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Antibiotic Prophylaxis in Closed Fractures: A Systematic Literature Review

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ABSTRACT

Introduction: Surgical site infection remains an important complication following surgical fixation of closed fractures. This systematic literature review aimed to summarize the types of prophylactic antibiotics used and their administration protocols in patients with closed fractures.

Methods: PubMed, Google Scholar, and Semantic Scholar were searched for studies published from 2019 to 2023 using the terms "closed fracture," "infection," and "antibiotic prophylaxis." Eligible studies included patients with closed fractures who received prophylactic antibiotics and reported postoperative infection outcomes. Data were synthesized descriptively.

Results: Five studies involving 650 patients met the inclusion criteria. Prophylactic regimens varied in antibiotic selection, dosage, timing, dosing interval, and duration. Cefazolin and cefazedone were the most commonly used first-generation cephalosporins, while cefuroxime and cefotaxime represented second- and third-generation cephalosporins, respectively. All antibiotics were administered intravenously, generally 30–60 minutes before incision. Prophylaxis ranged from a single dose to repeated administration for up to 3 days, although most studies limited administration to 24 hours or less.

Conclusion: Cephalosporins were the predominant prophylactic antibiotics used in closed-fracture surgery, particularly first-generation agents. Although regimens varied across studies, intravenous administration before incision and prophylaxis of 24 hours or less were the most commonly reported approaches.

Keywords: antibiotic prophylaxis; cephalosporins; fractures, closed; surgical wound infection.

INTRODUCTION

Closed fractures are characterized by a disruption of bone continuity without a breach of the overlying skin. Consequently, the fracture site does not communicate with the external environment, although varying degrees of swelling, erythema, and soft-tissue injury may occur.[1] Soft-tissue damage can still accompany closed fractures; however, the injury is generally less extensive than that observed in open fractures.[2] Despite the absence of direct communication with the external environment, postoperative infection remains an important complication following surgical fixation of closed fractures, with a reported incidence of approximately 0.5–5%.[3] Surgical site

infections (SSIs) following fracture fixation have commonly been classified according to the time of onset after surgery as early (<2 weeks), delayed (2–10 weeks), or late (>10 weeks) infections.[4] This classification has been widely used because the timing of infection may influence clinical presentation and treatment strategies. Although delayed and late infections may share overlapping characteristics, the three-category classification remains clinically useful in the assessment and management of infection following fracture fixation.[5]

Surgical site infection is a serious postoperative complication that can adversely affect fracture healing, increase patient morbidity, prolong hospitalization, and impose a substantial economic burden on both patients and healthcare systems.[6] Preventive strategies are therefore essential in orthopedic trauma surgery. Appropriate perioperative antibiotic prophylaxis is one of the principal measures used to reduce the risk of postoperative infection and has been reported to reduce the incidence of infection following closed-fracture surgery by up to 35%.[7] Nevertheless, variations remain in the selection of prophylactic antibiotics, dosage, timing of administration, route of administration, and duration of prophylaxis in patients undergoing surgical treatment for closed fractures. Therefore, this systematic literature review aimed to evaluate the available evidence regarding antibiotic prophylaxis in the surgical management of closed fractures, with particular emphasis on the types of antibiotics used and their administration protocols.

METHODS

Search strategy and data sources

A systematic literature search was conducted using PubMed, Google Scholar, and Semantic Scholar to identify studies evaluating antibiotic prophylaxis in patients with closed fractures. The search included studies published between 2019 and 2023 and used combinations of the following keywords: “closed fracture,” “infection,” and “antibiotic prophylaxis.” The final literature search was performed on May 29, 2023. Articles identified through the search were subsequently screened for relevance according to the predefined eligibility criteria.

Eligibility criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) included patients with closed fractures; (2) evaluated the use of prophylactic antibiotics; (3) reported the incidence of infection following antibiotic prophylaxis; and (4) were published in either English or Indonesian. Studies were excluded if they involved patients with closed fractures who had an established infection before the administration of prophylactic antibiotics or patients who had received antibiotic therapy before the intervention evaluated in the study.

