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SYSTEMATIC REVIEWS

Extended antibiotic prophylaxis in primary total knee arthroplasty: A narrative review of current evidence and controversies

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Abstract

BACKGROUND

Periprosthetic joint infection (PJI) remains one of the most serious complications following primary total knee arthroplasty (TKA), associated with high morbidity, functional loss, and economic burden. Standard perioperative antibiotic prophylaxis – initiated pre-incision and discontinued within 24 hours – has long been considered optimal. However, extended oral antibiotic (EOA) prophylaxis administered for several days postoperatively has gained attention, particularly for high-risk patients.

AIM
To evaluate the current evidence and controversies surrounding extended prophylaxis.

METHODS
A comprehensive literature search of PubMed, EMBASE, and Scopus was conducted for studies published between 2000 and 2025. Eligible studies included randomized trials, cohort studies, registry analyses, systematic reviews, and meta-analyses assessing prophylaxis beyond 24 hours in primary TKA. Data extraction focused on regimen type, duration, patient risk stratification, infection outcomes, and antimicrobial resistance (AMR). Reference lists of included studies and prior reviews were manually screened to ensure completeness.

RESULTS
Eleven studies met the inclusion criteria. Extensive registry and meta-analysis data consistently showed no reduction in PJI with prophylaxis extended beyond 24 hours in unselected populations. Early retrospective studies suggested the benefit of 7-day oral cephalosporin regimens in high-risk patients, but subsequent larger institutional and population-level analyses failed to reproduce these findings. Evidence also indicates an increase in AMR with prolonged prophylaxis, while rates of *Clostridioides difficile* and drug toxicity remained low. No major guideline (Centres for Disease Control and Prevention, World Health Organization, American Academy of Orthopaedic Surgeons and American Association of Hip and Knee Surgeons, International Consensus Meeting) currently endorses routine EOA.

CONCLUSION
Extended antibiotic prophylaxis beyond 24 hours does not reduce the incidence of PJI in standard-risk primary TKA patients and may contribute to the development of AMR. While selective benefit in narrowly defined high-risk groups remains possible, current evidence is conflicting and limited by retrospective design. Routine use of EOA is not recommended; future multicenter randomized trials with standardized risk stratification are urgently needed to clarify its role. Until then, adherence to ≤ 24-hour prophylaxis as endorsed by international guidelines remains the most evidence-based and stewardship-aligned approach.

Key Words: Periprosthetic joint infection; Antibiotics; Extended spectrum; Antimicrobial resistance; Antibiotic stewardship

Core Tip: Extended oral antibiotic prophylaxis after primary total knee arthroplasty has not demonstrated consistent benefit in reducing periprosthetic joint infection compared with standard ≤ 24-hour regimens. While early retrospective data suggested possible value in high-risk patients, larger studies and meta-analyses show no advantage and highlight antimicrobial resistance concerns. Current international guidelines recommend limiting prophylaxis to 24 hours, with future randomized trials needed to clarify extended oral antibiotic's role in selected populations.

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INTRODUCTION

One of the most devastating side effects following primary total knee arthroplasty (TKA) is periprosthetic joint infection (PJI), which is linked to severe morbidity, reduced function, readmission to the hospital, and a significant financial burden[1-3]. For many years, the backbone of infection prevention in total joint arthroplasty (TJA) has been standard perioperative antibiotic prophylaxis, which typically involves administering a first-generation or second-generation cephalosporin within 60 minutes before incision and maintaining it for ≤ 24 hours[4-6]. This concept is clinically relevant because both bacterial load and host immune competence during the first 24 hours after surgery significantly influence the risk of infection[7]. The initial 6-hour window is often referred to as the 'golden period', during which the host immune response is most effective at reducing bacterial contamination. Beyond this phase, residual organisms may proliferate rapidly. Appropriately timed perioperative antibiotics suppress early bacterial replication and effectively prolong this golden period, thereby reducing the likelihood of subsequent infection[7]. Nonetheless, concerns remain about the optimal duration and potential benefits of continuing antibiotic prophylaxis beyond 24 hours, particularly in high-risk patients who are more susceptible to infection[8].

Extended oral antibiotic (EOA) prophylaxis, typically administered for 5-10 days postoperatively, has been increasingly adopted in some centres[9-12]. Supporters argue that high-risk patients (those with obesity, diabetes, immunosuppression, or prior infection) may derive incremental benefit from additional antimicrobial coverage. Critics highlight the lack of randomized evidence, potential toxicity, cost, *Clostridioides difficile* (*C. difficile*) risk, and global concerns regarding antimicrobial resistance (AMR).

This narrative review aims to evaluate the current evidence surrounding extended antibiotic prophylaxis in primary TKA, with four objectives: (1) Summarize the effectiveness of EOA in reducing PJI compared with standard prophylaxis; (2) Examine patient factors and comorbidities modifying the effect of EOA; (3) Assess broader implications including resistance, adverse effects, and cost-effectiveness; and (4) Identify evidence gaps and priorities for future research.

