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Review Article

Role of cefuroxime as antibiotic prophylaxis for general surgery: An expert opinion

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ABSTRACT

Surgical site infections (SSIs) are serious postoperative complications reported globally, which lead to perioperative antibiotics use during routine practice in surgical procedures. Selection of appropriate antibiotic/s for prophylaxis is a vital step in the management and care of invasive surgical procedures. This expert opinion review was developed based on expert discussion and literature search on scientific databases with special emphasis on cefuroxime in surgical prophylaxis for general surgeries. Cephalosporins are globally considered to be the drugs of choice for surgical prophylaxis in general surgeries owing to good safety, bactericidal activity, penetration to critical tissues, and proven efficacy in clinical trials. Cefuroxime, a 2nd generation cephalosporin, is an effective, safe and low-cost antibiotic for surgical prophylaxis in general surgeries, in particular for patients who need sequential antibiotic therapy. Cefuroxime can be administered alone or in combination with other classes of antibiotics based on clinical characteristics of individual patients and surgeon's discretion to reduce the risk of postoperative SSIs, abscess, septicemia, and microbial growth.

Key Messages: Cefuroxime can be administered alone or in combination with other classes of antibiotics based on clinical characteristics of individual patients and surgeon's discretion to reduce the risk of postoperative SSIs, abscess, septicemia, and microbial growth.

1. Introduction

A surgical site provides easy access to exogenous organisms increasing the risk of local or systemic infections and posing serious threat to patients' lives. Surgical site infections (SSIs) are serious postoperative complications that significantly impacts morbidity and mortality rate.[1] According to the type of surgical procedures, rates of SSIs vary from 2.5% to 41.9% globally.[2–4] Approximately 2% of general surgical procedures result in patients contracting SSIs.[4] The SSIs rate for surgeries on 'contaminated' or 'dirty' sites is up to 10%, which is higher than the surgeries on sterile/clean sites (<2%).[5]

Globally, more than one-third of postoperative mortalities are related to SSIs. In India the SSI-related postoperative mortality rate is approximately 5%.[6,7] Patients who develop SSIs are 60% more likely to spend

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more time in an intensive care unit and are 5 times more likely to be readmitted. The mortality rate in patients with SSIs is twice than that in non-infected patients.[1] Patients with SSIs have to bear additional treatment-related cost.[4]

Despite improvements in hospital practices, surgical instrument sterilization methods, surgical techniques and meticulous efforts in infection prevention strategies, SSIs still remain a major cause of hospital acquired infections (HAIs).[2] Therefore, use of perioperative antibiotics has become a routine practice in surgical procedures. Surgical antibiotic prophylaxis is defined as the administration of antibiotics prior to performing surgery to help minimize the risk of postoperative infections. Use of antimicrobial prophylaxis reduces the incidence of SSIs post-surgery; thus reduces morbidity, length of hospitalization, post-surgical antibiotic usage, and mortality due to sepsis.[8] Commonly recommended class of antibiotics for prophylaxis in general surgeries are penicillin, fluoroquinolone, aminoglycoside and cephalosporins.[9] However, benefits of the prophylactic use of antibiotics for surgical procedures must be assessed in the light of risk for toxicity, allergic drug reactions, adverse drug interactions, emergence of drug-resistant bacteria, and super infections.[9] Selection of appropriate antibiotics for surgical prophylaxis is therefore vital for the prevention of SSIs. The goal when determining the appropriate antibiotic is to achieve a relatively narrow spectrum of activity while ensuring that most common organisms that cause SSIs are effectively targeted.[10] Major factors influencing the selection of antibiotic are: bactericidal activity, safety, ease of administration, pharmacokinetic profile, hospital antibiotic resistance patterns, and cost.[10]

Cephalosporins are globally considered to be the drugs of choice for surgical prophylaxis owing to good safety, potent antibacterial activity against the organisms that cause postoperative infection, penetration to critical / deeper tissues, and proven efficacy in clinical trials.[11,12] There are 3 generations of cephalosporins available for surgical prophylaxis. However, the bactericidal activity against bacteria causing SSIs, the availability as step-down antibiotic for specific cases, and the ability to cross the blood−brain barrier vary among individual agents across the cephalosporin classes. Therefore, it is clinically important for physicians to select the appropriate cephalosporin antibiotic among the multiple variants currently available.[8] Since the introduction of 3rd generation cephalosporins in the mid-1980s, they have been more commonly used for surgical prophylaxis.[13] However, caution must be exercised in selecting an extended-spectrum antibiotic due to the risk of antibiotic resistance.