Study selection

Articles identified through the literature search were assessed for eligibility based on the predefined inclusion and exclusion criteria. Relevant studies meeting all eligibility criteria were included in the final review. The literature identification and selection process is summarized in Figure 1.

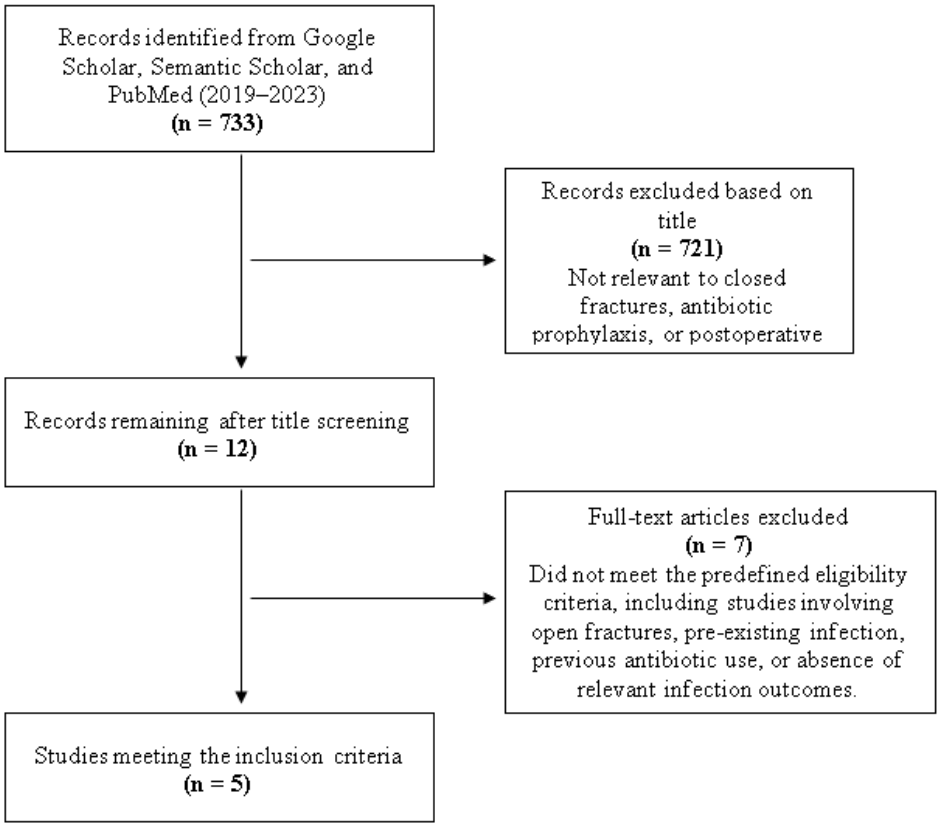


Figure 1. Flow diagram of the literature search and study selection process

Data synthesis

Data from the eligible studies were extracted and synthesized descriptively. The analysis focused primarily on the types of prophylactic antibiotics used, their administration protocols, and the reported incidence of postoperative infection following prophylactic antibiotic administration in patients with closed fractures. Findings from the included studies were subsequently compared and summarized to identify patterns in antibiotic selection and prophylactic administration strategies.

RESULTS

Three clinical reports met the exact-age eligibility criteria: one retrospective cohort with a separately Five studies involving a total of 650 patients with closed fractures met the inclusion criteria. The included studies comprised retrospective case-control and prospective interventional designs. Study characteristics and main findings are summarized in Table 1, while prophylactic antibiotic regimens are presented in Table 2.