MATERIALS AND METHODS

A systematic search of PubMed, EMBASE, and Scopus was undertaken to capture relevant studies from 2000 to 2025 for inclusion in this narrative review. The objective of this review was to identify all studies evaluating postoperative antibiotic prophylaxis protocols that extended beyond 24 hours following primary TKA. Eligible studies were required to be English-language, human research articles addressing postoperative antibiotic prophylaxis following TKA (Figure 1). No restrictions were placed on year of publication. Included studies specifically evaluated oral or intravenous antibiotic regimens extended beyond 24 hours postoperatively in primary TKA procedures. Studies not meeting these criteria were excluded. Search terms included: (1) Total knee arthroplasty; (2) Antibiotic prophylaxis; (3) Extended oral antibiotics; (4) Extended antibiotic prophylaxis; (5) Prophylaxis duration; and (6) Periprosthetic joint infection.

Eligibility criteria

Randomized trials, cohort studies, case-control studies, registry analyses, meta-analyses, and relevant editorials were included. Studies exclusively evaluating acute PJI treatment or suppression therapy were excluded except where resistance data were directly relevant to prophylaxis. Priority was given to higher-level evidence such as randomized controlled trials and well-adjusted comparative cohorts.

Statistical analysis

Data extraction included prophylaxis regimen, antibiotic class, duration, risk stratification, statistical methods, and infection outcomes. To enhance the search strategy and uncover more relevant literature, we reviewed the reference lists of all the included studies and relevant systematic reviews and meta-analysis on the same subject. All the articles were screened by two independent reviewers, and any discrepancy in inclusion was resolved through discussion with the senior author.

RESULTS

A total of 11 studies met the inclusion criteria, published between 2000 and 2024. Detailed characteristics are summarized in Tables 1, 2, and 3[8,9,12-20]. Across the 11 included studies, the extended antibiotic prophylaxis regimens varied widely in terms of route, duration, and clinical context.

Four studies used exclusively oral antibiotics as the extended regimen after the initial perioperative IV dose. These included Inabathula *et al*[13], and Kheir *et al*[15] both of whom administered 7 days of oral cephalexin to high-risk arthroplasty patients, as did Carender *et al*[16] and Bundschuh *et al*[17] who prescribed 7-14 days of postoperative oral antibiotics in morbidly obese patients or universally across all patients, respectively. Only one study by Flynn *et al*[9] evaluated a universal institutional transition to extended prophylaxis, implementing 10 days of oral cephalexin for all primary arthroplasty procedures regardless of risk category. Although Inabathula *et al*[13] and Kheir *et al*[15] reported lower PJI rates in high-risk patients receiving EOAs, both studies were observational and non-randomized, with potential for confounding by indication and institutional protocols.

Two extensive population-level studies investigated IV-only postoperative antibiotic extension beyond 24 hours. Veltman *et al*[14] using the Dutch national joint registry, compared single-dose, 24-hour, and multi-day IV prophylaxis protocols, whereas Dhodapkar *et al*[18] analyzed United States administrative data comparing postoperative day-0 *vs* day-0+1 IV dosing. In both analyses, extending IV prophylaxis failed to reduce infection risk. Three additional studies evaluated extended prophylaxis regimens but did not clearly distinguish the route of administration. These included the Kelly *et al*[12] cohort assessing EOA after two-stage reimplantation, Hong *et al*'s narrative review[8], and the systematic review by Siddiqi *et al*[20] all of which encompassed mixed IV and oral protocols.

This non-overlapping classification demonstrates that extended regimens fall into three primary patterns: Oral-only, universal IV-to-PO transition, and IV-only, with the majority of modern extended prophylaxis protocols relying on oral antibiotics rather than extended intravenous dosing[12,21]. Across all categories, the overall incidence of PJI remained low, and no consistent benefit was observed with extended prophylaxis in unselected patient populations.

Standard single-dose vs ≤ 24-hour prophylaxis in PJI/surgical site infection reduction

A landmark systematic review and meta-analysis by Siddiqi *et al*[20] found no decrease in surgical site infection (SSI) or PJI when antibiotics were continued beyond the initial preoperative dose; however, the certainty of evidence was low due to small sample sizes and rare infection events.