2. Materials and Methods

In the quest of widening therapy knowledge of cephalosporins in surgical prophylaxis for general surgeries, with special emphasis on cefuroxime, an expert discussion was sought. This work was supported by Alkem Laboratories Ltd, India. The views expressed in this article are solely for an educational purpose and constitute the views of the authors exclusively. Medical practitioners are advised to make decisions based on their own clinical acumen.

The panel comprised of 10 surgeons each having a minimum experience of 15 years in the field of surgery. This article was formulated based on the experts' discussions held on July 14, 2018; September 08, 2018; and November 17, 2018 at Pune, Hyderabad and Kolkata; and a review of the available evidence in the scientific literature. A literature search was performed on scientific databases such as PubMed, Google scholar, etc. Randomized clinical trials, narrative reviews, meta-analysis, retrospective and prospective studies were included in the literature search. Literature available in the English language was included. Experts reviewed the contents of the literature search and shared their suggestions, following which a manuscript draft was finalized. Table 1 summarizes the literature search strategy used in this article.

3. General Recommendations

3.1. Overall incidence in India

The SSIs rate has been reported to range from 1.7% to 8.3% in India in a study by International Nosocomial Infection Control Consortium (INICC).[14] A study by Subramanian et al. at the All India Institute of Medical Sciences estimated SSIs rate of 24.8%.[15,16] A similar study by Ganguly et al. in Aligarh reported an SSI rate of 38.8%.[15,17] According to a prospective, multicenter cohort study, approximately 14% and 23% of patients undergoing gastrointestinal surgery in the middle and low Human Development Index (HDI) countries had SSIs after surgery, respectively.[18] In India, urological surgeries have approximately a 5% chance of developing SSIs post-surgery.[1] In a systematic review of SSIs in low and middle Human Development Index countries including India for inguinal hernia repair surgeries, SSIs was estimated to be 4.1% in cases of open hernia repairs and 0.4% in laparoscopic hernia repairs.[19] Moreover, factors such as diabetes mellitus, prolonged preoperative hospital stay, American Society of Anesthesiologists (ASA) score >3, emergency surgery, prolonged duration of surgery (more than 75th percentile of National Nosocomial Infection Surveillance NNIS duration cut point), and contaminated and dirty surgical sites were found to be associated with a higher rate of SSI.[20] The incidence of SSIs is higher in rural populations compared to urban populations.[21]

3.2. Common organisms causing SSIs

Among the pathogens causing SSIs, Staphylococcus aureus is a commonly cultured organism. Further, the

Table 1: Literature search strategy

Database for search		Results	Remarks
PubMed, Google scholar and Google search	Cefuroxime in surgical antibiotic prophylaxis, cephalosporin in surgical antibiotic prophylaxis, surgical site infection and cefuroxime, cefuroxime in gastrointestinal surgeries, cefuroxime in abdominal surgeries, cefuroxime in surgical prophylaxis of urological surgeries, second generation cephalosporins in surgical site infection	Randomized controlled trials, prospective and retrospective studies, guidelines, narrative reviews, systematic reviews and meta-analysis	Literature in English language related to clinical studies including cefuroxime as surgical antibiotic prophylaxis only are included in this article

incidence of methicillin-resistant S. aureus is rising globally.[22–24] Other organisms causing SSIs include gram-negative bacilli, coagulase-negative staphylococci, Enterococcus spp., and Escherichia coli.[22,25] Similarly in India, S. aureus is the most common organism isolated from SSIs followed by E. coli. The pattern of other organisms causing SSIs in India was also similar to that reported globally.[26,27]

3.3. Time and dosage of antibiotic prophylaxis

Postoperative administration of prophylactic antibiotic is usually unnecessary and is harmful. If prophylaxis is continued for more than 24 hours, the risk of emergence of drug resistant bacteria increases. Therefore, a single-dose prophylaxis administered directly after the induction of anesthesia is sufficient to achieve therapeutic drug levels at the time of maximal endogenous or exogenous contamination risk, but not sufficient to allow selection of bacteria resistant to the drug.[28] Prophylactic antibiotics are in general not recommended for clean surgeries except in the following: 1) prolonged surgical procedures with a high risk of infection; 2) surgeries involving vital organs: heart, lungs, brain; 3) surgeries with foreign body implantation; 4) surgeries in patients with high risk of infection chances: diabetes, malnutrition, immune dysfunction.[29] An expert panel in India recommends administration of the first dose of antimicrobial agent approximately 60 minutes before surgical incision. The administration of fluoroquinolones and vancomycin should begin 120 minutes before surgical incision because of the prolonged infusion times required for these drugs. Cefuroxime is given 30 minutes to 60 minutes before surgery via the intravenous (i.v.) route, which can be followed by oral cefuroxime being administered postoperatively according to patient's conditions. The recommended dose is 1.5 g cefuroxime i.v. before surgery.[30] If surgery is delayed or prolonged, a second dose of an antimicrobial drug with a shorter half-life is required. Therefore, a long-acting antimicrobial agent with good protein binding is preferred.[28]

