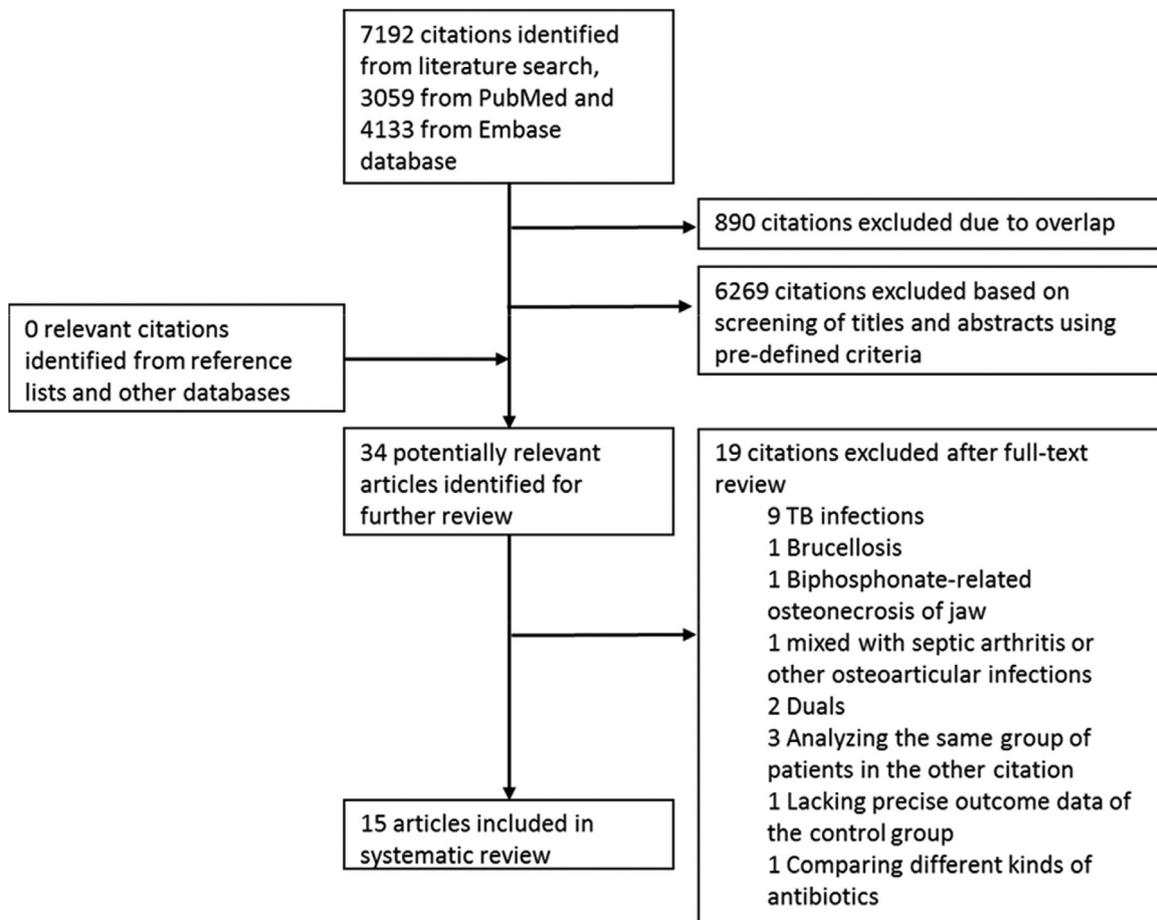
Fig. 1. Flow diagram of the selection process. TB, tuberculosis.

result was not statistically significant, a subgroup analysis was conducted when a study characteristic was clinically relevant. The presence and the effect of publication bias was examined using a combination of the Begg's and Egger's tests [25,27,28]. This procedure considers the hypothetical possibility of studies that were missed, imputes their ORs, and recalculates a pooled OR that incorporates these hypothetical missing studies [27]. Statistical analyses were performed using Stata Statistical Software: Release 10.1 (StataCorp LP, College Station, TX). The metan, metabias, galbr and metareg macros were used for meta-analytic procedures. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Search results

By searching the PubMed and Embase databases, 3059 and 4133 articles, respectively, were found. After excluding 890 duplicate citations, 6268 articles were screened for titles and abstracts. Thirty-four articles were identified for full-text review. No additional articles were identified from other databases or the reference lists of retrieved articles in the initial search. Finally, 15 articles were eligible for inclusion in this review by applying the pre-defined criteria. The selection process is shown in Fig. 1.

3.2. Study characteristics and quality assessment

The 15 studies consisted of 5 RCTs (555 patients) and 10 observational studies (3043 patients). The main characteristics of individual studies are given in Table 1 [29–43]. Among the 15 included studies, 7 studies focused on vertebral osteomyelitis, 6 studies on

acute osteomyelitis in childhood, 1 study on chronic osteomyelitis and 1 study on diabetic foot osteomyelitis. None of the five RCTs were double-blinded, whilst the studies by Bernard et al. [32] and Jaberi et al. [42] were investigator-blinded. Three of the RCTs adopted computer-generated random sequences as the randomisation process, whilst the other two did not specify the randomisation processes. Quality assessment for the five RCTs is summarised in Table 2.

All ten observational studies were retrospective studies. Three were graded to have 'good' quality, three 'fair' and the other four 'poor'. Either multivariate analysis or a propensity score model was adopted by the four studies in which the adjusted OR could be assessed. On the other hand, the four studies graded 'poor' lacked a comparable background between patients receiving a long and short course of antibiotics, which implies a high risk of selection bias. Quality assessment of the ten observational studies is shown in Table 3.

3.3. Effect of short- versus long-course antibiotics

Overall there was no significant difference in the rate of treatment failure in patients with osteomyelitis treated with short-course regimens compared with long-course regimens (OR = 1.50, 95% CI 0.97–2.34; total 3598 patients) (Fig. 2). However, a trend favouring a longer-course regimen was observed, and moderate heterogeneity ($I^2 = 41.4\%$) was found between the studies.

3.3.1. Randomised controlled trials

No difference in outcomes was found between short- and long-course antibiotic regimens, with low heterogeneity among five RCTs (OR = 1.18, 95% CI 0.83–1.67; $I^2 = 0.0\%$) (Fig. 3A).