Extensive registry-based analyses have reproduced these findings. The Dutch Arthroplasty Registry study by Veltman *et al*[14] analysed over 240000 total hip arthroplasty/TKA cases and reported no difference in the 1-year risk of PJI between hospitals using single-dose *vs* 24-hour or multi-dose prophylaxis. Dhodapkar *et al*[18] examined more than 860000 United States TKAs and found no difference in 30-day SSI whether prophylaxis was limited to day 0 or extended

Table 1 Characteristics of included observational cohort studies evaluating antibiotic prophylaxis beyond 24 hours in primary total knee arthroplasty and related arthroplasty cohorts (2000 to 2025)

Ref.	Design	Setting/population	Arthroplasty type	Sample size	High-risk definition	Extended prophylaxis regimen	Comparator	Follow-up/endpoint	Primary outcome measure	Key finding	Limitations
Inabathula *et al*[13]	Retrospective cohort	Single system or multi-site cohort; high-risk primary arthroplasty patients	Primary TKA and THA	2181 primary TKAs	Composite: Obesity, diabetes, immunosuppression, prior infection, other comorbidities	Oral cephalexin 7 days after standard perioperative IV prophylaxis	Standard prophylaxis; no extended oral course	90 days	90-day PJI	Lower 90-day PJI reported in high-risk patients receiving 7-day EOA	Retrospective; confounding by indication; risk definition not universally validated; applicability to routine-risk patients uncertain
Veltman *et al*[14]	Registry-based observational cohort	Dutch Arthroplasty Register; hospital-level protocol comparison	Primary THA and TKA	242179 hip and knee arthroplasties	Not risk-stratified (population-level analysis)	Compared single-dose *vs* 24-hour *vs* multiple-dose IV perioperative protocols	Other duration protocols	1 year (revision for infection in registry)	Revision for infection (proxy for PJI)	Similar revision-for-infection risk across single-dose and multiple-dose strategies	Registry endpoint is revision, not all PJIs; limited microbiology and adherence detail; confounding by hospital-level practice
Kheir *et al* [15]	Prospective cohort (American Association of Hip and Knee Surgeons award study)	High-risk primary arthroplasty cohort	Primary TKA and THA	3855 total (TKA + THA)	High-risk composite (study-specific criteria)	Oral cefadroxil 500 mg twice daily for 7 days after standard perioperative IV prophylaxis	Standard prophylaxis; no EOA	1 year	1-year PJI	PJI decreased in high-risk patients receiving 7-day EOA (as reported)	Non-randomized; potential selection bias; generalizability depends on local baseline infection rate and perioperative pathway
Carender *et al*[16]	Retrospective cohort	Morbidly obese primary arthroplasty patients	Primary TJA (445 TKAs reported)	445 TKAs	Morbid obesity (body mass index ≥ 40)	Oral antibiotics 7-14 days (agent not standardised across all centres)	Standard prophylaxis; no EOA	Early postoperative period	Early PJI; wound complications	No significant reduction in early PJI or wound complications in morbidly obese subgroup receiving EOA	Limited power for rare events; heterogeneity in antibiotic selection and adherence; retrospective confounding
Kelly *et al* [12]	Cohort study (reimplantation context)	Two-stage exchange for PJI; not primary TKA prophylaxis	Reimplantation after PJI	Not applicable to primary TKA	Not applicable	Prolonged oral antibiotics after reimplantation	No prolonged antibiotics	Recurrence window per study	Recurrent PJI; resistance profile	Higher proportion of resistant organisms among recurrent PJIs in prolonged-antibiotic group (as reported)	Not primary TKA; included for resistance plausibility and stewardship implications only

Bundschuh *et al*[17]	Retrospective cohort (single-surgeon experience)	Universal extended prophylaxis in primary and aseptic revision cases; single-surgeon protocol	Primary and aseptic revision TJA (approximately 1250 primary TKAs)	Approximately 1250 primary TKAs	Not risk-stratified (universal protocol)	Oral cefdinir 7 days; concomitant intra-wound vancomycin powder	Historical or contemporary non-EOA comparator	3 months	3-month PJI	Lower short-term PJI reported with protocol; attribution to EOA *vs* vancomycin powder unclear	Strong confounding by co-intervention (vancomycin powder); single-surgeon external validity limits; before-after design vulnerable to secular trend
Flynn *et al* [9]	Retrospective institutional policy-change cohort	High-volume institutional transition to universal EOA	Primary TJA (> 4500 TJAs including TKA)	> 4500 primary TJAs	High-risk subgroup analyses performed (definition study-specific)	Oral cephalexin 10 days for all primary arthroplasty cases	Pre-policy standard prophylaxis (≤ 24 hours)	90 days and 1 year	PJI at 90 days and 1 year	No reduction in PJI overall or in high-risk subgroups (as reported)	Before-after design; adherence and outpatient completion difficult to verify; baseline PJI already low limits absolute benefit
Dhodapkar *et al*[18]	Administrative database cohort	United States claims/administrative dataset	Primary TKA	> 860000 TKAs	Not specified	Postoperative day-0 only *vs* day-0 plus day-1 IV dosing	Shorter duration	30 days	30-day SSI	No difference in 30-day SSI with extension to postoperative day 1; antibiotic choice influenced outcomes	Addresses intraoperative antibiotic choice rather than post-discharge duration; administrative dataset; limited clinical granularity

EOA: Extended oral antibiotic; IV: Intravenous; PJI: Periprosthetic joint infection; SSI: Surgical site infection; TJA: Total joint arthroplasty; TKA: Total knee arthroplasty; THA: Total hip arthroplasty.

