

Procalcitonin Guided Antibiotic Therapy in Children with Lower Respiratory Tract Infections a Systematic Review and Meta Analysis

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Article Information

Submitted: 26 September 2026

Accepted: 09 October 2026

Publish: 22 October 2026

Keyword: Procalcitonin;
Antibiotic Stewardship; Lower
Respiratory Tract Infection;

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Year: 2026

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Abstract

Introduction: Lower respiratory tract infections remain a major cause of morbidity and antibiotic exposure in children. **Objective:** This study aimed to evaluate the efficacy and safety of procalcitonin-guided antibiotic therapy in children with lower respiratory tract infections. **Methods:** Randomized controlled trials and cohort studies published up to April 15, 2025, were searched in PubMed, ScienceDirect, and the Cochrane Library. Risk of bias was assessed using the Risk of Bias 2.0 tool and the Newcastle-Ottawa Scale. Meta-analysis was performed using Review Manager 5.4, with fixed- or random-effects models selected according to heterogeneity. Sensitivity analysis was conducted using the Duval and Tweedie trim-and-fill method. **Results and Discussion:** Six studies involving 3,838 children were included, comprising four randomized controlled trials and two cohort studies. Procalcitonin-guided therapy significantly reduced antibiotic treatment duration by 2.16 days (95% confidence interval -3.29 to -1.03) and hospital stay by 0.44 days (95% confidence interval -0.86 to -0.01). No significant differences were observed in antibiotic prescription, hospital readmission, or antibiotic-related adverse events. **Conclusions:** Procalcitonin-guided antibiotic therapy was associated with shorter antibiotic treatment duration and hospital stay in children with lower respiratory tract infections, without significant differences in antibiotic prescription, readmission, or adverse events. Further studies are warranted.

Introduction

Antimicrobial stewardship is increasingly important in pediatric practice, particularly in lower respiratory tract infections (LRTIs), where antibiotics are often prescribed empirically despite the predominantly viral etiology of many respiratory illnesses. LRTIs, particularly pneumonia and bronchiolitis, remain major causes of morbidity and mortality in children worldwide. Pneumonia is the leading infectious cause of death in children under 5 years, accounting for approximately 740,180 deaths in 2019 (World Health Organization, 2022; World Health Organization, 2025; World Health Organization, 2026).

Distinguishing bacterial from viral LRTI in children remains challenging because of overlapping clinical, laboratory, and radiological findings and the limited ability of conventional investigations to establish the etiology with certainty (Baer *et al.*, 2013; Wu *et al.*, 2017). Consequently, antibiotics may be initiated or continued when bacterial infection cannot be confidently excluded, resulting in unnecessary or prolonged treatment. This diagnostic uncertainty remains an important barrier to effective antimicrobial stewardship (Baer *et al.*, 2013; Wu *et al.*, 2017). The need to optimize antibiotic use is increasingly urgent because unnecessary antibiotic exposure contributes to antimicrobial resistance, drug-related adverse events, and avoidable healthcare costs (World Health Organization, 2026; World Health Organization, 2026). Current pediatric guidelines therefore recommend avoiding antibiotics in bronchiolitis unless there is a concomitant bacterial infection or strong suspicion of one (Manti *et al.*, 2023; National Institute for Health and Care Excellence, 2016).

Procalcitonin (PCT) has emerged as a potential tool to support antimicrobial stewardship by assisting decisions regarding antibiotic initiation, continuation, and discontinuation (Gregoriano *et al.*, 2020). However, PCT is an adjunctive biomarker rather than a definitive diagnostic test, as PCT levels cannot reliably distinguish bacterial from viral infections in every case and should be interpreted alongside clinical findings, other laboratory results, and the patient's overall condition. PCT-guided treatment has been shown to reduce antibiotic exposure in acute respiratory tract infections, providing a rationale for its use as part of antibiotic stewardship strategies (Schuetz *et al.*, 2017). Pediatric studies have reported variable findings. The ProPAED trial demonstrated a reduction in antibiotic duration among children and adolescents with LRTI receiving PCT-guided treatment (Baer *et al.*, 2013). Similarly, PCT-guided management in hospitalized children with community-acquired pneumonia was associated with fewer antibiotic prescriptions, shorter antibiotic exposure, and fewer antibiotic-related adverse events (Esposito *et al.*, 2011). In infants with severe bronchiolitis, implementation of a PCT-guided protocol was also associated with reduced antibiotic use and treatment duration without observed adverse outcomes (Alejandre *et al.*, 2020). These findings support the potential value of PCT in guiding antibiotic decisions but do not establish that PCT can independently determine the presence or absence of bacterial infection or replace clinical assessment.

However, the effectiveness of PCT-guided antibiotic therapy in children remains uncertain across different clinical settings. A randomized trial in critically ill children found no significant difference in antibiotic days of therapy between PCT-guided treatment and usual care despite integration with antimicrobial stewardship audit and feedback (Katz *et al.*, 2021). More recently, the multicentre BATCH trial found that PCT-guided treatment did not significantly reduce the duration of intravenous antibiotic therapy in hospitalized children with suspected or confirmed bacterial infection, although

the strategy was non-inferior to usual care for safety outcomes (Waldron *et al.*, 2025). Differences in patient populations, disease severity, clinical settings, PCT thresholds, and treatment algorithms may contribute to these inconsistent findings.