Table 2: Expert opinion on general aspects

1. SSIs are a predominant contributor to HAIs in India. There is an urgent need for optimal surgical antimicrobial prophylaxis to reduce SSIs in hospitals where general surgeries are practiced in India.
2. The most common organisms causing SSIs are Staphylococcus aureus, followed by Enterococcus spp., Escherichia coli, and Proteus spp
3. Injectable antibiotics used for prophylaxis are to be given 30 minutes to 60 minutes before surgery and prophylactic management may extend to postoperative day 1 or day 2, and in certain cases of high risk, patients may be discharged with prescription for oral antibiotics
4. Selection of antibiotics depends on various factors, such as type of surgery − clean or contaminated; risk of contamination during the surgery by instrumentation; bowel preparation; spillage in the peritoneal cavity during the surgery; and patients' characteristics − old age, smoking, immune compromised states, obesity, and uncontrolled diabetes. These factors also affect the overall outcomes of surgeries and post-surgical infections.
5. Clean surgeries either require no antibiotics or only single-dose preoperatively, while contaminated surgeries, such as gall bladder surgery, require antibiotic prophylaxis preoperatively and postoperatively extended for 5 days.

4. Introduction of Cefuroxime

Cefuroxime is a 2nd generation cephalosporin with high ß-lactamase stability.[31] It is effective in the management of infections caused by ß-lactamase-producing strains of Haemophilus influenzae, Branhamell catarrhalis, and S. aureus. It also shows activity against the common urinary tract pathogen Escherichia coli, with mean minimum inhibitory concentration for 90% of strains (MIC_{90}) values of 4 mg/L and 8 mg/L.[32] It has an average oral bioavailability of 67.9%. Cefuroxime is detectable in therapeutic concentrations in plasma (66.8±18.9 mcg/mL), muscle (60.1±15.2 mcg/mL), and in adipose tissue (39.2±26.4 mcg/mL).[33] It distributes into interstitial fluid of subcutaneous tissue of morbidly obese patients undergoing abdominal surgery.