Table 1. Characteristics of included studies on antibiotic prophylaxis in patients with closed fractures

Author (Year)	Population	Study Design	Main findings
Frank et al., (2019) [8]	314 patients with isolated ankle fractures, January 2012 - June 2016 (OTA classifications 44A1-3, 44B1-3, and 44C1-3)	Retrospective case-control study	To compare the surgical site infection (SSI) rates in ankle fracture patients receiving either single preoperative intravenous (IV) dose (SD) or multidose 24 hours IV postoperative (MD) perioperative IV antibiotic prophylaxis. Method: All patients received preoperative antibiotics within 1 hour before incision. Weight-based cefazolin was utilized for all patients

			unless they had an allergy in which case weight-based clindamycin was utilized. We utilized the US Centers for Disease Control guidelines, and defined superficial SSI as those requiring local wound care and oral antibiotics, and deep SSI as those requiring return to operating room for debridement. Results: There were 99 patients in the SD group and 215 patients in the MD group. The overall SSI rate was 5.1% in the SD group versus 2.8% in the MD group (P = .312). The superficial SSI rate was 2.0% in the SD group versus 1.4% in the MD group not significant (NS). The deep SSI rate was 3.0% in the SD group versus 1.4% in the MD group (NS). Conclusion: The SSI rates in isolated closed ankle fractures receiving either SD or MD perioperative IV antibiotic prophylaxis were similar. Further studies should be considered to help guide the standard of care for perioperative IV antibiotic prophylaxis.
Jha et al., (2019) [9]	100 patients with closed fracture of limb requiring open reduction or closed reduction with internal fixation, November 2016 to November 2018	Prospective interventional study	Our primary objective is to assess the efficacy of short course antibiotic prophylaxis in preventing surgical site infection (SSI) in surgery of closed orthopedic fracture. Method: Short course antibiotic prophylaxis was administered in peri-operative period to all patients in given format: 3 divided doses of intravenous 1.5 grams cefuroxime during peri-operative period followed by no intravenous or oral antibiotics; 1st dose half an hour before incision; 2nd and 3rd dose repeated at 12 hours interval. The surgical wound was clinically observed on 2nd post-operative day (POD) when the dressing was done. Patients was asked daily for any excess local pain or discomfort, and daily temperature charting was done by nursing staff. Most of the patients were discharged from hospital on 2nd POD. Wound dressing was done on every 3rd day or as advised by the vising surgeon. Clinical follow-up was done on 14th POD for suture removal. Surgical site assessment for SSI was done on every routine follow-up at our outpatient clinic at 6 weeks, 12 weeks, 6 months, and 1 year post surgery. SSIs were initially diagnosed clinically and defined and classified according to criteria described by center for disease control and prevention as superficial 2 incisional SSI, deep incisional SSI or organ/space SSI. Results: Of total 100 patient, three developed surgical site infection till one year follow-up; one patient was suspected SSI on 1st POD, two patients developed a SSI within one year follow up. All three patients with surgical site infection were treated successfully with intravenous antibiotic based on the culture sensitivity report. Conclusions: Short course antibiotic prophylaxis regimen is equally effective for preventing SSI in surgery of closed fracture of limbs. There was no significant increase in rate of surgical site infection with short course antibiotic prophylaxis, rather it was less expensive and may have less adverse