Table 2 Systematic reviews and meta-analyses evaluating prophylaxis duration in primary hip and knee arthroplasty (2000-2025)

Ref.	Scope and database	Arthroplasty types covered	Studies/patients included	Prophylaxis strategies compared	Infection outcome (PJI/SSI)	Certainty of evidence and key limitations
Siddiqi *et al* [20]	Systematic review and meta-analysis of total joint arthroplasty literature	TKA and THA	Multiple RCTs and observational studies; specific *n* per protocol in paper	Prolonged prophylaxis *vs* shorter protocols (varied definitions across included studies)	No reduction in SSI or PJI beyond initial dosing; certainty limited by low event rates	Low-certainty; heterogeneous protocols and eras; underpowered RCTs; rare-event bias; variable reporting of harms
Fernandes *et al*[19]	Systematic review and meta-analysis of primary hip and knee arthroplasty literature	TKA and THA	Nearly 300000 TKAs as stated in manuscript	Single-dose *vs* extended prophylaxis (definition of extended varies across included cohorts)	Lower PJI odds with single-dose *vs* extended (reported odds ratio = 0.78; 95%CI: 0.63-0.98); SSI trend favoured single-dose but did not reach significance	Meta-analysis inherits confounding from observational studies; definition of extended differs across cohorts; harms and resistance variably captured across included studies

PJI: Periprosthetic joint infection; RCT: Randomised controlled trial; SSI: Surgical site infection; TKA: Total knee arthroplasty; THA: Total hip arthroplasty.

Table 3 Narrative reviews and non-primary evidence sources [narrative reviews included for contextual synthesis (not primary evidence)]

Ref.	Scope	Arthroplasty focus	Principal themes addressed	Contribution to evidence base and key caveats
Hong *et al*[8]	Narrative review	Total knee arthroplasty (primary or revision focus)	EOA strategies; controversy around post-discharge prophylaxis; antibiotic stewardship concerns	Highlights lack of randomised evidence for EOAs; draws attention to stewardship implications; not primary evidence and dependent on quality of included studies reviewed

EOA: Extended oral antibiotic.

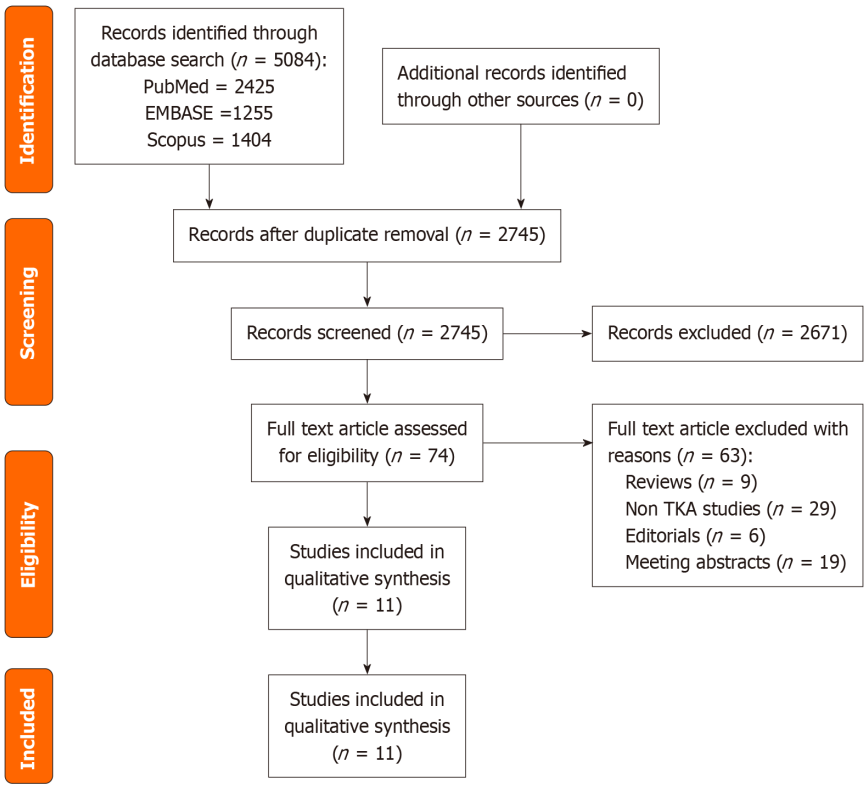


Figure 1 Schematic flow diagram of inclusion of studies. TKA: Total knee arthroplasty.

to postoperative day 1. Only antibiotic choice (cefazolin superior to clindamycin/vancomycin) influenced outcomes.