Table 1

Characteristics of included studies

First author (country, year)	Study design	OM type	Age (years)	Diagnostic criteria	Abx route and duration	Outcome definition	Adjustment	OR (95% CI)	Sample size
Chang WS (Taiwan, 2018)	SC, retro. cohort	Haematogenous VO	Mean (S.D.): 61.6 (13.4)	Clinical S/S, imaging, with or without culture	i.v. + oral, <4 weeks vs. ≥4 weeks	Recurrence: clinical signs, laboratory data or received second course of Abx	Polymicrobial infection, male, multiple vertebral body involvement, any abscess formation and treated medically alone	3.74 (1.20–11.68)	330
McNeil JC (USA, 2017)	SC, retro. cohort	Acute haematogenous OM and SA in children, *Staphylococcus*	Median (IQR): short, 7.8 (5.8–12.5); long, 7.3 (5.7–9.7)	Clinical S/S, imaging, culture	i.v. + oral, <7 days vs. ≥7 days	Long-term orthopaedic complications: growth problems, chronic OM	–	0.48 (0.09–2.43)	35
Park KH (Korea, 2016)	Multicentre, retro. cohort	Haematogenous VO	Median (IQR): 65 (58–72)	Imaging, culture	i.v. + oral, ≤6 weeks vs. >6 weeks	Recurrence: clinical S/S or received a second course of parenteral Abx	–	3.66 (1.62–8.24)	314
Bernard L (France, 2015)	Multicentre, RCT, non-inferiority design	VO	Mean (S.D.): 61 (17)	Imaging, culture	i.v. + oral, 6 weeks vs. 12 weeks	Cure: no clinical S/S, CRP ≤ 10 mg/L	–	0.99 (0.58–1.69)	319
Tone A (France, 2015)	Multicentre, RCT	Diabetic foot OM	Mean (S.D.): 64.2 (10.5)	Presence of wound, imaging, culture	i.v. + oral, 6 weeks vs. 12 weeks	Remission: no S/S and no need for surgery	–	1.56 (0.42–5.76)	40
Babouee Flury B (Switzerland, 2014)	SC, retro. cohort	Haematogenous VO	Median (IQR): 65 (51–76)	Clinical S/S, imaging, culture	Switch from i.v. to oral therapy after 2 weeks vs. >2 weeks	Recovery: no clinical S/S	–	1.88 (0.04–98.29)	61
Arnold R (USA, 2014)	SC, retro. cohort	Haematogenous VO	Mean: 55	Clinical S/S, imaging, laboratory data	i.v., ≤6 weeks vs. >6 weeks	Treatment failure: need to re-operate or to administer a second complete course of Abx	HIV status, level of surgery (lumbar/sacral), type of Abx and organism type	2.57 (0.62–10.70)	94
Locke T (UK, 2014)	SC, retro. cohort	Spontaneous MSSA VO	Median (IQR): 65 (22)	Clinical S/S, imaging, culture	i.v. + oral, ≤12 weeks vs. >12 weeks i.v., ≤4 weeks vs. >4 weeks	Cure: no clinical S/S or residual problems	–	8.51 (0.43–169.97)	39
Bouchoucha S (France, 2013)	SC, RCT	Acute haematogenous OM of childhood	Mean (S.D.): 7.32 (3.735)	Clinical S/S with any of the following: imaging, culture	i.v., 7 days vs. 14 days	Cure: no clinical S/S and no findings on imaging	–	8.67 (0.44–169.06)	53

Table 1 (*continued*)

First author (country, year)	Study design	OM type	Age (years)	Diagnostic criteria	Abx route and duration	Outcome definition	Adjustment	OR (95% CI)	Sample size
Rod-Fleury T (Switzerland, 2011)	SC, retro. cohort	Chronic OM (mainly long bones)	Median: 41	Presence of bone abscess, imaging, culture, ≥3 months	i.v. + oral, ≤6 weeks vs. > 6 weeks	Remission: no clinical S/S, mechanical sequelae were allowed	Age, immunosuppression, number of surgical interventions, duration of i.v. therapy	1.25 (0.17–9.01)	49
Peltola H (Finland, 2010)	Multicentre, RCT, non-inferiority design	Acute haematogenous OM of childhood	Median: 9.2. Range: 3 months to 15 years	Clinical S/S, culture	i.v. (2–4 days) + oral, 20 days vs. 30 days	Full recovery: no S/S with no re-administration	–	1.16 (0.34–4.01)	131
Zaoutis T (USA, 2009)	Multicentre, retro. cohort	Acute OM of childhood	Range: 2 months to 17 years	ICD-9-CM code	Prolonged i.v. therapy (procedure code 38.93: venous catheterisation, not elsewhere classified) vs. early transition to oral therapy	Treatment failure: re-hospitalisation with code of OM, complication or surgery	Age, sex, race, surgical procedure, anatomic location, *S. aureus* or MRSA (by code), PHIS case mix index (severity based on relative weights)	0.77 (0.49–1.21)	1969
Roblot F (France, 2007)	Multicentre, retro. cohort	VO	Mean (S.D.): 64 (16)	Imaging, culture	i.v. + oral, ≤6 weeks vs. >6 weeks	Recovery: no clinical S/S	–	0.49 (0.10–2.39)	120
Jaberi FM (Iran, 2002)	SC, RCT	Acute haematogenous OM and SA in children	OM patients: mean (range): 9.8 (2–14)	Clinical S/S, imaging, culture, laboratory data	OM patients: i.v., 10 days vs. 2 weeks	Scoring system: functional status, imaging, discharge/drainage	–	7.22 (0.28–189.19)	12 (OM patients)
Vinod MB (Australia, 2002)	SC, retro. cohort	Acute OM and SA in children	OM patients: median (range): 5.0 (0.6–14.1)	Clinical S/S, imaging, culture, laboratory data	i.v. + oral, ≤3.5 weeks vs. >3.5 weeks	Cure: no residual disability or limitation of movement, growth disturbance or chronic disease	–	5.00 (0.09–280.02)	32 (OM patients)

OM, osteomyelitis; Abx, antibiotic(s); OR, odds ratio; CI, confidence interval; SC, single-centre; retro., retrospective; VO, vertebral osteomyelitis; S.D., standard deviation; S/S, signs or symptoms; i.v., intravenous; SA, septic arthritis; IQR, interquartile range; RCT, randomised control trial; CRP, C-reactive protein; MSSA, methicillin-sensitive *Staphylococcus aureus*; HIV, human immunodeficiency virus; ICD, International Statistical Classification of Diseases and Related Health Problems; MRSA, methicillin-resistant *S. aureus*; PHIS, Pediatric Health Information System.

Table 2
Quality assessment of the randomised controlled trials

First author (country, year)	Topic	Randomisation adopted	Appropriate randomisation method	Investigator blinded	Appropriate blinding method	Withdrawals described	Total score
Bernard L (France, 2015)	Vertebral osteomyelitis	1	1	1	0	1	4
Tone A (France, 2015)	Diabetic foot osteomyelitis	1	1	0	0	1	3
Bouchoucha S (France, 2013)	Acute haematogenous osteomyelitis of childhood	1	0	0	0	1	2
Peltola H (Finland, 2010)	Acute haematogenous osteomyelitis of childhood	1	1	0	0	1	3
Jaberi FM (Iran, 2002)	Acute haematogenous osteomyelitis of childhood	1	0	1	0	1	3

3.3.2. Observational studies

Summary estimates of the ten observational studies revealed that short-course antibiotic regimens might increase the rate of treatment failure, but the result was not statistically significant with high heterogeneity between studies (OR = 1.72, 95% CI 0.98–3.02; $I^2 = 80.6\%$) (Fig. 3B). The difference between a long and short course of antibiotics decreased when observational studies adopting multivariate analysis or propensity score model alone were analysed separately, and the heterogeneity also decreased (OR = 1.60, 95% CI 0.64–4.04; $I^2 = 63.0\%$). In addition, an analysis was performed where those observational studies adopting multivariate analysis or propensity score model were pooled with RCTs. The results of nine studies with 2997 patients revealed no difference in treatment failure between short- and long-course regimens (OR = 1.33, 95% CI 0.86–2.06; $I^2 = 31.7\%$).