Therefore, this systematic review and meta-analysis aimed to evaluate whether PCT-guided antibiotic therapy reduces antibiotic exposure in children with LRTI compared with standard or clinically guided treatment, while maintaining comparable clinical and safety outcomes. By synthesizing the available evidence, this study seeks to clarify the potential role of PCT-guided therapy as an antimicrobial stewardship strategy in pediatric LRTI.

Method

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, available at <http://www.prismastatement.org/>. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261509588. No changes to the registered protocol were made during the study.

Eligibility Criteria

Following the literature search, studies were further screened using predetermined inclusion and exclusion criteria. All studies evaluating the effectiveness and safety of procalcitonin (PCT)-guided antibiotic therapy in children with lower respiratory tract infections (LRTIs) were eligible for inclusion. The inclusion criteria used in this study were: (1) randomized controlled trials (RCTs) or observational studies; (2) children diagnosed with LRTIs; (3) PCT-guided antibiotic therapy as the intervention, using a predefined PCT-based algorithm to guide antibiotic initiation, continuation, or discontinuation; and (4) reporting at least one relevant clinical outcome. Studies were excluded if they: (1) involved animal or in vitro studies; (2) included only adult participants; (3) included mixed pediatric and adult populations; (4) did not evaluate PCT-guided antibiotic therapy; or (5) did not report relevant outcome data or had insufficient information for data extraction.

Information Source and Search Strategy

Three authors (NMTN, DMM, and PRA) systematically searched the PubMed, ScienceDirect, and Cochrane Library databases using the following keywords: (“procalcitonin” OR “procalcitonin-guided” OR “PCT-guided”) AND (“lower respiratory tract infection” OR LRTI OR pneumonia OR bronchiolitis OR “community-acquired pneumonia”) AND (child OR children OR pediatric OR paediatric OR infant OR adolescent). The search was conducted from database inception until 15 April 2025. The search was also conducted for unpublished or ongoing trials through ClinicalTrials.gov. The reference lists of eligible articles and relevant systematic reviews were manually screened to identify additional studies. Supplementary Data 1 displays the source databases and detailed search strategies, including the keywords used for each database.

Study Selection

Duplicates were detected with Rayyan AI before screening process and removed manually. Subsequently, three independent reviewers (NMTN, DMM, and PRA)

screened the titles and abstracts of the identified studies based on the predefined eligibility criteria. Any disagreements were discussed further until a consensus was reached. A detailed overview of the planned literature search procedure is presented in Figure. 1.

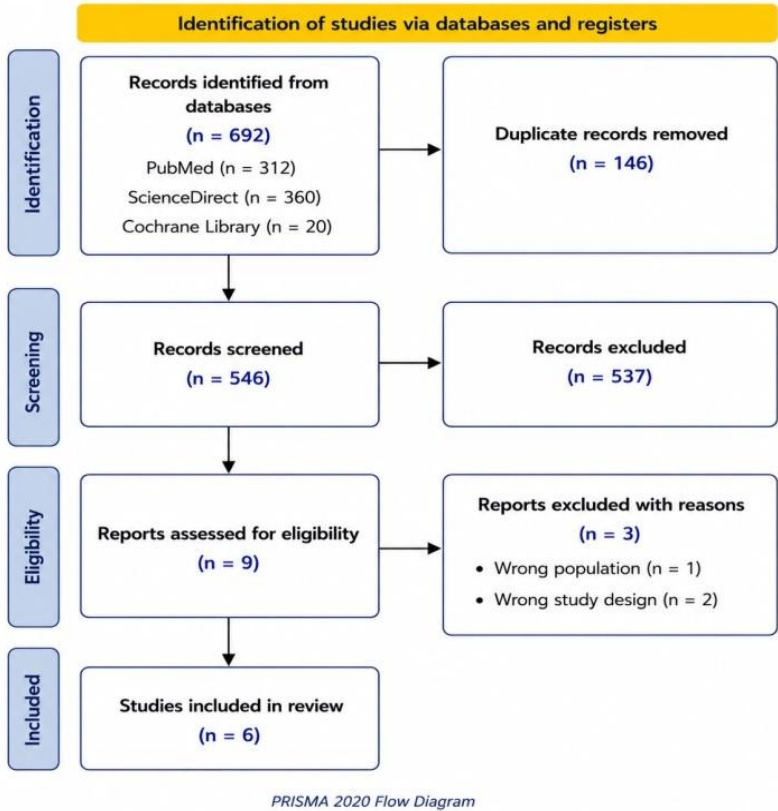


Figure 1. Diagram Flow of Searching Strategies

Data Extraction

Data extraction was conducted independently by three reviewers (NMTN, DMM, and PRA), after which the extracted information was discussed until consensus was achieved. The data collected comprised the authors and year of publication, study design, study setting, participant characteristics, follow-up period, interventions, and outcomes, which were reported based on efficacy and safety measures.

Data Item

The outcomes of this study are defined further in Table 1.