Table 3: Clinical studies evaluating cefuroxime effect on SSIs

Author	Study design and duration	Treatment arms	Results and conclusion
Gastrointestinal surgery			
Hares MM et al. 1981[34]	Prospective randomized controlled trial in patients undergoing gastric surgery; 2 weeks	Cefuroxime 1.5 g i.v. before surgery, N=27; Cefuroxime 1.5 g intra-incisional after surgery, N=26; or Control, N=28	Cefuroxime 1.5 g iv: wound sepsis: 2(7%); abscess: 0(0%); septicemia: 0(0%) Intra-incisional cefuroxime 1.5 g: wound sepsis: 1(4%); abscess: 5(19%); septicemia: 1(4%) Control: wound sepsis: 10(35%); abscess: 8(29%); septicemia: 6(21%)Systemic Cefuroxime was superior (p<0.05) to intra-incisional administration.
Mitchell NJ et al. 1980[35]	Randomized trial in patients undergoing elective gastrointestinal surgery; 2 weeks	Cefuroxime 1.5 g i.v., N=52; Cefuroxime 1.5 g + metronidazole 0.5 g i.v., N=48; or Control, N=56	Cefuroxime 1.5 g i.v.: sepsis: 5(9.6%) Cefuroxime 1.5 g + metronidazole 0.5 g i.v.: sepsis: 3(6.7%) Control: sepsis: 18(32.2%) Cefuroxime showed good efficacy when used alone or in combination with metronidazole to prevent SSIs in patients compared to control group (p<0.001).
Croton RS et al. 1981[36]	Randomized trial in patients undergoing biliary surgery; 5 days	Cefuroxime 750 mg intramuscular (i.m.) premedication and 8 hourly for 3 days, N=35; Cefuroxime 1.5 g i.v.,N=40; or Control, N=39	Cefuroxime 750 mg i.m.: wound infection: 3(9%) Cefuroxime 1.5 g i.v.: wound infection: 1 (2%) Control: wound infection: 11(28%) Cefuroxime showed higher efficacy via i.v. route compared to the i.m. route in patients. Significant reduction (p<0.05) in wound infection post-surgery was seen in patients with prophylactic cefuroxime i.v. compared to those in control group.
Agrawal CS et al. 1999[37]	Prospective, randomized double-blind study in patients undergoing elective cholecystectomy; 14 days	Cefuroxime 700 mg i.v. before surgery, N=45; or Control, N=30; or Ciprofloxacin 200 mg i.v. before surgery, N=45; or Ciprofloxacin 200 mg i.v after surgery, N=35	Cefuroxime 700 mg i.v.: wound infection: 3 Control: wound infection: 8 Ciprofloxacin i.v. before surgery: wound infection: 2Ciprofloxacin after surgery: wound infection: 9 Cefuroxime i.v. was more effective in preventing wound infections compared to ciprofloxacin i.v.
Meijer WS et al. 1993[38]	Randomized controlled double-blind multi-center trial in patients undergoing biliary tract surgery; 6 weeks	Cefuroxime 1.5 g i.v. one dose regimen before surgery, N=501; or Cefuroxime i.v. three dose regimen (1.5 g before and two doses of 0.75 g after surgery), N=503	Cefuroxime 1.5 g i.v. one dose regimen: wound infections: 6.6% minor wounds; 4.6% major wound Cefuroxime 1.5 g i.v. three dose regimen: wound infection: 6.2% minor wounds; 3.8% major wounds No significant difference was found between the two groups: p=0.78 for minor wounds; p=0.52 for major wounds. One dose of cefuroxime is as effective as a three-dose regimen in preventing major wound infection after biliary tract operation. The estimated difference in the major wound infection rate between the two groups was 0.8% (95%CI: -1.7 to 3.3%).
Abdominal surgery			

Continued on next page

Table 3 continued

Barbour A et al. 2009[39]	A single centre, prospective, open-label study in patients undergoing abdominal surgeries; 6 hours post dosing	Cefuroxime 1.5 g i.v. within 1 hour of incision	Total peak concentration in plasma C_{max}: 66.8±18.9 μg/mL Free level in the interstitial space fluid (ISF) of muscle C_{max}: 60.1±15.2 μg/mL Free level in subcutaneous (s.c.) adipose tissue C_{max} : 39.2±26.4 μg/mL Mean area under the free concentration–time curve ratios: muscle/total plasma:1.0±0.2; s.c. adipose tissue/total plasma: 0.6±0.5 Cefuroxime distributes into the ISF of muscle and s.c. adipose tissue and concentrations in the ISF of soft tissues following a single 1.5 g dose may be high enough to prevent SSI.
Brummer THI et al. 2013[40]	Observational non-randomized 1-year prospective study in women undergoing hysterectomy; 6 hours post surgery	Combination of cefuroxime and metronidazole, N=532; or Cefuroxime, N=405; or metronidazole, N=178	Risk reduction in total infection with cefuroxime alone: OR, 0.29; 95% CI, 0.22–0.39 Total infections in abdominal hysterectomy: Cefuroxime + metronidazole: 31(5.8%); cefuroxime: 28 (6.9%); metronidazole: 27 (15.2%) Total infections in laparoscopic hysterectomy: Cefuroxime + metronidazole: 50 (6.2%); cefuroxime: 37 (5.7%); metronidazole: 13 (14.4%) Total infections in vaginal hysterectomy: Cefuroxime + metronidazole: 35 (3.8%); cefuroxime: 38 (3.9%); metronidazole: 31 (12.4%) Metronidazole appeared to be ineffective, with no additional risk-reductive effect when combined with cefuroxime. Cefuroxime had higher efficacy to prevent SSI compared to metronidazole.
Petignat C et al. 2008[41]	Double-blind, placebo-controlled randomized trial in patients undergoing herniated disc surgery; 6 weeks	Cefuroxime 1.5 g, N=613; or placebo, N=623	Cefuroxime: relative risk of SSI, 0.45, 95%CI, 0.20–1.03,p=0.07; SSI: 8(1.3%)Placebo: 18(2.9%) Cefuroxime significantly reduces the risk of SSI, notably spondylodiscitis, after surgery for herniated disc.
Zhuo Y et al. 2016[42]	Retrospective observational study in patient undergoin elective inguinal hernia repair with mesh; 30 days	Cefuroxime 1.5 g, N=33; or Placebo, N=222	Cefuroxime: SSI: 10 (2.8%), p=0.001 vs. placebo Placebo: 22(9.4%) Treatment with cefuroxime was effective for preventing SSI in patients undergoing hernia repair with mesh.
Girish P et al. 2019[43]	Randomized control study in patient undergoing open prolene-mesh hernioplast; 3 months	Cefuroxime 1.5 g i.v. 30 min before incision and 1.5 g i.v. TDS for 2 days followed by 500 mg tab BD for 5 days, N=50; or Amoxicillin + clavulanate 1.2 g i.v., N=50	Cefuroxime 1.5 g i.v.: wound infection: 4% Amoxicillin + clavulanate 1.2 g i.v.: wound infection: 6% Cefuroxime alone was more effective in preventing wound infections compared to a combination of amoxicillin + clavulanate.