3.3.3. Subgroup analysis—type of osteomyelitis

When the route of infection was considered, nine studies with a total of 1067 patients only included patients infected by haematogenous spread. Of these, five studies focused on vertebral osteomyelitis and four studies focused on acute osteomyelitis in childhood. The pooled result revealed a significantly higher rate of treatment failure in patients treated with short-course antibiotic regimens (OR = 2.68, 95% CI 1.58–4.56; $I^2 = 74.7\%$).

When the type of osteomyelitis was considered, there were seven studies with a total of 1277 patients with vertebral osteomyelitis, six studies with a total of 2232 patients with acute osteomyelitis in childhood, one study on chronic osteomyelitis and one study on diabetic foot osteomyelitis. First, the seven studies on vertebral osteomyelitis demonstrated a significantly higher rate of treatment failure in patients treated with a short course of antibiotics (OR = 2.06, 95% CI 1.18–3.57) (Fig. 4A). However, great heterogeneity existed ($I^2 = 80.5\%$). When the three studies that defined short-course antibiotics as total (i.v. plus oral) antibiotics shorter than 6 weeks were combined, there was no significant difference between short- and long-course antibiotics (OR = 1.30, 95% CI 0.52–3.25; $I^2 = 83.5\%$). Second, the six studies on acute osteomyelitis in childhood found similar outcomes between short- and long-course antibiotics with large heterogeneity (OR = 1.86, 95% CI 0.75–4.64; $I^2 = 85.5\%$) (Fig. 4B). Third, as there was only one article on each of chronic osteomyelitis and diabetic foot osteomyelitis it was not possible to conduct a subgroup analysis. However, both studies reported no significant difference in primary outcome between short- and long-course antibiotics. A summary of the subgroup analysis is shown in Table 4.

3.3.4. Subgroup analysis—treatment factors

The seven studies assessing the duration of i.v. treatment were analysed and it was found that the duration of i.v. antibiotics did not significantly affect treatment outcomes (OR = 1.69, 95% CI 0.85–3.36, $I^2 = 84.9\%$). On the other hand, the nine studies addressing the impact of the total duration of antibiotic treatment revealed that a shorter total duration of antibiotics may be associated with an unfavourable outcome (OR = 1.85, 95% CI 1.07–3.20; $I^2 = 74.7\%$). The six studies that exclusively enrolled patients who underwent surgical debridement were also analysed and no difference was found between short- and long-course antibiotic treatment (OR = 1.38, 95% CI 0.82–2.31; $I^2 = 53.7\%$). The results are shown in Table 4.

3.3.5. Meta-regression

The cause of the significant heterogeneity among studies regarding vertebral osteomyelitis was further explored. The proportion of *S. aureus* infection was identified to be an important factor. Studies with a higher proportion of *S. aureus* infection tended to report a higher risk of treatment failure in patients with vertebral osteomyelitis treated with short-course antibiotics (coef. = 4.996; $P = 0.032$) (Fig. 5).

3.4. Publication bias and heterogeneity analysis

There was no significant publication bias in the meta-analysis, as demonstrated by Begg's test ($P = 0.62$) and Egger's test ($P = 0.94$). A funnel plot is shown in Fig. 6. Three outlier studies (Locke T, Park KH and Zaoutis T [31,36,40]) were identified in heterogeneity analysis based on the Galbraith plot (Fig. 7). After excluding the outlier studies, an analysis of the seven observational studies resulted in a similar effect estimate with reduced heterogeneity (OR = 1.58, 95% CI 0.83–3.01; $I^2 = 16.5\%$) compared with the analysis of all ten observational studies (OR = 1.72, 95% CI 0.98–3.02; $I^2 = 80.6\%$) (Table 4).

4. Discussion

This study showed that short-course antibiotics might be as effective as long-course antibiotics for patients with osteomyelitis, although there were inconsistent results in studies on vertebral osteomyelitis. Such inconsistency was multifactorial. First, different definitions of short and long courses of antibiotics adopted by different studies may be one of the most important factors. For example, the study by Chang et al. [29] adopted a shorter cut-off point (4 weeks) of total antibiotic duration for the definition of a long antibiotic course, whilst other studies used a cut-off point of >6

Table 3
Quality assessment of the observational studies

First author (country, year)	Study design	Selection component		Comparability	Outcome component		Total score
		Diagnosis	Exposure		Outcome	Follow-up	
Chang WS (Taiwan, 2018)	Single-centre, retrospective cohort	Some patients did not have positive culture	☆ Medical record with precise Abx duration was studied	☆ Age of two groups was not reported; multivariate analysis was done	☆ Recurrence	At least 6 months after treatment stopped	3 Fair
McNeil JC (USA, 2017)	Single-centre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	There was difference in age; sex of two groups was not reported; multivariate analysis was not done	☆ Long-term orthopaedic complication	Not specified	3 Poor
Park KH (Korea, 2016)	Multicentre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	☆☆ There was no difference in age and sex; multivariate analysis was done. Lengths of Abx were compared in separate risk groups	☆ Recurrence	Not specified	5 Good
Babouee Flury B (Switzerland, 2014)	Single-centre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	☆ There was no difference in age and sex; there was difference in CRP levels without correction	☆ Recovery	At least 1 year after diagnosis	4 Fair
Arnold R (USA, 2014)	Single-centre, retrospective cohort	Imaging was obtained but culture was not	☆ Medical record with precise Abx duration was studied	☆☆ There was no difference in age and sex; multivariate analysis was done	☆ Treatment failure	At least 4 weeks post-operatively	4 Good
Locke T (UK, 2014)	Single-centre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	Age and sex of two groups were not reported; multivariate analysis was not done	☆ Cure	Not specified	3 Poor
Rod-Fleury T (Switzerland, 2011)	Single-centre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	☆☆ There was no difference in age and sex; multivariate analysis was done	☆ Remission	☆ At least 2 years after treatment (median, 7.2 years)	6 Good
Zaoutis T (USA, 2009)	Multicentre, retrospective cohort	Defined by ICD-9 code	Transition from i.v. to oral therapy was defined by ICD-9 code, no exact duration of Abx exposure	☆☆ There was no difference in age and sex; propensity score analysis was done	☆ Treatment failure	At least 6 months after initial admission	3 Fair
Roblot F (France, 2007)	Multicentre, retrospective cohort	☆ Both imaging and culture were obtained	☆ Medical record with precise Abx duration was studied	There was difference in age; sex of two groups was not reported; multivariate analysis was not done	☆ Recovery	At least 6 months after treatment	3 Poor
Vinod MB (Australia, 2002)	Single-centre, retrospective cohort	Some patients did not have positive culture or imaging sign	☆ Medical record with precise Abx duration was studied	Author stated that age was not associate with Abx duration; age and sex of two groups were not reported; multivariate analysis was not done	☆ Cure	Not specified	2 Poor