A 2024 meta-analysis by Fernandes *et al*[19] which included nearly 300000 TKAs reported lower PJI rates with single-dose prophylaxis compared to extended regimens (odds ratio = -0.78; 95%CI: 0.63-0.98; I^2 = 0%; P < 0.05), suggesting no efficacy advantage to extended dosing. This trend was similarly noted in incidence of SSI wherein single-dose antibiotic prophylaxis showed reduced SSI rates compared to extended antibiotic prophylaxis, although not statistically significant (relative risk = 0.76; 95%CI: 0.56-1.03; I^2 = 0%; P = 0.081)[19].

EOAs (> 24 hours) in high-risk patients

Early supportive evidence (selective EOA in high-risk patients): Two widely cited studies suggested benefits of 7-day EOA in high-risk arthroplasty patients. Inabathula *et al*[13] in their retrospective cohort study on 2181 primary TKAs reported a five-fold reduction in 90-day PJI among high-risk patients receiving 7-day EOA with cephalexin. Similarly, Kheir *et al*[15] in their prospective study on 3855 patients (TKA and total hip arthroplasty) found 1-year PJI decreased from 2.64% to 0.89% in high-risk patients receiving 7-day EOA with Cefadroxil 500 mg, twice daily. These findings seeded enthusiasm for selective EOA in high-risk patients with significant comorbidities. These findings should however be interpreted with caution. Both studies were observational and prone to selection bias and confounding from institution-specific protocols, limiting causal inference. As such, they should be considered hypothesis-generating rather than practice-changing, pending validation through well-designed prospective trials.

However, subsequent conflicting evidence from more recent, larger datasets have challenged this benefit. Carender *et al*[16] in their retrospective study on 445 TKAs found no significant reduction in early PJI rates or wound complications among morbidly obese (body mass index ≥ 40) patients receiving EOA for 7-14 days after surgery. Similar findings were also observed with in the large retrospective cohort study of Flynn *et al*[9] which evaluated over 4500 primary TJAs after a system-wide shift to 10-day EOA for all patients. The study found no difference in PJI at 90 days or 1 year, even among high-risk subgroups. They however, also did not find any increased antibiotic resistance or increase of *C. difficile*

infections with the use of EOA.

Recent studies from Bundschuh *et al*[17] analyzed a single-surgeon experience using 7 days of oral cefdinir for all primary and aseptic revision TJA. The authors noted lower 3-month PJI (0.23% *vs* 0.74%) which included about 1250 primary TKAs. However, all patients also received intra-wound vancomycin powder which may be a conflicting factor.

Impact beyond PJI: C. difficile, toxicity, and microbiological resistance

AMR: The strongest evidence comes from Kelly *et al*[12], who evaluated EOA after two-stage reimplantation. They found 67% of recurrent PJIs in the EOA group were resistant to the prophylactic antibiotic, compared with 0% in patients without extendedtherapy. Although this study focuses on reimplantation rather than primary TKA, it provides unique real-world evidence that EOA oral antibiotics select for resistance[12]. Similarly, Flynn *et al*[9] found no reduction in resistant infections with EOA and noted that most PJIs were caused by organisms already resistant to the initial prophylactic agent. These data support the antimicrobial stewardship position that extended prophylaxis may drive AMR without improving outcomes.

***C. difficile* infection:** Large cohorts show very low absolute *C. difficile* rates after primary TKA (< 0.1%). Both Flynn *et al* [9] and Kheir *et al*[15] reported no increase in *C. difficile* with a 7-10 day EOA course. However, guidelines emphasize that longer exposure increases theoretical *C. difficile* risk, especially with clindamycin or fluoroquinolones.

Renal/drug toxicity: Vancomycin and aminoglycoside-based regimens are associated with higher postoperative kidney injury rates. While most EOA regimens use safer oral cephalosporins, extended use still increases the probability of hypersensitivity reactions and drug interactions but has not been reported in literature with the use of EOA.

Economic considerations: EOA adds minimal direct cost (inexpensive oral cephalosporins), but the *indirect* costs of AMR, adverse events, and potential overtreatment should be considered. No high-quality cost-effectiveness analysis currently supports routine EOA.

Guidelines and consensus recommendations

Centres for Disease Control and Prevention (2017): Single preoperative dose; no postoperative antibiotics[22].

World Health Organization (2016): Do not continue prophylaxis after wound closure[23].

American Academy of Orthopaedic Surgeons and American Association of Hip and Knee Surgeons (2017-2020): Disagree with Centres for Disease Control and Prevention; endorse ≤ 24 hours of prophylaxis for TKA; do *not* support EOA[24].

International Consensus Meeting (2018) and (2025): Prophylaxis should not exceed 24 hours[25].

No major guideline: Currently endorses extended prophylaxis (> 24 hours) in primary TKA, even in high-risk patients.