Continued on next page

Table 3 continued

Urological surgery			
Qiang W et al. 2005[44]	Systematic review 28 trials, 10 placebo controlled and 18 no treatment controlled trials for antibiotic prophylaxis in men undergoing transurethral resection of the prostate (TURP)	Antibiotic prophylaxis; or placebo	Prophylaxis antibiotic treatment: Reduction in incidence of bacteriuria, -0.17 (95% CI 0.20, -0.15); high fever, -0.11 (95%CI -0.15, -0.06), bacteremia, -0.02 (95%CI -0.04, 0.00) and additional antibiotic treatment, -0.20 (95%CI -0.28, -0.11) Better clinical outcome was achieved with antibiotic prophylaxis in patients undergoing surgery.
Seyrek et al 2012[45]	Randomized trial in patients undergoing nephrolithotomy	Sulbactam-ampicillin, N=95; or Cefuroxime, N=96	Sulbactam-ampicillin: systemic inflammatory response syndrome (SIRS), 13 (43.3%) Cefuroxime: systemic inflammatory response syndrome (SIRS), 17 (56.7%), p=0.44 Cefuroxime was equally safe and efficacious as sulbactam-ampicillin to prevent SIRS in patients.
Wikdahl AM et al. 1997[46]	Prospective, randomized, study in patients commencing peritoneal dialysis; 10 days	Cefuroxime 1.5 g, N=18; or Placebo: N=20	Cefuroxime: microbial growth in dialysis fluid, 0 (0%) Placebo: microbial growth in dialysis fluid, 6(30%), p=0.021 vs. cefuroxime Cefuroxime was effective in preventing microbial growth in dialysis fluid of patients.

The half-life of cefuroxime is 1.5 hour for patients with normal renal function and 4.9 hours in patients with renal impairment.[32] The overall equilibrium distribution volume is approximately 0.22 L/kg and is not affected by renal insufficiency. Therefore, cefuroxime does not need dose adjustment in patients with renal insufficiency, although caution should be exercised in patients with severe uremia.[35]

4.1. Clinical evidence supporting the use of cefuroxime as surgical prophylactic agent for general surgeries

Even with the advent of advanced surgical procedures, SSIs remain a major postoperative complication. In this article, the evidence supporting use of cefuroxime is restricted to general surgery and limited to gastrointestinal, abdominal and urological surgeries (Table 3).

4.2. Gastrointestinal surgery

A randomized study evaluating antibiotic effect of cefuroxime in 150 patients undergoing elective gastrointestinal surgery showed that a single preoperative dose of cefuroxime without addition of metronidazole can significantly reduce wound sepsis after surgeries involving the upper gastrointestinal tract.[35] However, the microbiological flora in the large bowel is predominantly anaerobic and in recto-colonic surgery metronidazole is undeniably more effective compared to cefuroxime.[35] In line with the above study, a prospective randomized controlled trial (RCT) in patients undergoing gastric surgery compared single- dose systemic cefuroxime or intra-incisional cefuroxime versus a control group. In this study, approximately 7% of the patients who received systemic cefuroxime developed wound sepsis with no cases of abscess or septicemia compared to those with intra-incisional cefuroxime (4% wound sepsis, 19% abscess and 4% septicemia) and control (35% wound sepsis, 29% abscess and 21% septicemia).[34]