Abx, antibiotic; CRP, C-reactive protein; ICD, International Statistical Classification of Diseases and Related Health Problems; i.v., intravenous.
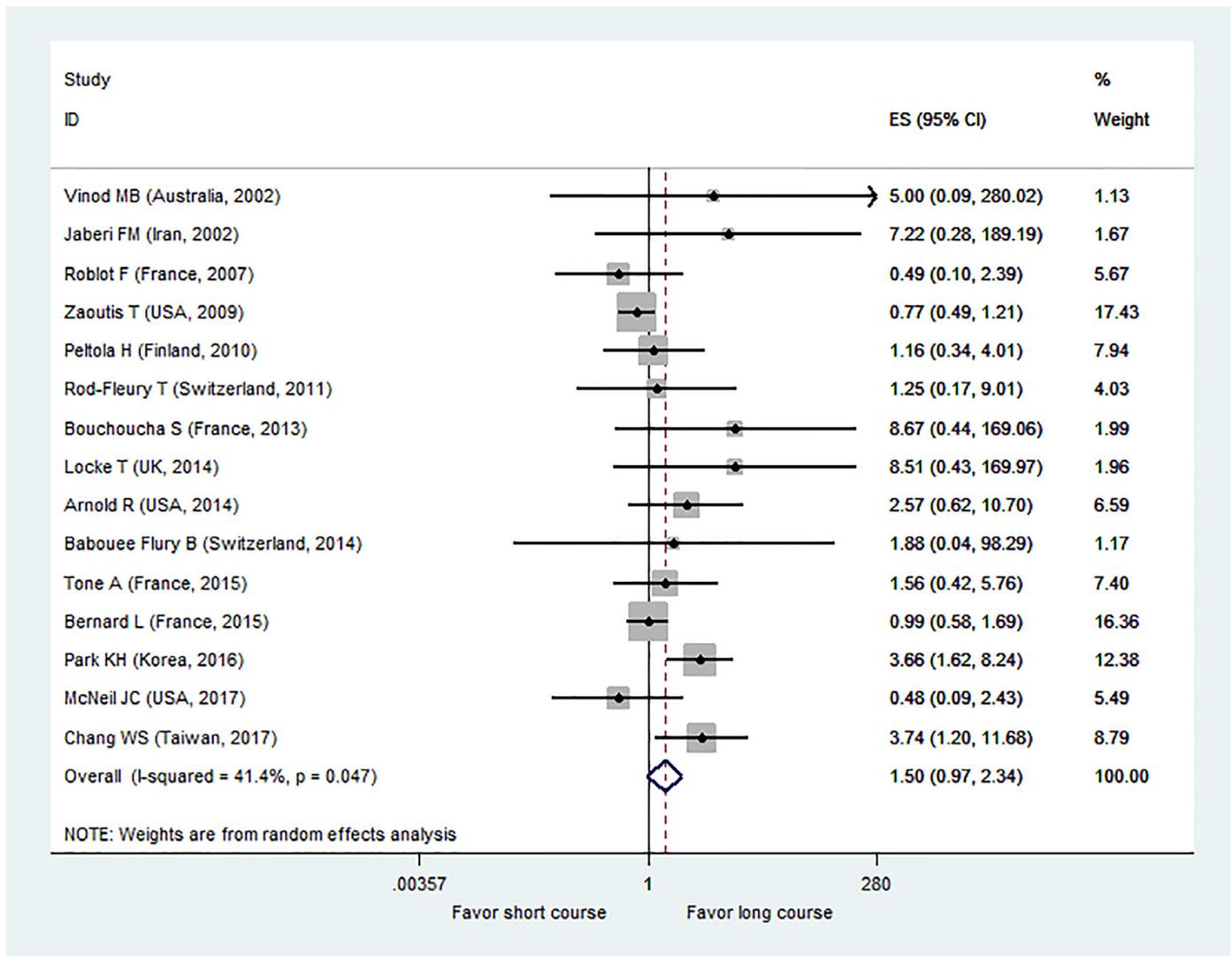
Fig. 2. Random-effects meta-analysis of the effects of short- versus long-course antibiotics on treatment failure in osteomyelitis—overall analysis. A DerSimonian and Laird random-effects model was adopted. ES, effect estimate (odds ratio); CI, confidence interval.

weeks of total antibiotic duration. This could explain why Chang et al.'s study found a short course of antibiotics to be associated with a poor outcome. Second, the result of the meta-regression showed that proportion of *S. aureus* infection in patients with osteomyelitis may account for the discrepancy between studies. This result confirmed previous observations that patients with vertebral osteomyelitis infected by *S. aureus* are generally considered more difficult to treat compared with those infected by other micro-organisms [44]. Furthermore, methicillin-resistant *S. aureus* (MRSA) was associated with worse outcomes compared with methicillin-susceptible *S. aureus* infection [45,46]. In the studies by Roblot et al. [41] and Bernard et al. [32] only 8% and 2.3% of patients, respectively, had MRSA infection, whilst in the studies by Chang et al. [29] and Park et al. [31] 20% and 25% of patients had MRSA infection, respectively. The higher incidences of MRSA infection in the latter two studies could explain the overall better outcomes in patients who received a long course of antibiotics. Third, effective choice of antibiotics may avoid the need for longer treatment duration. Vancomycin therapy has been found to be related to a higher treatment failure rate, which may be due to its poor penetrability [23]. Addition of rifampicin has been recommended to treat *S. aureus* infection owing to its high capability to penetrate biofilm [47] and was related to a more favourable outcome in prosthetic

joint infections compared with other antibiotics [48]. Rifampicin use was much more frequent in *S. aureus* infection in the study by Bernard et al. (73%) [32] compared with the study by Park et al. (9.9%) [31], which may be associated with the higher success rate in treating *S. aureus* infection in Bernard et al.'s study, regardless of treatment duration. The choice of antimicrobial agents may be guided by the resistance profile, patients' tolerability and clinicians' choices, which could be determinants of prognosis.

Other factors that were previously identified to be associated with treatment failure in vertebral osteomyelitis include the presence of an epidural abscess, osteomyelitis at an additional site and the presence of diabetes mellitus as co-morbidity [49]. At least 6 weeks of antibiotics, as suggested by the current guidelines, appear to be necessary in treating patients with vertebral osteomyelitis who have *S. aureus* infection or another co-morbidity to be considered as high-risk patients. In low-risk patients, a shorter course of antibiotics may be sufficient.