			effect, in terms of antibiotic resistance and antibiotic side effects on long run.
Azeem & Patil, (2019) [10]	50 patients with clean and closed orthopedic operations	Prospective interventional study	The purpose of this test was to evaluate whether the fight against infection of a perioperative part was successful in counteracting. Method: Participants were administered a single antibiotic of 1 g of cefotaxime intravenously 30 minutes before surgery followed by 12 hourly for 3 days. Patient were mobilized after 12 hours and discharged on 3rd day. The incidence of postoperative complications such as wound infections, wound re-suturing, etc. was monitored. Results: The study included 50 clean and closed orthopedic operations out of which only one patient had superficial wound infection. The organisms isolated from wound infection were E. coli, Pseudomonas, which were sensitive to cotrimoxazole. The normal duration of the stay was only 3 days. Conclusions: A single antibiotic of cefotaxime is equally effective, early mobilization and early discharge is useful and safe for orthopedic surgery.
Jokar, et al. (2022) [11]	140 patients with closed lower limb fracture from hip to the ankle that underwent Open reduction and internal fixation (ORIF)		This study aimed to evaluate the effectiveness of prophylactic antibiotics to prevent infection in closed lower limb fracture surgery. Methods: The patients who received one gram of intravenous cefazolin 1 hour before and up to 24 hours (every 6 hours) after the surgery were allocated to the first group, and patients who received one gram of intravenous cefazolin 1 hour before and up to 72 hours (every 6 hours) after the surgery were categorized in the second group. The criterion for the presence of infection was based on clinical manifestations such as heat, redness and swelling, pain and infectious secretions, and laboratory tests. Washing, debridement, suture, and wound dressing were similarly done in all patients, if possible. Drains were removed within 24 hours after the operation, and patients were discharged if their nutrition tolerance and mobility were improved and did not have a fever. Results: Of 140 patients with closed lower limb fractures, two patients (1.4%), one from each study group, were infected. The culture of two patients with infection resulted in Staphylococcus aureus, and both patients showed fever and chill symptoms. Infection rates in patients, who received prophylactic antibiotics for 24 hours, had no significant difference with those who received antibiotics for 72 hours (p=0.99). Conclusion: The 24-hour prophylactic antibiotic administration to reduce risks of postoperative infection of the closed lower limb fracture in patients can be a suitable alternative for the long-term use of antibiotics.
Kim & Kwack, (2022) [12]	46 patients with distal radius fracture (DRF) treated with internal fixation		The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are representative inflammatory markers. The aim of this study was to compare serial serum ESR and CRP levels in distal

			radius fracture (DRF) patients according to the period of prophylactic antibiotic use. Methods: A retrospective study was conducted on 46 patients with DRF treated with internal fixation. Twenty-two patients were in group A and 24 patients comprised group B. The patients in group A were administered the first-generation cephalosporin for 1 week, as was customary. Group B received 1-day antibiotic prophylaxis. The surgical wounds and serum ESR and CRP levels were examined before surgery, 2 days after surgery, and 1 week after surgery and compared between the two groups. Results: In all cases in group B and 21 cases in group A, surgical wounds were clean. Only one case in group A, surgical wound was clean-contaminated 2 days after surgery. However, antibiotics were used until the first week of surgery in group A, and the surgical wound was clean after the first week of surgery. The mean ESR levels on the day before surgery, day 2 after surgery, and week 1 after surgery were 22.3±15.9 mm/hr, 20.2±17.0 mm/hr, and 18.9±13.5 mm/hr in group A and 12.8±8.9 mm/hr, 11.6±7.0 mm/hr, and 13.3±9.8 mm/hr in group B. There was no significant difference in the change of ESR over time ($p=0.393$). The mean CRP levels on the day before surgery, day 2 after surgery, and week 1 after surgery were 0.3±0.2 mg/dL, 1.9±1.4 mg/dL, and 0.5±0.7 mg/dL in group A and 0.5±0.7 mg/dL, 3.3±3.3 mg/dL, and 0.6±0.8 mg/dL in group B. There was a statistically significant difference in CRP changes over time ($p<0.001$); however, there was no statistically significant difference between the two groups ($p=0.076$). The CRP level, but not the ESR, changed significantly over time within each group. However, no statistically significant difference was observed between the two groups, and there were no surgical site infections. Conclusion: The use of antibiotics for more than 1 day after DRF surgery is not very effective in reducing ESR and CRP or lowering the infection rate compared to the use of antibiotics for only 1 day.

Prophylactic regimens varied across studies in antibiotic selection, dosage, timing, dosing interval, and duration. The antibiotics used included cefazolin, cefuroxime, cefotaxime, and cefazedone. All were administered intravenously, generally 30–60 minutes before surgical incision, with prophylaxis continued for 24 hours to 3 days.