Table 1
Definition Outcomes Study

Definition	
Procalcitonin (PCT)-guided antibiotic therapy	An antibiotic management strategy in which serum procalcitonin measurements are incorporated into a predefined clinical algorithm to guide the initiation, continuation, or discontinuation of antibiotic treatment (Baer <i>et al.</i> , 2013; Esposito <i>et al.</i> , 2011; Alejandre <i>et al.</i> , 2020).
Duration of antibiotic therapy	The total duration of antibiotic treatment, expressed in days, from initiation to discontinuation of antibiotic therapy (Baer <i>et al.</i> , 2013; Waldron <i>et al.</i> , 2025).
Antibiotic prescription	The proportion of participants who received antibiotic therapy during the study period, reflecting the rate of antibiotic initiation or prescribing (Baer <i>et al.</i> , 2013; Wu <i>et al.</i> , 2017).
Length of hospital stay	The duration of hospitalization, calculated from hospital admission to hospital discharge and expressed in days (Agency for Healthcare Research and Quality, n.d.-a).
Hospital readmission	A subsequent hospital admission occurring after discharge from the index hospitalization within the follow-up period specified by the study (Agency for Healthcare Research and Quality, n.d.-b).
Antibiotic-related adverse events	Any harmful or undesirable event associated with antibiotic exposure, including adverse drug reactions and other medication-related harm (Centers for Disease Control and Prevention, n.d.; Agency for Healthcare Research and Quality, n.d.).
Clinical safety outcomes	Outcomes used to assess whether PCT-guided antibiotic therapy results in clinically important harm, including treatment failure, recurrence, readmission, serious adverse events, or mortality, according to the definitions used in each study (Baer <i>et al.</i> , 2013; Alejandre <i>et al.</i> , 2020; Waldron <i>et al.</i> , 2025).

Study Risk of Bias

The included studies were also assessed in terms of their quality using the Cochrane Risk of Bias Tool for Randomized Trials (ROB 2.0) and Newcastle-Ottawa Scale for Cohort studies (Supplementary Data 2). The quality assessment was performed by three reviewers (NMTN, DMM, and PRA) with each other blinded to each other's scoring and then discussed until consensus was reached. GRADE Assessment (Supplementary Data 3) was also done to assess the quality of evidence among included studies. A completed PRISMA checklist is displayed in Supplementary Data 4.

Data Synthesis

We analysed the data using Review Manager software (RevMan v5.4). We calculated the pooled estimates as the mean differences (MD) and risk ratio (RR), both with the corresponding 95% confidence intervals (CIs). Statistical heterogeneity among studies was evaluated by I^2 with the cut-off values of 0%, 25%, 50%, and 75% for insignificant, low, moderate, or high heterogeneity, respectively. We utilized fixed effect models for the meta-analysis of trials with low heterogeneity and random effect models for trials with high heterogeneity. Furthermore, sensitivity analyses were performed using Duval and Tweedie's trim-and-fill

Results and Discussion

1. Results

The initial literature search from PubMed, ScienceDirect, and the Cochrane Library identified a total of 692 records, consisting of 312 records from PubMed, 360 from ScienceDirect, and 20 from the Cochrane Library. After the removal of 146 duplicate records, 546 records were screened based on their titles and abstracts, of which 537 were excluded. A total of 9 reports were then assessed for eligibility. Of these, 3 reports were excluded due to a different population ($n = 1$) and a different study design ($n = 2$). As a result, 6 studies were included in the final review and qualitative and quantitative synthesis (Figure. 1)

Study Characteristic and Findings

The detailed characteristics of the included studies are presented in Table 2. Overall, 6 studies involving a total of 3,838 pediatric participants were included in this review. The studies were conducted in Italy, Switzerland, Spain, China, the United States, and the United Kingdom, including both single-centre and multicentre settings. The included studies comprised randomized controlled trials and observational studies, with follow-up periods ranging from 14 to 30 days, while one observational study primarily assessed outcomes during hospitalization. Most studies compared PCT-guided antibiotic therapy with standard or usual care, while one study evaluated outcomes before and after implementation of a PCT-guided antibiotic stewardship protocol. The primary outcomes assessed the effectiveness of PCT-guided therapy in reducing antibiotic prescribing and duration of antibiotic treatment, while safety and clinical outcomes included antibiotic-related adverse events, length of hospital stay, readmission, and other clinical outcomes.

Risk of Bias and Certainty of Evidence

The risk of bias assessment showed that three randomized controlled trials (Esposito *et al.*, 2011; Katz *et al.*, 2021; and Waldron *et al.*, 2025) had some concerns, whereas Baer *et al.* (2013) was assessed as having a low risk of bias. The two included cohort studies, Wu *et al.* (2017) and Alejandre *et al.* (2020), were considered to have high methodological quality, with Newcastle-Ottawa Scale scores of 8/9. Details of the risk of bias assessment are presented in Supplementary Data 2.

GRADE assessment (Supplementary Data 3) indicated that the certainty of evidence was high for duration of antibiotic therapy, with no serious concerns regarding risk of bias, inconsistency, indirectness, or imprecision. The certainty of evidence for length of hospital stay was moderate, with no serious concerns in the assessed domains. The certainty of evidence for antibiotic prescription was moderate, with serious inconsistency and serious imprecision leading to downgrading. The certainty of evidence for hospital readmission was low, with serious risk of bias as the reason for downgrading. For antibiotic-related adverse events, the certainty of evidence was moderate, with serious inconsistency leading to downgrading.