Another randomized study demonstrated that administration of 1.5 g cefuroxime i.v. was effective in reducing wound sepsis following biliary surgery.[36] Further, a randomized, controlled, double-blind multicenter trial compared the prophylactic effect of a two-dose regimen of cefuroxime in patients undergoing biliary surgery who had a high risk of infection. No significant difference was found between one- and three-dose cefuroxime regimens in preventing postoperative wound infection. Overall, data showed that one dose of short-acting agent preoperatively is as effective as a three-dose regimen to prevent major wound infections after biliary surgery.[38]

A prospective, randomized, double-blind study was undertaken to compare the prophylactic efficacy of ciprofloxacin and cefuroxime in 155 patients undergoing elective cholecystectomy. In this study, patients were randomly assigned to prophylactic cefuroxime, no antibiotic, prophylactic ciprofloxacin, or postoperative ciprofloxacin. Patients who received ciprofloxacin or cefuroxime as prophylaxis had significantly reduced incidence of SSIs (4.44% and 6.67%, respectively, $p<0.005$ vs. 26.7% in the group who received no antibiotic) with no statistically significant difference found between ciprofloxacin vs. cefuroxime.[37] However, as expected, authors of this study advise caution on using antibiotics due to risk of antibiotic resistance.[37]

4.3. Abdominal surgery

In a double-blind, placebo-controlled, RCT, the efficacy of a pre-operative single dose of cefuroxime (1.5 g) was assessed in 1234 patients for the prevention of SSIs after surgery for herniated disc over a 6-month period. Eight (1.3%) patients in the cefuroxime group and 18 patients (2.8%) in the placebo group developed SSIs ($p=0.073$). A diagnosis of spondylodiscitis or epidural abscess was made in 9 patients in the placebo group, but none in the cefuroxime group ($p<0.01$). There were no significant adverse events attributed to either cefuroxime or placebo.[41] Thus, a single preoperative dose of cefuroxime significantly reduced the risk of organ-space infection, most notably spondylodiscitis, after surgery for herniated disc. These results are consistent with a small pilot study of patients undergoing abdominal surgeries which showed that cefuroxime administered at 1.5 g yields a concentration in the interstitial space fluid (ISF) of soft tissues that is sufficient for prevention of infections against gram-positive organisms.[39] However, high frequency of dosing is required for preventing infections with gram-negative organisms.[39]

An observational, non-randomized 1-year prospective cohort study reported efficacy of cefuroxime for prophylaxis in patients undergoing hysterectomy (abdominal/vaginal/laparoscopic hysterectomies).[40] Further, a retrospective observational study conducted in China in patients (n=605) undergoing elective inguinal hernia repair with mesh showed that SSI rates were significantly lower in patients receiving a single i.v. injection of cefuroxime (1.5 g) within 2 hours prior to surgery versus those without preoperative antibiotic prophylaxis (2.8% vs. 9.4%; $p<0.001$).[42]

In a retrospective study in India, women (n=60) who underwent hysterectomy (abdominal/vaginal/laparoscopic hysterectomies), a clean-contaminated surgery, cefuroxime was found to be more effective for prophylaxis against SSIs compared to metronidazole.[47] Efficacy of cefuroxime to prevent wound infections was also compared with amoxicillin + clavulanate. An RCT compared the clinical efficacy of cefuroxime versus amoxicillin + clavulanate for prevention of wound infections in patients undergoing open prolene−rolenhernioplasty for inguinal hernia.[43] Patients received cefuroxime i.v. or amoxicillin + clavulanate i.v. prior to surgery, and continued for 2 days, followed by oral tablets for 5 days post-surgery. There was nonsignificant difference in overall wound infection rates between cefuroxime (4%) and amoxicillin + clavulanate group (6%), and side-effects in the cefuroxime group were less (4%). Therefore, cefuroxime was reported to be safe and effective for use as surgical prophylaxis in patients undergoing clean elective operations, such as open inguinal prolene mesh hernioplasty.[43]

4.4. Urological surgery

Prophylactic antibacterial therapy is recommended for urethral catheterization, endoscopy of the urinary tract, prostate biopsy, transurethral surgery, and selected open urologic procedures.[48] Most often, broad-spectrum cephalosporins and penicillins are used in these surgeries.[48] A systematic review including 28 trials comprising 4694 patients showed that prophylactic antibiotics significantly reduced the incidence of bacteriuria post-transurethral resection of prostate (RR: -0.17 [95% CI -0.20, -0.15]), high fever (-0.11 [-0.15, -0.06]), bacteremia (-0.02 [-0.04, 0.00]) and additional antibiotic treatment (-0.20 [-0.28, -0.11]).[44]