DISCUSSION

The principal finding of this narrative review is that extended antibiotic prophylaxis beyond 24 hours does not consistently reduce PJI rates following primary TKA when applied to unselected patient populations. While early retrospective investigations suggested a potential benefit of EOA prophylaxis in carefully defined high-risk cohorts subsequent large registry analyses, administrative database studies, and institutional policy evaluations have failed to reproduce these findings[13,15]. Moreover, emerging evidence indicates that EOA exposure may contribute to AMR without improving infection-related outcomes, reinforcing concerns related to antibiotic stewardship[26-28].

These early signals of benefit must also be interpreted within the broader hierarchy of evidence. Observational cohort studies are inherently vulnerable to residual confounding, particularly in settings where extended antibiotic protocols are implemented alongside institution-specific infection prevention pathways, surgeon experience, and postoperative surveillance intensity. As the literature has evolved, larger registry-based analyses, administrative database studies, and institutional policy-change cohorts representing substantially greater sample sizes and contemporary arthroplasty practice have not demonstrated a reproducible reduction in PJI with extended prophylaxis. The failure of these higher-level data sources to confirm early findings suggests that the apparent benefit observed in initial reports may be attributable to unmeasured confounders rather than a true causal effect of extended antibiotic exposure. Accordingly, the totality of evidence currently supports EOA prophylaxis as hypothesis-generating rather than practice-changing in primary TKA.

Extended prophylaxis in standard-risk populations

Across population-level datasets, prolongation of prophylactic antibiotics – whether intravenously or orally beyond the standard perioperative period did not reduce infection risk. These studies consistently demonstrated that antibiotic choice, rather than duration, was the dominant factor influencing SSI rates, with cefazolin-based regimens outperforming alternative agents such as clindamycin or vancomycin.

These findings are concordant with systematic reviews and meta-analyses reporting non-inferiority of single-dose or ≤ 24-hour prophylaxis compared with extended regimens[19,20]. Importantly, these analyses reflect modern arthroplasty practice, incorporating standardized perioperative pathways, improved operating-room environments, and contem-

porary infection surveillance definitions[29,30]. Given the already low baseline PJI rates following primary TKA often below 1% the absolute potential for further risk reduction with extended prophylaxis is minimal[31,32]. In this context, routine extension of antibiotic duration appears unlikely to offer clinically meaningful benefit.

High-risk patients: True benefit or residual confounding

The most debated aspect of extended prophylaxis relates to its use in patients deemed at high risk for infection. Two influential retrospective studies reported significantly lower early PJI rates among high-risk patients receiving 7 days of postoperative oral antibiotics[13,15]. These findings led to increased adoption of EOA protocols in select centers and stimulated further investigation.

However, subsequent studies have challenged the generalizability of these results. Carender *et al*[16] focusing on morbidly obese patients, found no reduction in PJI or wound complications with extended prophylaxis. More notably, an extensive institutional policy-change analysis evaluating universal 10-day oral prophylaxis demonstrated no decrease in PJI, even when high-risk subgroups were analyzed independently[9]. These conflicting findings suggest that the benefit observed in early studies may reflect selection bias, residual confounding, or unmeasured perioperative variables, rather than an actual causal effect of EOA exposure.

Furthermore, definitions of "high risk" varied substantially across studies, encompassing different combinations of obesity, diabetes mellitus, smoking, chronic kidney disease, autoimmune disease, and nasal colonization with staphylococcus aureus. The absence of a validated and standardized risk stratification model limits the ability to identify patients who may reliably benefit from extended prophylaxis. Until such criteria are prospectively validated, selective use of EOA remains hypothesis-generating rather than evidence-based.

AMR and stewardship considerations

Beyond clinical outcome data, there is strong microbiological plausibility to support concerns regarding extended antibiotic prophylaxis. EOA exposure increases selective pressure on both pathogenic and commensal organisms, facilitating preferential survival of resistant strains and disruption of normal host flora. This ecological alteration may promote colonization by multidrug-resistant organisms and reduce microbial diversity, thereby increasing the likelihood that subsequent infections are caused by pathogens inherently resistant to first-line prophylactic agents. In addition, extended exposure to the same antibiotic class may select for resistance mechanisms such as altered penicillin-binding proteins, efflux pump upregulation, and biofilm-associated tolerance, which are particularly relevant in prosthetic joint infections. These mechanisms provide biological context for clinical observations demonstrating higher proportions of resistant organisms following EOA use and reinforce the importance of aligning prophylaxis duration with antimicrobial stewardship principles.

Kelly *et al*[12] demonstrated a markedly higher proportion of resistant organisms among recurrent infections in patients receiving EOA after two-stage reimplantation. Although this study did not evaluate primary TKA, it provides compelling biological plausibility that extendedprophylaxis may compromise future infection management.

Similarly, the institutional analysis by Flynn *et al*[9] showed that extended prophylaxis neither reduced the incidence of resistant organism PJI nor altered pathogen profiles, indicating that prolonged exposure does not mitigate resistance-related infections. Given that many contemporary PJIs are already caused by organisms resistant to first-line prophylactic agents, extending exposure to the same antibiotics may offer diminishing returns while increasing ecological harm.