Procalcitonin Guided Antibiotic Therapy in Children with Lower Respiratory Tract Infections a Systematic Review and Meta Analysis**Table 2**
Table of Study Characteristics

First author, year	Study location	Study design	Subject characteristics	Intervention	Follow-up duration	Outcomes (Efficacy and Safety)
Esposito, 2011	Milan, Italy	Prospective, single-centre randomized controlled trial	319 hospitalized children aged >1 month to <14 years with uncomplicated community-acquired pneumonia (CAP); 155 PCT and 155 control were included in the final analysis.	PCT-guided antibiotic therapy using a 0.25 ng/mL cutoff versus standard guideline-based therapy. Antibiotics were withheld when admission PCT was <0.25 ng/mL and discontinued when PCT decreased to ≤ 0.25 ng/mL.	28 days; follow-up visits at 14 ± 2 and 28 ± 3 days after admission.	Efficacy: antibiotic prescription, duration of antibiotic treatment, recurrence of respiratory symptoms. Safety: antibiotic-related adverse events, clinical deterioration, hospital readmission, and disease-specific failure.
Baer, 2013	Basel and Aarau, Switzerland	Randomized controlled trial; two-centre pediatric study	337 children and adolescents, aged 1 month-18 years, presenting to emergency departments with LRTI; 168 PCT and 169 control.	PCT-guided antibiotic treatment algorithm versus clinically guided standard care. PCT guidance was used to determine initiation and duration of antibiotic therapy.	14 days after randomization	Efficacy: antibiotic prescription, duration of antibiotic treatment, hospitalization and duration of hospitalization. Safety: antibiotic side effects, complications, serious adverse events, hospital readmission, recurrent infection, and disease-specific treatment failure.
Alejandre, 2020	Barcelona, Spain	Prospective observational before-and-after cohort study	706 infants <1 year with severe bronchiolitis, suspected bacterial infection, and PICU admission; 340 before and 366 after implementation of the PCT protocol.	Implementation of a PCT-guided antibiotic stewardship protocol to guide withholding, initiation, withdrawal, and narrowing of antibiotic therapy according to clinical and laboratory response.	Not explicitly reported; outcomes were assessed during PICU/hospital care, with follow-up after PICU discharge required for inclusion.	Efficacy: antibiotic prescription/use, duration of antibiotic treatment, stewardship and antibiotic-withdrawal decisions, PICU/hospital stay. Safety: recurrent infection and mortality; no adverse outcomes were observed following protocol implementation.
Wu, 2017	Changzhou, Jiangsu	Single-centre retrospective cohort study	357 pediatric patients <14 years with LRTI discharged from the pediatric ward; 183	PCT-guided antibiotic algorithm versus standard guideline-based treatment.	Clinical reassessment on days 3, 5, and 7	Efficacy: antibiotic prescription rate, duration of antibiotic exposure, length of hospital stay.

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	Province, China		PCT and 174 standard-care patients. Diagnoses included pneumonia, bronchitis, bronchiolitis, and other LRTIs.	Antibiotic initiation/continuation was discouraged at low PCT levels and early discontinuation was recommended when PCT decreased below predefined thresholds.	and at discharge; post-discharge readmission/return was also recorded.	Safety: antibiotic-related adverse effects, readmission/return to pediatric department, and antimicrobial complications.
Katz, 2021	Nashville, Tennessee, USA	Single-centre, pragmatic randomized prospective clinical trial	270 critically ill children admitted to the PICU and started on intravenous antibiotics; 137 PCT and 133 usual care.	PCT-guided antibiotic algorithm with antimicrobial stewardship guidance versus usual care with routine stewardship audit and feedback. PCT was measured on days 0, 1, 2, and 4.	14 days for antibiotic outcomes; clinical outcomes assessed through 30 days after randomization.	Efficacy: antibiotic days of therapy, length of antibiotic therapy, broad-spectrum antibiotic use, time to antibiotic modification. Safety/clinical outcomes: mortality, ICU stay, hospital stay, and other clinical outcomes.
Waldron, 2025 (BATCH)	England and Wales, UK	Pragmatic, multicentre, open-label, individually randomized controlled trial	1,949 children aged 72 h-18 years hospitalized with suspected or confirmed serious bacterial infection and expected to require IV antibiotics for >48 h; 977 PCT and 972 usual care.	PCT-guided antibiotic algorithm added to usual clinical management. PCT was measured at baseline and every 1-3 days during IV antibiotic treatment to guide discontinuation and de-escalation.	28 days after randomization; additional day-28 follow-up for health-care use and quality-of-life outcomes.	Efficacy: duration of IV antibiotic treatment, total antibiotic duration, time to hospital discharge, time to antibiotic de-escalation. Safety: composite safety outcome including unplanned admission/readmission, restarting IV antibiotics, and mortality; adverse drug reactions and hospital-acquired infection.