This meta-analysis showed that short-course antibiotics might be as effective in children with acute osteomyelitis. Current guidelines indicate that a short course of antibiotics could be considered but should be adjusted based on clinical presentations and laboratory data, such as C-reactive protein [11,50]. A recent systematic review of 34 studies on acute osteomyelitis in childhood
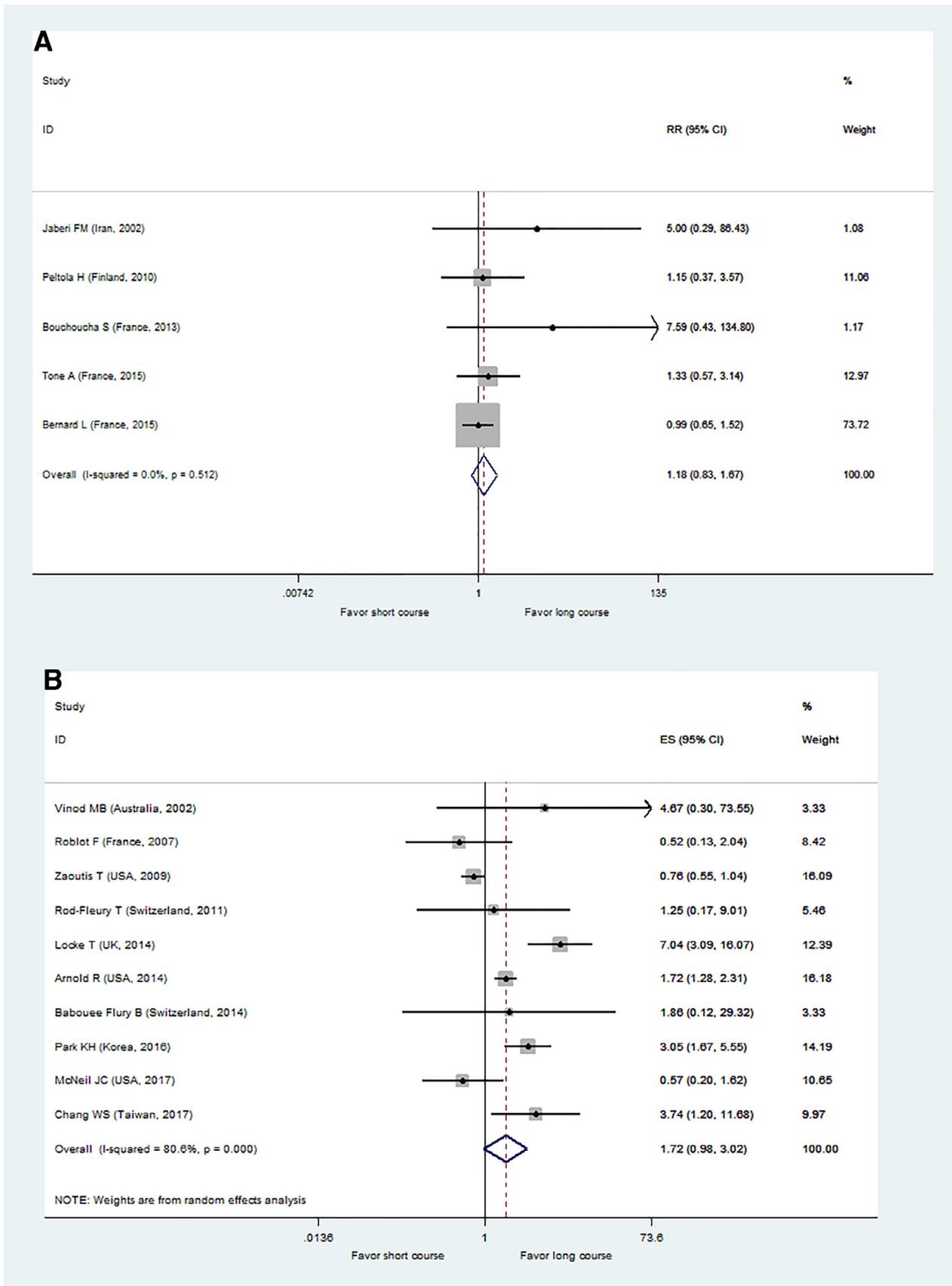
Fig. 3. Random-effects meta-analysis of the effects of short- versus long-course antibiotics on treatment failure in osteomyelitis, by study design: (A) randomised controlled trials; and (B) observational studies. A DerSimonian and Laird random-effects model was adopted. RR, risk ratio; CI, confidence interval; ES, effect estimate (odds ratio).
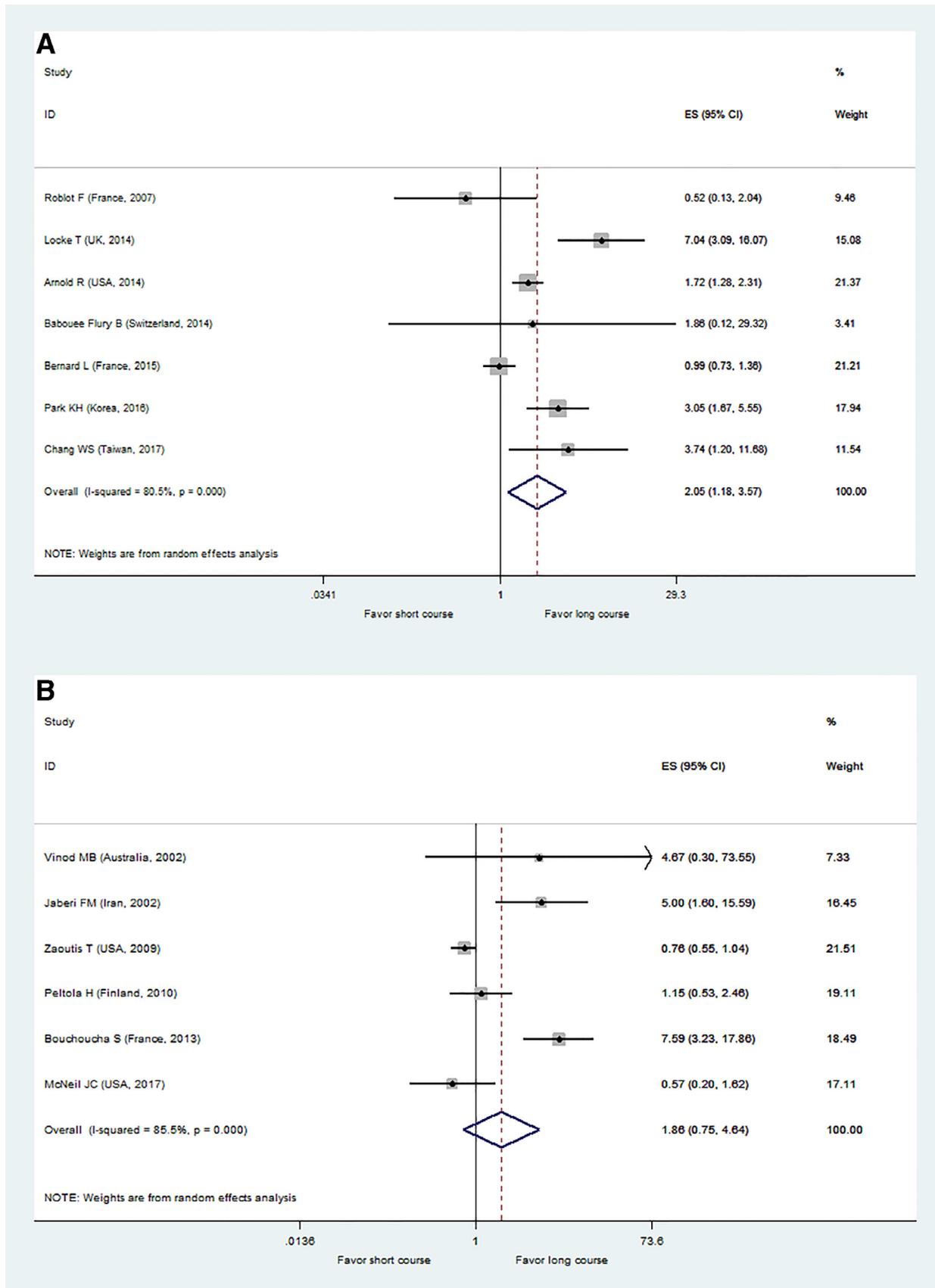
Fig. 4. Random-effects meta-analysis of the effects of short- versus long-course antibiotics on treatment failure in osteomyelitis, by type of osteomyelitis: (A) vertebral osteomyelitis; and (B) acute osteomyelitis in childhood. A DerSimonian and Laird random-effects model was adopted. ES, effect estimate (odds ratio); CI, confidence interval.