Table 2. Characteristics of prophylactic antibiotic regimens in patients with closed fractures

Author, (Year)	Prophylactic Antibiotic Regimen						Follow-up Period
	Antibiotic	Dose	Dosing Interval	Duration	Route of Administration	Timing of Administration	
Frank et al., (2019) [8]	Cefazolin	Weight-based, single dose	-	Single dose	Intravenous (IV)	1 h before incision	≥3 months
Jha et al., (2019) [9]	Cefuroxime	1.5 g	Every 12 h	3 doses	Intravenous (IV)	30 min before incision, repeated every 12 h	Post-operative days 2 and 14; weeks 6 and 12; 6 months; 1 year
Azeem & Patil, (2019) [10]	Cefotaxime	1 g	Every 12 h	3 days	Intravenous (IV)	12 h before surgery and 30 min before incision, followed by administration every 12 h for 3 days	-
Jokar, et al. (2022) [11]	Cefazolin	1 g	Every 6 h	24 h	Intravenous (IV)	1 h before incision, followed by administration every 6 h for 24 h	-
Kim & Kwack, (2022) [12]	Cefazedone	1 g	Every 12 h	24 h	Intravenous (IV)	Before incision, followed by administration every 12 h	Post-operative day 2 and week 1

DISCUSSION

Cephalosporins

Cephalosporins are β-lactam antibiotics classified into several generations, largely according to their antimicrobial spectrum. In general, later generations demonstrate greater activity against Gram-negative organisms, although their activity against Gram-positive organisms varies across generations (Figure 2). First-generation cephalosporins, including cefazolin, cephalexin, and cefadroxil, provide reliable activity against many Gram-positive organisms and are commonly used for perioperative prophylaxis to prevent surgical site infections. Their antimicrobial spectrum, relatively low cost, and favorable safety profile make them suitable agents for surgical prophylaxis. These antibiotics are also used in the management of skin and soft-tissue infections, methicillin-susceptible Staphylococcus aureus (MSSA) bloodstream infections, osteomyelitis, and endocarditis. When used for surgical prophylaxis, the duration of antibiotic administration should be carefully limited, as continuation beyond 24 hours is rarely justified. Prolonged prophylaxis has not

been shown to further reduce infection rates and may contribute to the development of antimicrobial resistance within healthcare settings.

Second-generation cephalosporins, including cefuroxime, cefoxitin, cefotetan, cefprozil, and cefaclor, generally provide broader Gram-negative coverage but somewhat reduced Gram-positive activity compared with first-generation agents. They are commonly used for respiratory tract infections and community-acquired pneumonia, while selected agents such as cefuroxime, cefoxitin, and cefotetan may also be used for surgical prophylaxis. Third-generation cephalosporins, including ceftriaxone, cefotaxime, ceftazidime, cefdinir, cefpodoxime, and cefixime, have greater activity against Gram-negative organisms than first- and second-generation cephalosporins. Most agents in this generation also provide good activity against streptococci but more limited activity against staphylococci. Their clinical indications include lower respiratory tract infections, pyelonephritis, meningitis, gonorrhea, skin and soft-tissue infections, and selected nosocomial infections. Ceftazidime additionally provides activity against Pseudomonas aeruginosa and may be used in nosocomial infections and febrile neutropenia.

Fourth-generation cephalosporins, particularly cefepime, have a broad antimicrobial spectrum encompassing both Gram-positive and Gram-negative organisms, including Pseudomonas aeruginosa. Cefepime is commonly used for severe infections such as febrile neutropenia, hospital-acquired pneumonia, post-neurosurgical meningitis, and other serious nosocomial infections. Ceftaroline, sometimes classified as a fifth-generation or anti-MRSA cephalosporin, is distinguished by its ability to bind penicillin-binding protein 2a, which confers activity against methicillin-resistant Staphylococcus aureus (MRSA). However, its Gram-negative activity is less extensive than that of cefepime and is more comparable to that of ceftriaxone. Ceftaroline may therefore be considered an alternative to agents such as vancomycin or daptomycin for selected MRSA infections.[13]