Meta-analysis of Antibiotic and Clinical Outcomes

The pooled analysis showed that PCT-guided antibiotic therapy significantly reduced the duration of antibiotic treatment compared with standard care (MD -2.16 days, 95% CI -3.29 to -1.03; $p = 0.0002$), making antibiotic treatment duration the primary outcome of this meta-analysis. However, the magnitude of this effect varied substantially across studies, as indicated by considerable heterogeneity ($I^2 = 97\%$), limiting the interpretation of the pooled estimate as a uniform treatment effect across pediatric populations. Sensitivity analysis excluding Waldron *et al.* (2025) yielded a larger reduction in antibiotic treatment duration (MD -2.59 days, 95% CI -3.83 to -1.36; $p < 0.00001$), while considerable heterogeneity persisted ($I^2 = 93\%$). This variability may reflect differences in the diagnoses studied, ranging from community-acquired pneumonia and mixed LRTIs to severe bronchiolitis, disease severity and care settings, from emergency departments and general pediatric wards to the PICU, PCT-guided algorithms and thresholds, study designs, including randomized trials and observational cohorts, and existing antimicrobial stewardship practices in the control groups. These factors may have influenced the extent to which PCT-guided therapy reduced antibiotic exposure.

For length of hospital stay, PCT-guided antibiotic therapy was associated with a statistically significant reduction compared with standard care (MD -0.44 days, 95% CI -0.86 to -0.01; $p = 0.04$), with considerable heterogeneity ($I^2 = 74\%$), as shown in Figure. 3. Sensitivity analysis excluding Alexandre *et al.* (2020) resulted in a nonsignificant difference (MD -0.30 days, 95% CI -0.72 to 0.12; $p = 0.17$), with heterogeneity remaining considerable ($I^2 = 68\%$). For antibiotic prescription, no significant difference was observed between PCT-guided and standard-care groups (RR 0.94, 95% CI 0.69 to 1.26; $p = 0.65$), with considerable heterogeneity ($I^2 = 89\%$), as shown in Figure. 4. Sensitivity analysis excluding Wu *et al.* (2017) yielded an RR of 1.13 (95% CI 0.99 to 1.28; $p = 0.07$), with heterogeneity reduced to 37% ($I^2 = 37\%$). The pooled effect remained statistically nonsignificant.

Similarly, PCT-guided antibiotic therapy was not associated with a significant difference in antibiotic readmission compared with standard care (RR 0.95, 95% CI 0.76 to 1.19; $p = 0.68$), with low heterogeneity ($I^2 = 27\%$), as shown in Figure. 5. For adverse events, no significant difference was observed between PCT-guided and standard antibiotic therapy (RR 0.57, 95% CI 0.29 to 1.12; $p = 0.10$), although considerable heterogeneity was observed ($I^2 = 84\%$), as shown in Figure. 6. Sensitivity analysis excluding Esposito *et al.* (2011) yielded an RR of 0.89 (95% CI 0.71 to 1.12; $p = 0.32$), with no observed heterogeneity ($I^2 = 0\%$).

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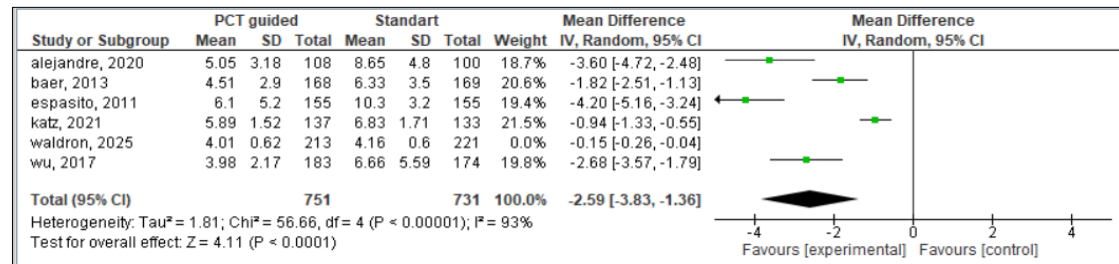
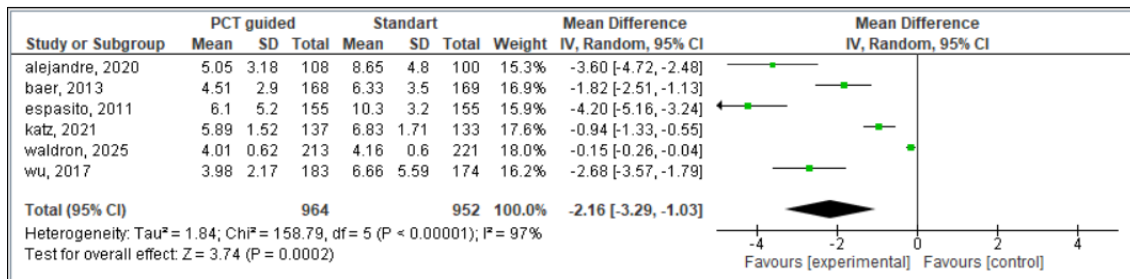


Figure 2. Forest plots of the length of therapy comparing PCT-guided antibiotic and standart of usual care; (a) Forest plot of analysis, (b) Sensitivity analysis