A RCT compared sulbactam-ampicillin and cefuroxime for prophylaxis of percutaneous nephrolithotomy and assessing optimal regimen for antibiotic maintenance to prevent systemic inflammatory response syndrome (SIRS).[45] Incidence of SIRS was similar in sulbactum-ampicillin and cefuroxime groups (43.3% vs. 56.7%; p=0.44).[45] Further, a prospective randomized study in patients starting peritoneal dialysis showed no microbial growth in dialysis fluid during the postoperative period in patients who received prophylactic treatment of 1.5 g i.v. pre- and 250 mg i.p. perioperative cefuroxime compared to the control (no prophylactic antibiotic) group (30%, p=0.021).[46] In addition, the results suggest that cefuroxime prophylaxis may reduce the risk of microbial growth and peritonitis after insertion of Tenchkhoff catheter.[46]

4.5. Sequential therapy

Sequential therapy or de-escalation therapy is antibacterial treatment which is initiated as i.v. therapy (~2 to 3 days) and subsequently changed to oral therapy (~5 to 10 days).[31,50] A large multicenter study has investigated the efficacy of sequential therapy using cefuroxime. A retrospective single-center, cost-analysis study showed that intravenous cefuroxime/oral cefuroxime axetil sequential therapy was less expensive compared to a full parenteral course of cefuroxime.[51] Sequential regimen with i.v. cefuroxime followed by oral cefuroxime axetil is effective and well tolerated as switch therapy and has the potential to reduce overall healthcare costs and improve patient satisfaction.[31,50]

Table 4: Key box 2: Expert opinion on antibiotic selection

1.	Among the antibiotics indicated for prophylaxis use in surgeries, cephalosporins are a preferred choice. However, preference for which generation of cephalosporin is used varies among practicing surgeons.
2.	Cefuroxime is given preoperatively as a prophylactic antibiotic in surgery units for minimal access/laparoscopic surgeries at a standard dose of 1.5 g.[49]
3.	Cefuroxime, a 2nd generation cephalosporin, is widely used for surgical prophylaxis in general surgeries as it is active against gram-positive and gram-negative bacteria and is the most stable ß-lactum antibiotic with an acceptable pharmacokinetic profile.
4.	Cefuroxime in 1.5 g dose is indicated for open surgeries specific to bowel surgery.
5.	Experts opined that prophylaxis with systemic cefuroxime is more effective compared to intra-incisional or oral cefuroxime. However, for prolonged surgeries intra-operative re-dosing of cefuroxime can provide better results for preventing postoperative infections.
6.	For the cases of upper gastrointestinal surgeries, antibiotic prophylaxis with cefuroxime is effective. In addition, in cases of transrectal core biopsy, cefuroxime is equally as effective as piperacillin/tazobactum
7.	In hernia repair surgery, cefuroxime appears to be an effective prophylactic antibiotic compared to the fixed-dose combination of amoxicillin and clavulanate.
8.	For the elective transuretheral resection and extracorporeal shock wave lithotripsy (ESWL) in patients with sterile urine prior to surgery, evidence shows that antibiotic prophylaxis is not indicated. However, it was reported in a systematic review that prophylaxis antibiotics significantly reduce the incidence of infection post-transurethral resection of prostate.[46]
9.	Experts also opined that for percutaneous nephrolithotomy, cefuroxime in a single-dose prophylaxis could be enough to prevent SSI with similar efficacy as that of sulbactam-ampicillin
10.	Cefuroxime with quinolones is the preferred alternative of amoxyclav (amoxicillin + clavulanic acid) in uncomplicated gall bladder surgeries.
11.	Combination of cephalosporins/penicillin group with β-lactamase inhibitor can be used against resistant organisms.
12.	Cefuroxime is the only cephalosporin available for long duration sequential prophylaxis in patients with fewer complications.

Table 5: Recommendations of cephalosporin for antibiotic prophylaxis in gastrointestinal surgery