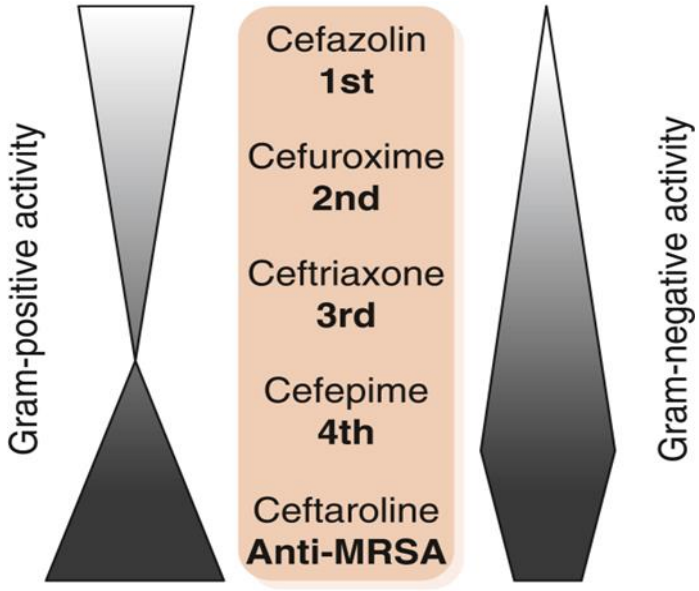


Figure 2. Cephalosporin activity by generation

Types, Doses, Timing, and Duration of Prophylactic Antibiotics

According to the Indonesian Ministry of Health Regulation No. 28 of 2021 on Guidelines for Antibiotic Use, prophylactic antibiotics are administered before, during, and after surgery to prevent infectious complications, particularly surgical site infections (SSIs). Their primary purpose is to prevent bacterial colonization and

proliferation in tissues exposed during surgery. Surgical antibiotic prophylaxis (SAP) is generally indicated for clean-contaminated procedures and selected clean procedures, particularly those involving prosthetic implants. The World Health Organization (WHO) similarly defines SAP as the administration of effective antimicrobial agents before exposure to potential intraoperative contamination. [14,15] However, SAP is intended to prevent intraoperative contamination and does not prevent SSIs caused by postoperative contamination.

The WHO does not recommend a specific antibiotic agent for surgical prophylaxis,[15] whereas Indonesian Ministry of Health Regulation No. 28 of 2021 recommends first-generation cephalosporins, particularly cefazolin. Among the five studies included in this review, first-generation cephalosporins were the most frequently used agents. Several studies used cefazolin [8,11], while others used cefazedone.[12] Another study used cefuroxime, a second-generation cephalosporin,[9] whereas another one used cefotaxime, a third-generation cephalosporin.[10] Antibiotic selection rationale varied across studies and was based on factors such as pharmacokinetic and pharmacodynamic properties, existing clinical guidelines, and previous surveys of commonly used prophylactic antibiotics.

The choice of antibiotic should generally be tailored to the surgical procedure, anatomical site, and expected microorganisms. First-generation cephalosporins remain the most commonly selected agents because of their effectiveness against organisms frequently associated with postoperative orthopedic infections. A study selected cefazolin based on recommendations for SSI prevention,[8] while other used cefazedone according to previously published SSI prevention guidance.[12] Another study also used cefazolin, although it did not explicitly describe the basis for its selection.[11] In contrast, a study used cefotaxime based on previous findings from India indicating frequent use of third-generation cephalosporins for perioperative prophylaxis.[10] One selected cefuroxime because of its favorable tissue and serum bioavailability after a single dose and its reported efficacy in preventing perioperative infection.[9]

Regarding dosage, Indonesian Ministry of Health Regulation No. 28 of 2021 recommends cefazolin 2 g for surgical prophylaxis. The Sanford Guide similarly recommends cefazolin 2 g for prophylaxis, with a usual therapeutic dose of 1–2 g every 8 hours.[15] In the included studies, cefazolin was administered at 1 g.[8,11,12] Another study administered cefuroxime 1.5 g,[9] which is consistent with the prophylactic dose reported in the Sanford Guide.[14] A study administered cefotaxime 1 g;[10] although this dose is within the usual therapeutic range, the Sanford Guide does not specifically recommend cefotaxime as a prophylactic antibiotic.[14]