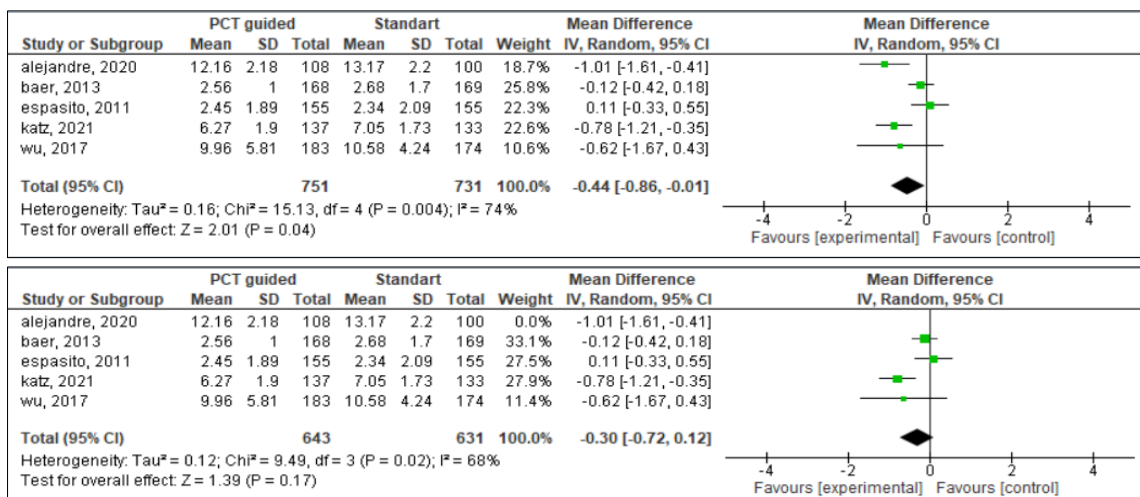


Figure 3. Forest plots of the length of hospital-stay comparing PCT-guided antibiotic and standart of usual care; (a) Forest plot of analysis, (b) Sensitivity analysis

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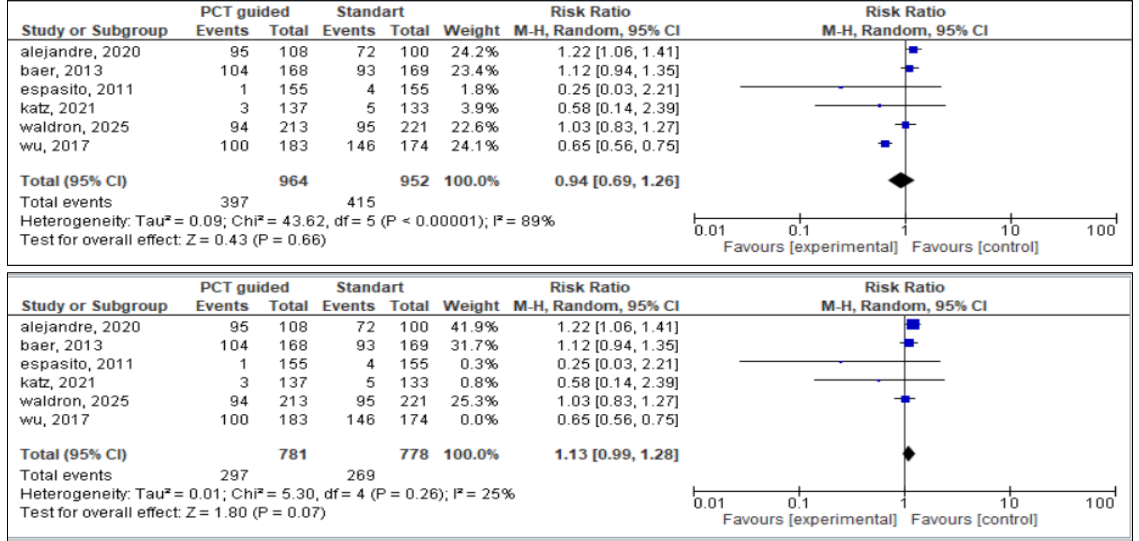


Figure 4. Forest plots of antibiotic re-prescription comparing PCT-guided antibiotic and standart of usual care; (a) Forest plot of analysis, (b) Sensitivity analysis

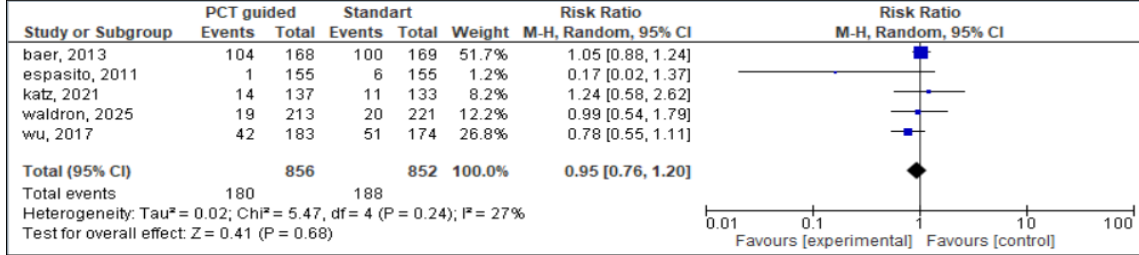


Figure 5. Forest plots of antibiotic re-admission comparing PCT-guided antibiotic and standart of usual care