Table 4

Summary of subgroup analysis of short- versus long-course antibiotics on treatment failure in osteomyelitis

Category	No. of studies	Summary estimate (95% CI)	I^2 (%)	P-value	Meta-regression P
Overall	15	1.50 (0.97–2.34)	41.4	0.047	NA
Design factors					
RCTs	5	1.18 (0.83–1.67)	0.0	0.368	0.718
Observational studies	10	1.72 (0.98–3.02)	80.6	0.058	0.718
Observational studies/outliers excluded	7	1.58 (0.83–3.01)	16.5	0.161	0.392
Observational studies/adjusted	4	1.60 (0.64–4.04)	63.0	0.318	0.592
RCTs + observational studies/adjusted	9	1.33 (0.86–2.06)	31.7	0.208	0.892
Long-term follow-up (≥6 months)	11	1.46 (0.92–2.32)	74.9	0.106	0.148
Treatment factors					
i.v. antibiotics	7	1.69 (0.85–3.36)	84.9	0.134	0.990
i.v. and oral antibiotics	9	1.85 (1.07–3.20)	74.7	0.028	0.990
i.v. duration (cut point, 2 weeks)	3	6.07 (3.13–11.79)	0.0	<0.001	0.042
Total duration (cut point, 6 weeks)	5	1.80 (0.85–3.83)	85.7	0.127	0.921
With surgical debridement	6	1.38 (0.82–2.31)	53.7	0.055	0.281
Type of osteomyelitis					
Vertebral osteomyelitis	7	2.06 (1.18–3.57)	80.5	0.011	0.675
Vertebral osteomyelitis/outliers excluded	5	1.39 (0.85–2.27)	64.7	0.195	0.446
Vertebral osteomyelitis (cut point, 6 weeks)	3	1.30 (0.52–3.25)	83.5	0.576	0.426
Non-vertebral osteomyelitis	8	1.68 (0.85–3.31)	79.9	0.135	0.675
Acute osteomyelitis of childhood	6	1.86 (0.75–4.64)	85.5	0.182	0.933
Haematogenous osteomyelitis	9	2.68 (1.58–4.56)	74.7	<0.001	0.026
Geographic region					
Asia	4	3.48 (2.17–5.59)	0.0	<0.001	0.099
USA	3	0.98 (0.49–1.97)	87.4	0.962	0.107
Europe	8	1.85 (0.93–3.68)	81.	0.079	0.991

CI, confidence interval; NA, not applicable; RCT, randomised controlled trial; i.v., intravenous.
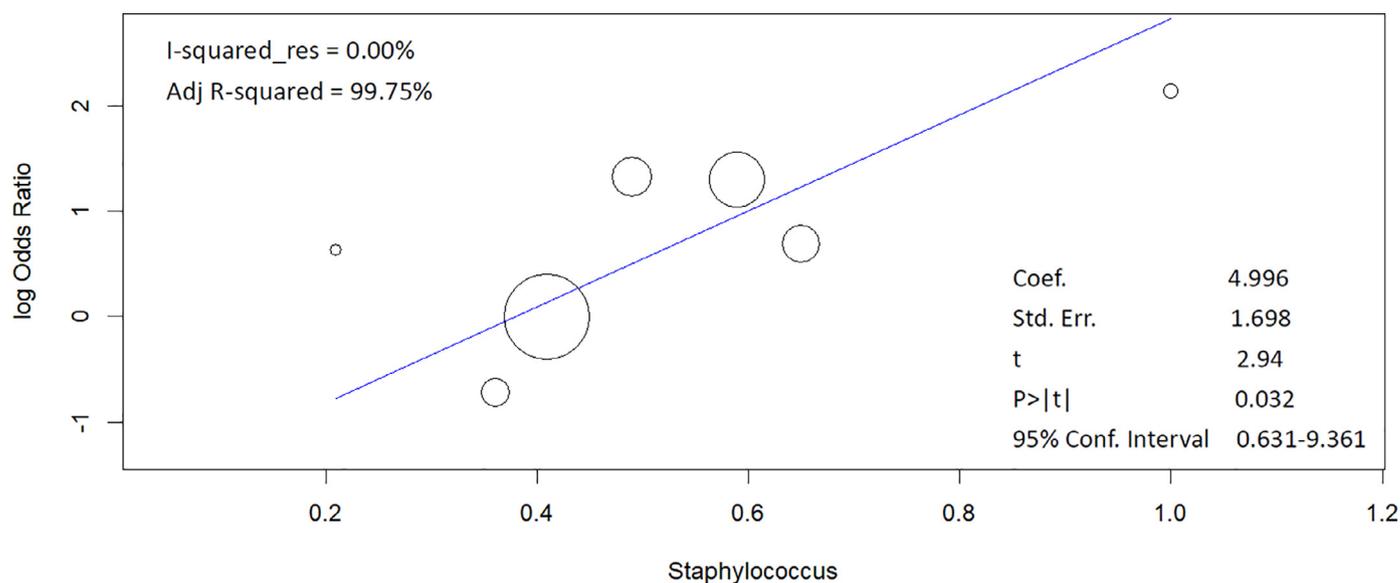

Fig. 5. Meta-regression of the proportion of *Staphylococcus aureus* infection (*x*-axis) and odds ratio of treatment failure in patients with vertebral osteomyelitis treated with short-course antibiotics (*y*-axis). Coef., β coefficient; Std. Err., standard error; I-squared_res, % residual variance due to heterogeneity; Adj R-squared, proportion of between-study variance explained with Knapp–Hartung modification.

also showed a short course of parenteral antibiotics followed by oral therapy could be as effective as prolonged i.v. therapy. However, it was criticised for including studies that only analysed the efficacy of one duration of antibiotic regimen rather than comparing different lengths of antibiotic regimens [20]. The current study solidified previous findings by including studies that directly compared short and long antibiotic courses. In addition, the analysis was updated by including two additional recent studies [30,37]. Based on the results of the current study, we confirmed that i.v. therapy for <1 week followed by oral therapy for 2–3 weeks is safe and effective in patients with childhood osteomyelitis, as opposed to traditionally-used i.v. antibiotics for several weeks.