SAP timing is an important determinant of its effectiveness in preventing SSI. Administration after surgical incision has been associated with a higher risk of SSI compared with administration before incision. Several professional guidelines recommend administration within 60 minutes before incision, while the WHO recommends administering SAP within 120 minutes before incision, considering the antibiotic half-life.[15] Agents with shorter half-lives may preferably be administered within 60 minutes before incision. Indonesian Ministry of Health Regulation No. 28 of 2021 recommends administration 30–60 minutes before incision to ensure adequate tissue concentrations at the time of surgery.

All five included studies initiated prophylactic antibiotics before surgical incision, although the exact timing varied. Several studies administered prophylaxis 1 hour before incision, [8,11] another study administered it 30 minutes before incision,[9] while others initiated prophylaxis 12 hours before surgery followed by another dose 30 minutes before incision,[10] and one

administered antibiotics before incision without specifying the exact timing.[12] Overall, most studies were broadly consistent with the WHO recommendation for pre-incisional administration, although timing varied.[15]

Regarding repeat dosing, WHO guidance refers to recommendations from the American Society of Health-System Pharmacists, which suggest intraoperative redosing when surgery exceeds approximately two antibiotic half-lives or when substantial blood loss occurs.[16] Indonesian Ministry of Health Regulation No. 28 of 2021 recommends single-dose prophylaxis, with repeat dosing considered when surgery exceeds 3 hours or when blood loss exceeds 1,500 mL. Prophylaxis should generally not exceed 24 hours from the initial dose.

The included studies showed considerable heterogeneity in dosing frequency and prophylaxis duration. A study used a single preoperative dose,[8] whereas others continued additional doses for 12–24 hours postoperatively at 6–12-hour intervals.[9,11,12] One reported the longest regimen, with postoperative antibiotic administration continued twice daily for up to 3 days.[10] These differences indicate that, despite international guidance, implementation of prophylactic antibiotic protocols remains variable across studies. Table 3 compares WHO recommendations with the regimens used in the included studies.

Table 3. Comparison between WHO recommendations and prophylactic antibiotic regimens reported in the included studies

Comparison Parameter	WHO Recommendation	Included Studies
Initial administration	Before surgical incision	Before incision [8-12]
Optimal timing of administration	Within 120 min before incision, considering the antibiotic half-life; antibiotics with a short half-life may be administered <60 min before incision	30 min before incision [9]; 1 h before incision [8,11]; 12 h before surgery and 30 min before incision [10]; before incision, exact timing not specified [12]
Antibiotic selection	No specific antibiotic is recommended	Cefazolin [8,11]; cefuroxime [9]; cefotaxime [10]]; cefazedone[12]
Dosing frequency and interval	Determined according to the antibiotic half-life, with intraoperative redosing when indicated during prolonged surgery	Single dose [8]; 3 doses at 12-h intervals [9]; every 12 h for up to 3 days [10]; every 6 h for up to 24 h[11]; 1 additional dose 12 h postoperatively [12]

Inappropriate use of prophylactic antibiotics may disrupt normal flora, promote antimicrobial resistance through selection pressure, and increase unnecessary healthcare costs. Therefore, adherence to evidence-based principles regarding antibiotic selection, dosage, timing, redosing, and duration is essential to maximize preventive benefit while minimizing antimicrobial-related harms.

CONCLUSION

Prophylactic antibiotics in patients with closed fractures were predominantly cephalosporins, particularly first-generation agents such as cefazolin and cefazedone, followed by cefuroxime and cefotaxime. All antibiotics were administered intravenously, generally 30–60 minutes before incision, with regimens ranging from a single dose to repeated administration for up to 3 days. Most studies limited prophylaxis to 24 hours or less.

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