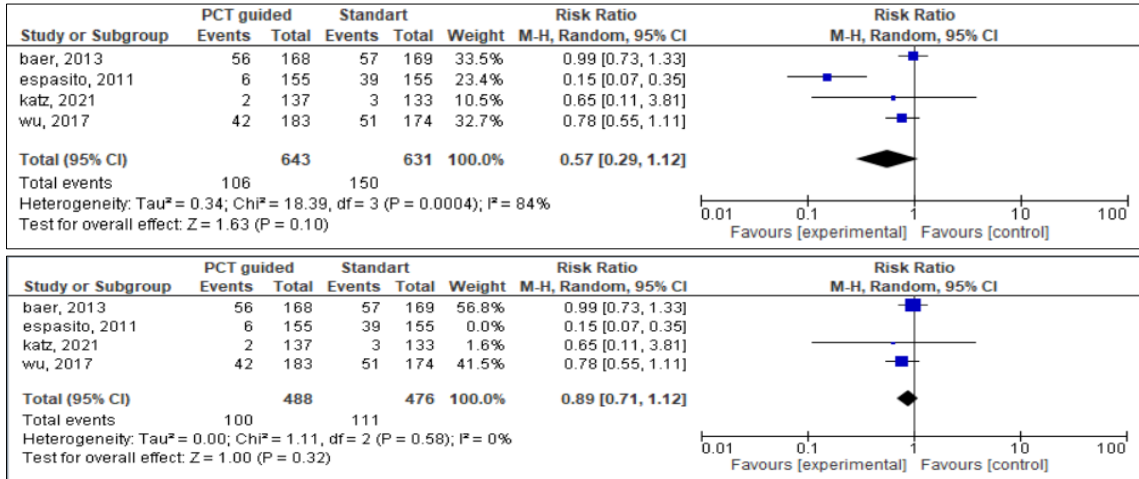


Figure 6. Forest plots of AEs comparing PCT-guided antibiotic and standart of usual care; (a) Forest plot of analysis, (b) Sensitivity analysis

2. Discussion

Duration of Antibiotic Therapy

The principal finding of this meta-analysis was a significant reduction in antibiotic treatment duration with PCT-guided therapy, with a pooled mean difference of -2.16 days (95% CI -3.29 to -1.03; $p = 0.0002$). This effect remained significant after excluding Waldron *et al.*, with a pooled reduction of -2.59 days (95% CI -3.83 to -1.36), although substantial heterogeneity remained ($I^2 = 93\%$). Despite the statistically significant pooled result, the high heterogeneity ($I^2 = 97\%$ in the primary analysis) indicates that the magnitude of the reduction differed considerably across studies and should not be assumed to apply equally to all pediatric patients with LRTIs. These findings are consistent with previous pediatric studies. Baer *et al.* reported shorter antibiotic exposure in children with LRTI, while Esposito *et al.* observed a reduction from 10.96 to 5.37 days (Baer *et al.*, 2013; Esposito *et al.*, 2011). Similar reductions were reported by Alejandre *et al.* and Wu *et al.* (Alejandre *et al.*, 2020; Wu *et al.*, 2017). The magnitude of the effect was also comparable with the previous meta-analysis by Li *et al.*, which reported a reduction of approximately 2.22 days (Li *et al.*, 2022).

The reduction may reflect the use of PCT within predefined clinical algorithms to support antibiotic discontinuation. However, the effect was not consistent across all studies. Katz *et al.* found no significant reduction in antibiotic days, and the BATCH trial also found no significant reduction in intravenous antibiotic duration (Katz *et al.*, 2021; Waldron *et al.*, 2025). The included studies investigated different diagnoses, including community-acquired pneumonia, mixed LRTIs, and severe bronchiolitis, and enrolled children across a range of disease severities and clinical settings. They also used different PCT thresholds, testing schedules, and antibiotic-management algorithms. Furthermore, randomized controlled trials and observational cohorts differ in their susceptibility to bias, while the level of antimicrobial stewardship already established in usual-care groups may influence the additional benefit attributable to PCT guidance. These findings suggest that the additional effect of PCT may be smaller when antibiotic prescribing is already optimized through established antimicrobial stewardship practices (Schuetz *et al.*, 2017).

Antibiotic Prescription

PCT-guided therapy was not associated with a significant reduction in antibiotic prescription (RR 0.94, 95% CI 0.69-1.26; $p = 0.65$; $I^2 = 89\%$). Individual studies showed inconsistent results. Esposito *et al.* and Wu *et al.* reported fewer antibiotic prescriptions, whereas Baer *et al.* found no significant difference (Esposito *et al.*, 2011; Wu *et al.*, 2017; Baer *et al.*, 2013). Differences in baseline prescribing practices and clinical settings may explain this variation. Settings with already low antibiotic use may have limited opportunity for further reduction, whereas higher baseline prescribing may provide greater opportunity for PCT-guided intervention (Baer *et al.*, 2013; Wu *et al.*, 2017). Thus, PCT may have a greater role in antibiotic reassessment and discontinuation than in the initial decision to prescribe antibiotics.