The single study on diabetic foot osteomyelitis showed no difference in outcome between a long- and short-course antibiotics

[33]. Diabetic foot osteomyelitis was traditionally treated with amputation. A study in 1996 implied that an aggressive surgical approach with minor amputation could prevent more patients from having to undergo major amputation compared with management with 3 days of antibiotics [51]. However, the study was criticised for its control arm because 3 days of antibiotics are not sufficient for diabetic foot osteomyelitis. A prospective randomised clinical trial compared a surgical approach with 90 days of antibiotic treatment, excluding patients with severe infection or severe comorbidity [52]. The rate of wound healing and healing time were found to be similar both in the surgical and medical groups. Accordingly, the 2012 guideline recommended 3 months of antibiotics for patients who did not receive surgery [16]. Despite being underpowered by a small sample size (n = 40), Tone et al.'s trial
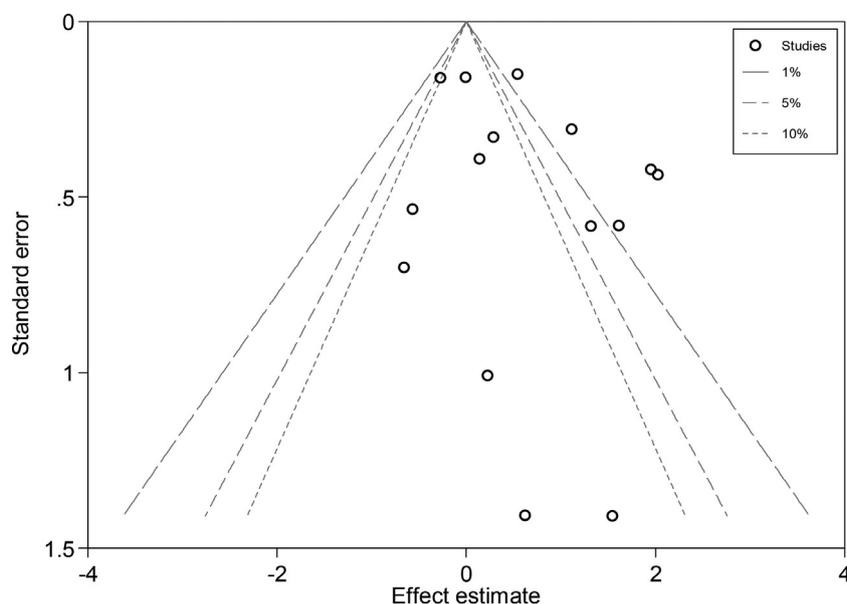
Fig. 6. Funnel plot of short- versus long-course antibiotics on treatment failure in osteomyelitis. *x*-axis, difference in effect estimate; *y*-axis, standard error.
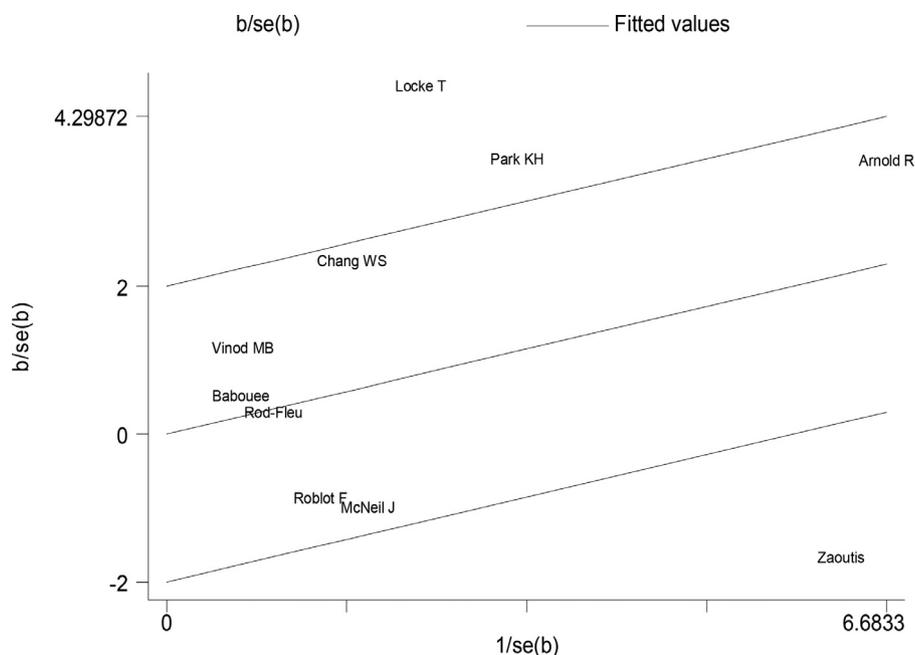

Fig. 7. Galbraith plot of short- versus long-course antibiotics on treatment failure in osteomyelitis. Three outlier studies (Locke T, Park KH and Zaoutis T [31,36,40]) were identified.

[33] indicated that 6 weeks of antibiotics might be as effective as 3 months and have fewer adverse effects. As a result, the most recent guideline in 2016 recommended 6 weeks of antibiotics for patients with diabetic osteomyelitis [53]. A confirmatory RCT with a larger number of patients is required to confirm the benefits of a short course of antibiotics.

The only included study on chronic osteomyelitis found no significant difference in primary outcome between a short and long course of antibiotics after surgery [38]. Currently, there is no definite duration of antibiotics for treating chronic osteomyelitis in the guidelines [54]. In chronic osteomyelitis, the necrotic bone lacking blood supply becomes foci called sequestra, which antibiotics have difficulty reaching [14]. Formation of biofilm also makes it harder for antibiotics to penetrate [55]. Thus, surgical debridement is

crucial in treating chronic osteomyelitis, and the effectiveness of prolonged antibiotics after surgery is controversial. The current results also showed that short courses of antibiotics may be more likely to be as effective as long courses if patients undergo adequate surgical debridement, emphasising the important role of surgical debridement both in acute and chronic osteomyelitis.