From an antibiotic stewardship perspective, these findings are significant. Prophylactic antibiotics are administered to a large population of otherwise uninfected patients, and even modest increases in resistance or adverse events can have substantial public health implications when extrapolated across millions of arthroplasty procedures annually[33]. Table 4 summarizes the evidence synthesis and controversies on the duration strategies, effect on infection, and stewardship implications in primary TKA[9,12-15,17-19].

Safety and cost implications

The reviewed studies reported low absolute rates of *C. difficile* infection and antibiotic-related toxicity, particularly when oral cephalosporins were used[9,15]. However, these events are rare, and most studies were underpowered to detect small but clinically meaningful differences. The absence of observed harm in retrospective cohorts should therefore not be interpreted as definitive evidence of safety.

From a health-economic perspective, the role of extended antibiotic prophylaxis in primary TKA remains insufficiently defined. Although the direct cost of short courses of oral cephalosporins is relatively low at the individual patient level, no formal cost-effectiveness analyses have demonstrated economic benefit for extended prophylaxis beyond standard ≤ 24-hour regimens. Importantly, existing studies have not accounted for downstream costs related to AMR, management of resistant PJIs, additional microbiological investigations, or prolonged hospital stays associated with treatment failure. In the absence of a demonstrable reduction in PJI rates, even modest increases in antibiotic exposure across large arthroplasty populations may translate into substantial cumulative healthcare costs. Accordingly, robust cost-effectiveness analyses incorporating resistance-related outcomes should be prioritized in future research before extended prophylaxis can be justified as a value-based intervention.

Guideline alignment and clinical implications

Current international guidelines uniformly recommend limiting antibiotic prophylaxis to ≤ 24 hours following primary arthroplasty. The Centres for Disease Control and Prevention and the World Health Organization advocate single-dose prophylaxis (Centres for Disease Control and Prevention, 2017; World Health Organization, 2016), while orthopaedic societies endorse discontinuation within 24 hours (American Academy of Orthopaedic Surgeons and American

Table 4 Evidence synthesis: Prophylaxis strategies, efficacy, and stewardship implications in primary total knee arthroplasty (restructured evidence synthesis comparing prophylaxis duration strategies – effect on infection outcomes and stewardship implications)

Ref.	Prophylaxis strategy	Typical regimen	Evidence sources in this review	Efficacy: Standard-risk primary TKA	Efficacy: High-risk subgroups	Harms and stewardship concerns	Practice interpretation (based on cited evidence)
Veltman *et al*[14]	Single pre-incision dose only	Cefazolin or equivalent within 60 minutes pre-incision; no postoperative doses	Registry comparisons; meta-analyses; guideline frameworks	No worse outcomes than longer courses in large registry and pooled analyses; single-dose performed as well or better than extended protocols in one meta-analysis (odds ratio = 0.78 favouring single-dose *vs* extended)	High-risk effects not established by randomised data; not specifically tested in defined high-risk subgroups in these analyses	Minimises antibiotic exposure; lowest selective pressure for resistance; lowest drug-related adverse event burden	Reasonable default in many guideline frameworks; strongest alignment with stewardship goals; supported by large-scale observational and registry evidence
Fernandes *et al*[19]	Standard prophylaxis ≤ 24 hours	Pre-incision dose plus limited postoperative dosing to complete 24 hours	Large observational datasets; orthopaedic society positions (American Academy of Orthopaedic Surgeons and American Association of Hip and Knee Surgeons-type frameworks as referenced in manuscript)	No consistent reduction beyond this window compared with single-dose in large observational datasets	No consistent evidence that extending past 24 hours adds benefit beyond perioperative coverage	Low but non-zero adverse event risk; still limited total exposure; modestly greater selective pressure than single-dose	Dominant orthopaedic standard; supported by society positions; appropriate for most primary TKA patients
Veltman *et al*[14]; Dhodapkar *et al*[18]	IV prophylaxis extended beyond 24 hours (multi-day IV)	Continued IV dosing for multiple postoperative days	Large registry and administrative analyses	No reduction in infection outcomes in population-level analyses	Not clearly beneficial; no data specifically supporting this approach in high-risk groups	Line-related risks if IV access prolonged; selection pressure; nursing and cost burden	Not supported for routine primary TKA; duration does not appear to be the modifiable driver relative to antibiotic choice and perioperative pathway optimisation
Inabathula *et al*[13]; Kheir *et al*[15]	Selective EOAs in high-risk patients	7 days of oral cephalexin or cefadroxil (typically 500 mg twice daily) after standard perioperative IV prophylaxis; applied only to defined high-risk patients	Two influential comparative cohort studies	Not intended for standard-risk patients in these studies; no data support routine use outside high-risk criteria	Reported reduction in early or 1-year PJI in study-defined high-risk cohorts; causality uncertain given non-randomised designs and confounding by indication	Potential for resistance selection; outpatient adherence variability; *Clostridioides difficile* risk biologically plausible even if not observed in these cohorts	Hypothesis-generating only; if used, should be restricted to protocolised, clearly defined high-risk criteria with stewardship oversight and robust surveillance; randomised evidence is absent
Flynn *et al*[9]; Bundschuh *et al*[17]	Universal EOA for all primary arthroplasty patients	7-10 days of oral antibiotics post-discharge for all patients regardless of risk	Large institutional policy-change cohort); universal single-surgeon protocol	No consistent reduction in 90-day or 1-year PJI when applied broadly	No benefit detected even in high-risk subgroup analyses in at least one large cohort; attribution problem compounded by co-interventions	Ecologic resistance risk at population scale; overtreatment of genuinely low-risk patients; adds unnecessary antibiotic exposure across the majority who would not benefit	Not supported by current evidence; routine universal EOA is difficult to justify given low baseline PJI rates and stewardship principles; should not be extrapolated from single-surgeon bundle studies
Bundschuh *et al*[17]	EOA plus co-interventions (*e.g.*, intra-wound vancomycin powder)	Oral antibiotics paired with local antibiotic adjuncts; protocol varies by institution	Single-surgeon protocol combining cefdinir with vancomycin powder	Any observed reduction in infection rate cannot be attributed to EOA alone given the bundled design	Same attribution problem; high-risk-specific effect cannot be isolated from the bundle	Risk of confounding and inappropriate extrapolation to EOA as an independent intervention	Results should be interpreted as bundle effects only; not proof of EOA efficacy; co-intervention designs are