Length of Hospital Stay

PCT-guided therapy was associated with a small reduction in hospital stay in the primary analysis (MD -0.44 days, 95% CI -0.86 to -0.01; $p = 0.04$). However, the effect became nonsignificant after excluding Alejandre *et al.* (MD -0.30 days, 95% CI -0.72 to 0.12; $p = 0.17$), indicating that the finding was not consistent across studies (Alejandre *et al.*, 2020). Hospital stay is influenced by factors beyond antibiotic duration, including

oxygenation, oral intake, disease severity, and the need for intravenous treatment (Baer *et al.*, 2013; Wu *et al.*, 2017). Therefore, the effect of PCT appears to be more directly reflected in antibiotic exposure than in hospitalization duration.

Antibiotic-related Readmission

No significant difference in antibiotic-related readmission was observed between PCT-guided and standard care (RR 0.95, 95% CI 0.76-1.19; $p = 0.68$; $I^2 = 27\%$). Previous studies similarly reported no meaningful increase in recurrent infection or subsequent antibiotic use following PCT-guided treatment (Baer *et al.*, 2013; Esposito *et al.*, 2011). This finding supports the safety of reducing antibiotic exposure when PCT is incorporated into appropriate clinical reassessment and monitoring. Such an approach is consistent with pediatric antimicrobial stewardship recommendations emphasizing reduction of unnecessary antibiotic exposure while maintaining clinical safety (McMullan *et al.*, 2023).

Adverse Events and Safety

No significant difference in adverse events was observed between PCT-guided and standard therapy (RR 0.57, 95% CI 0.29-1.12; $p = 0.10$; $I^2 = 84\%$). After excluding Esposito *et al.*, the effect became closer to the null and heterogeneity decreased substantially (Esposito *et al.*, 2011). Individual studies also reported variable findings, with some showing fewer adverse events and others finding no significant difference (Wu *et al.*, 2017; Baer *et al.*, 2013; Alejandre *et al.*, 2020). Overall, the available evidence does not indicate an increased risk of adverse clinical outcomes associated with PCT-guided reduction of antibiotic exposure.

Interpretation in the Context of Antimicrobial Stewardship

PCT should be considered an adjunct to clinical assessment, microbiological findings, and established antimicrobial stewardship rather than a stand-alone diagnostic tool (Schuetz *et al.*, 2017). Katz *et al.* reported increased antimicrobial stewardship recommendations and antibiotic de-escalation decisions despite no significant reduction in overall antibiotic duration (Katz *et al.*, 2021). Similarly, Alejandre *et al.* reported increased antibiotic-withdrawal decisions after implementation of a PCT-guided protocol (Alejandre *et al.*, 2020). The BATCH trial further illustrates that the effect of PCT may depend on the existing stewardship environment and adherence to the PCT algorithm (Waldron *et al.*, 2025). Therefore, PCT-guided therapy may be most appropriately viewed as one component of a multimodal antimicrobial stewardship strategy rather than an independent intervention (McMullan *et al.*, 2023).

Strengths and Limitations

This review included randomized and observational studies from different pediatric clinical settings and incorporated recent evidence from the BATCH trial. Both antibiotic-use and safety outcomes were evaluated. Several limitations should be considered. Only six studies were included, limiting subgroup analysis. The primary outcome, duration of antibiotic therapy, showed substantial heterogeneity ($I^2 = 97\%$), which persisted after sensitivity analysis ($I^2 = 93\%$). Differences in LRTI diagnoses, disease severity, clinical settings, PCT thresholds and algorithms, study designs, and baseline antimicrobial stewardship practices may have contributed to this variability. However, the available data did not allow these factors to be examined systematically as independent sources of

heterogeneity. In addition, combining randomized and observational studies may introduce methodological heterogeneity. The BATCH trial and Katz *et al.* also included broader hospitalized or critically ill populations rather than exclusively children with narrowly defined LRTI (Waldron *et al.*, 2025; Katz *et al.*, 2021). Finally, differences in PCT thresholds and implementation may have influenced the pooled estimates (Baer *et al.*, 2013).

Clinical and Research Implications

The findings suggest that PCT may be particularly useful for supporting antibiotic reassessment and discontinuation in children with LRTI. The most consistent effect was a reduction in antibiotic treatment duration, whereas effects on antibiotic prescription and hospital stay were less consistent. No significant increase in readmission or adverse events was observed. Future studies should determine optimal PCT thresholds and timing for different pediatric LRTI presentations and distinguish antibiotic initiation from discontinuation. Implementation factors, including clinician adherence, availability of PCT results, and integration with antimicrobial stewardship programmes, should also be evaluated (Katz *et al.*, 2021; Waldron *et al.*, 2025).

Conclusion

This systematic review and meta-analysis found that PCT-guided antibiotic therapy significantly reduced antibiotic treatment duration by approximately two days in children, although considerable heterogeneity remained. The reduction in length of hospital stay was not maintained in sensitivity analysis, while antibiotic prescription, antibiotic-related readmission, and adverse events did not differ significantly between PCT-guided and standard care. These findings support the role of PCT as a potential adjunct to antimicrobial stewardship and antibiotic de-escalation, rather than as a stand-alone determinant of antibiotic treatment.

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