Table 5 shows the antibiotic-associated adverse events reported in three studies. No significant adverse events were observed in the study by Bernard et al. [32]. In the study by Tone et al. [33], prolonged i.v. therapy was associated with more frequent antibiotic-related adverse events, including nausea, vomiting, diarrhoea and cholestasis, which were associated with rifampicin use for the treatment of diabetic foot osteomyelitis [56]. In the study by Zaoutis et al. [40], which included as many as 1969 patients

Table 5
Rate of adverse events related to antibiotics in short- and long-course treatment in osteomyelitis

First author (country, year)	Type of osteomyelitis	Rate of adverse event		P-value or adjusted OR
		Short-course treatment	Long-course treatment	
Bernard L (France, 2015)	Vertebral osteomyelitis	12/166 (7.2%)	9/175 (5.1%)	P = 0.66
Tone A (France, 2015)	Diabetic foot osteomyelitis	3/20 (15.0%)	9/20 (45.0%)	P = 0.04
Zaoutis T (USA, 2009)	Acute osteomyelitis of childhood	4/948 (0.4%)	15/1021 (1.5%)	Adjusted OR = 0.39 (95% CI 0.14–1.1)

OR, odds ratio; CI, confidence interval.
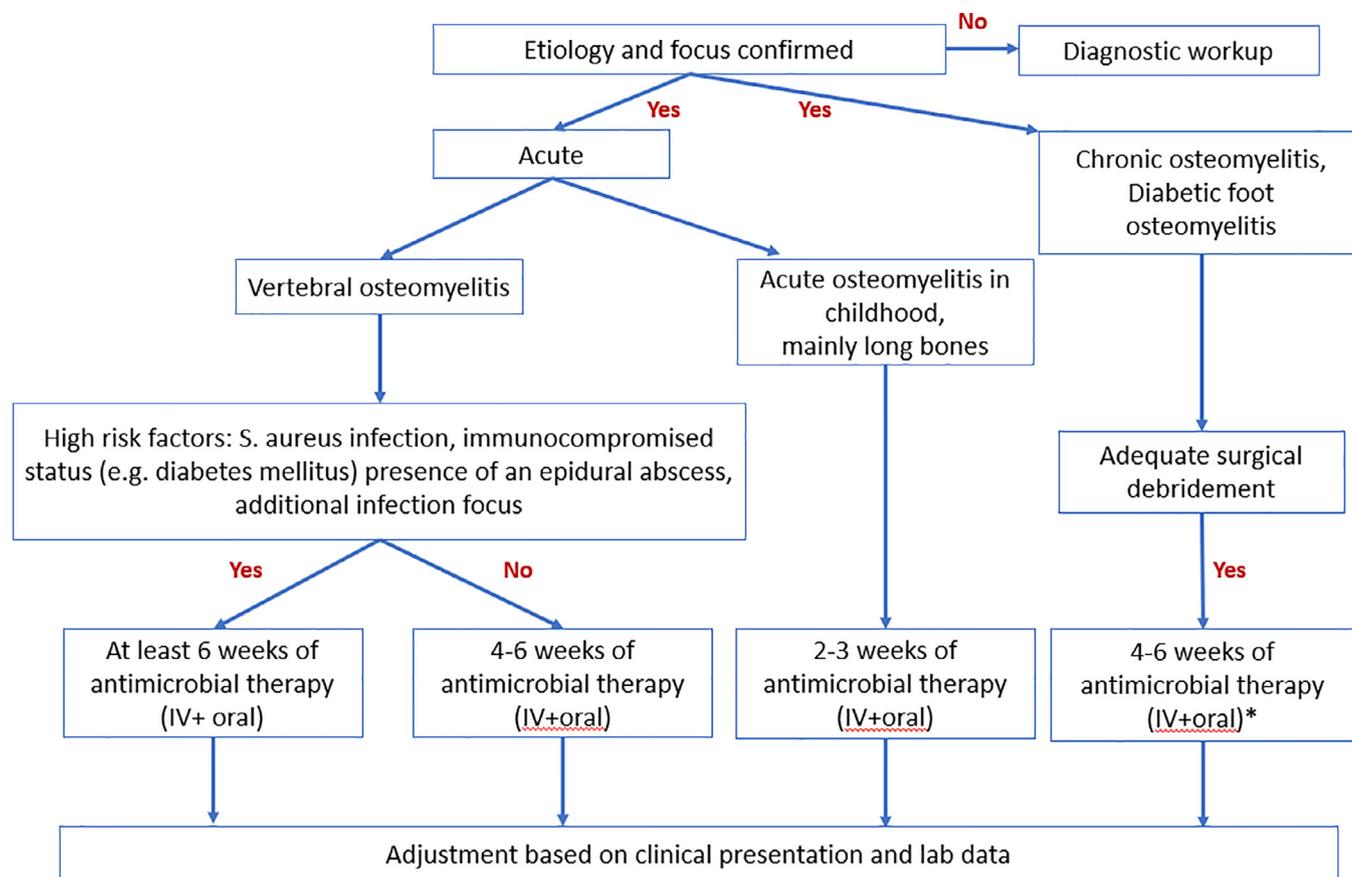
Fig. 8. Algorithm of antimicrobial therapy for osteomyelitis. * Only one study is included for each of chronic osteomyelitis and diabetic foot osteomyelitis. IV, intravenous.

from the Pediatric Health Information System in the USA, a short course of antibiotics was associated with a lower rate of adverse events, although the association did not reach a significant difference in the propensity score model. The adverse events in Zaoutis et al.'s study [40] included adverse drug reactions associated with antibiotics, *Clostridium difficile* infection and agranulocytosis.

The current study is the first meta-analysis on the comparative effectiveness between short- and long-course antibiotics in osteomyelitis. However, there are several limitations. First, there was a lack of high-quality studies. All five RCTs had an open-labelled design. Only four of the ten observational studies adopted statistical models to adjust for confounding factors, whilst another four observational studies were considered to lack comparability between groups and were graded to have poor quality. Second, articles included in this meta-analysis adopted different cut-off times to define short and long antibiotic courses, which might lead to different conclusions. Third, different pathogens and different choices of antibiotics might also lead to discrepancy among studies. Lastly, most of the studies had an inadequate follow-up duration. A previous article revealed that 78% and 95% of all osteomyelitis recurrences occurred within 6 months and 12 months, respectively [23]. Nevertheless, only one study in this review had

a minimum of 1-year follow-up for all patients, whilst four other articles had follow-up periods <6 months.

In conclusion, it is safe and effective to treat acute osteomyelitis of childhood with a short course (2–3 weeks) of antibiotics. A short antibiotic course (<4–6 weeks) may be similarly effective in diabetic foot osteomyelitis and chronic osteomyelitis, although the supporting evidence is relatively insufficient. A long course (6 weeks) of antibiotics may still be preferred in vertebral osteomyelitis, especially in patients infected with *S. aureus*. However, a short course of antibiotics may be initiated in uncomplicated vertebral osteomyelitis without *S. aureus* infection, undrained abscess or immunocompromised status and adjusted based on treatment response. Based on these conclusions, we have proposed an algorithm of antimicrobial therapy for osteomyelitis (Fig. 8).

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Competing interests

None declared.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.01.007.

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