							insufficient to inform isolated EOA policy decisions
Kelly *et al* [12]	Prolonged antibiotics in non-primary TKA settings (resistance signal)	EOAs after two-stage exchange reimplantation	Reimplantation cohort; included for stewardship implications not primary prophylaxis efficacy	Not applicable to primary TKA prophylaxis efficacy	Not applicable	Strong signal for selection of resistant organisms among failures in prolonged-antibiotic group; clinically meaningful change in microbiology of recurrent PJI	Supports stewardship caution: Prolonged antibiotic exposure can meaningfully alter the microbial landscape; findings are generalisable as a harm signal even if not directly applicable to primary prophylaxis

EOA: Extended oral antibiotic; IV: Intravenous; PJI: Periprosthetic joint infection; TKA: Total knee arthroplasty.

Association of Hip and Knee Surgeons, 2017-2020; International Consensus Meeting, 2018). None recommend routine extended prophylaxis, even in high-risk patients.

The divergence between guideline recommendations and evolving clinical practice reflects ongoing uncertainty rather than a consensus based on evidence. Based on the available data, routine extension of prophylactic antibiotics beyond 24 hours following primary TKA cannot be justified. When extended prophylaxis is considered, it should be approached cautiously, ideally within institutional protocols that emphasize antimicrobial stewardship and multidisciplinary oversight.

Limitations

The quality and heterogeneity of the underlying literature limits this review. Most studies evaluating extended prophylaxis are retrospective, which inherently introduces susceptibility to bias and confounding. Randomized controlled trials are notably absent, particularly in high-risk populations. Variability in antibiotic regimens, duration, follow-up intervals, and PJI definitions further complicates inter-study comparison along with a lack of formal cost-effectiveness analysis

While this review highlights clinically relevant associations between extended antibiotic exposure and AMR, an in-depth exploration of underlying microbiological mechanisms such as selective pressure, disruption of host microbiota, and emergence of resistant strains is beyond the scope of this narrative review. Extensive registry and administrative database studies, while powerful, often lack granular data on antibiotic route, adherence, and microbiological outcomes. These limitations underscore the need for carefully designed prospective investigations.

Future directions

Future research should prioritize multicenter randomized controlled trials comparing standard prophylaxis with extended oral regimens in clearly defined high-risk TKA populations. Such studies should incorporate standardized infection definitions, detailed microbiological analysis, and long-term surveillance for AMR along with economical implications including formal cost-effectiveness analysis. Development and validation of robust risk stratification tools may further clarify whether any subgroup derives a net benefit from extended prophylaxis.

CONCLUSION

The accumulated evidence including recent large datasets, meta-analyses, and resistance-focused studies indicate that extended antibiotic prophylaxis provides no added benefit for the general primary TKA population. Early encouraging findings in high-risk patients are counterbalanced by larger and more modern studies showing no reduction in PJI when EOA is used universally and emerging concerns regarding AMR. Currently, routine EOA after primary TKA is not recommended. Selective use in narrowly defined high-risk patients remains investigational and requires validation through rigorously designed randomized trials. Until such evidence emerges, adherence to established ≤ 24-hour prophylaxis as recommended by American Academy of Orthopaedic Surgeons and American Association of Hip and Knee Surgeons and global surgical guidelines represents the most prudent, stewardship-aligned, and evidence-supported approach.

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