Type of gastrointestinal surgery		Recommended cephalosporin
The American Society of Health System Pharmacist[52]		
Gastroduodenal	Bariatric, pancreaticoduodenectomy	AOC: Cefazolin AA: Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
	Antireflux, highly selective vagotomy for high-risk patients	AOC: Cefazolin AA: Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract	Open surgical procedure	AOC: Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin–sulbactam AA: Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone; metronidazole + aminoglycoside or fluoroquinolone
Laparoscopic procedure	Elective, high-risk surgical procedure	AOC: Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin–sulbactam AA: Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone; metronidazole + aminoglycoside or fluoroquinolone
	Colorectal surgery	AOC: Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin–sulbactam, ceftriaxone + metronidazole, ertapenem AA: Clindamycin + aminoglycoside or aztreonam or fluoroquinolone, metronidazole + aminoglycoside or fluoroquinolone
Essential Medicine Lists Guidance on surgical antibiotic prophylaxis[53]		
Upper gastrointestinal tract surgery		Cefazolin (or cefuroxime)
Colorectal surgery		Cefazolin (or cefuroxime) and metronidazole
Standard Treatment Guidelines and Essential Medicines List for South Africa[54]		
Upper gastrointestinal tract surgery		Cefazolin
Biliary surgery		Cefazolin and metronidazole
Colorectal and appendix surgery		Cefazolin and metronidazole

AOC: antimicrobial of choice; AA: alternative antimicrobial

Table 6: Recommendations of cephalosporin for antibiotic prophylaxis in intra-abdominal surgery

Type of surgery		Recommended cephalosporin
The American Society of Health System Pharmacist (ASHP guideline)[52]		
Vaginal or abdominal appendix	Hysterectomy	AOC: Cefazolin, cefotetan, cefoxitin, ampicillin–sulbactam AA: Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone; metronidazole + aminoglycoside or fluoroquinolone
	Appendectomy for uncomplicated appendicitis	AOC: Cefoxitin, cefotetan, cefazolin + metronidazole AA: Clindamycin + aminoglycoside or aztreonam or fluoroquinolone; metronidazole + aminoglycoside or fluoroquinolone
Small intestine	Small intestine, non-obstructed	AOC: Cefazolin AA: Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
Hernia repair	Hernioplasty and herniorrhaphy	AOC: Cefazolin AA: Clindamycin, vancomycin
The Surgical Infection Society Revised Guidelines on the management of intra-abdominal infection[55]		
Colorectal surgery	Low-risk patients	Cefuroxime, cefotaxime, ceftriaxone, cefoperazone–sulbactam
	High-risk patients	Ceftazidime, cefepime, ceftolozane-tazobactam, ceftazidime-avibactam
Essential Medicine Lists Guidance on surgical antibiotic prophylaxis[53]		
Hepato-pancreato-biliary surgery + cholecystectomy		Cefazolin (or cefuroxime)
Hernia surgery		Cefazolin (or cefuroxime)
Appendectomy		Cefazolin (or cefuroxime) and metronidazole

AA: alternative antimicrobial; AOC: antimicrobial of choice

Table 7: Recommendations of cephalosporin for antibiotic prophylaxis in urologic surgery

Type of surgery		Recommended cephalosporin
The American Society of Health System Pharmacist (ASHP guideline)[52]		
Lower tract instrumentation with risk factors for infection	Transrectal prostate biopsy	AOC: Fluoroquinolone, trimethoprim–sulfamethoxazole (TMP-SMX), cefazolin AA: Aminoglycoside with or without clindamycin
Urologic surgery	Clean without entry into urinary tract	AOC: Cefazolin (the addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [e.g., penile prosthesis]) AA: Clindamycin, vancomycin
Urologic surgery	Involving implanted prosthesis	AOC: Cefazolin ± aminoglycoside, cefazolin ± aztreonam, ampicillin–sulbactam AA: Clindamycin ± aminoglycoside or aztreonam, vancomycin ± aminoglycoside or aztreonam
Urologic surgery	Clean with entry into urinary tract	AOC: Cefazolin (addition of a single dose of an aminoglycoside may be recommended for placement of prosthetic material [e.g., penile prosthesis]) AA: Fluoroquinolone, aminoglycoside with or without clindamycin
Urologic surgery	Clean-contaminated	AOC: Cefazolin + metronidazole, cefoxitin AA: Fluoroquinolone, aminoglycoside + metronidazole or clindamycin
American Urological Association[56]		
Lower urinary tract instrumentation	Removal of external urinary catheter	AOC: Fluoroquinolone, TMP-SMX (trimethoprim-sulfamethoxazole) AA: Aminoglycoside (aztreonam) ± ampicillin, 1st/2nd generation cephalosporin, amoxacillin/clavulanate Duration of therapy: ≤24 hour
	Cystography, urodynamic study, or simple cystourethroscopy or with manipulation	AOC: Fluoroquinolone, TMP-SMX AA: Aminoglycoside (aztreonam) ± ampicillin, 1st/2nd generation cephalosporin, amoxacillin/clavulanate Duration of therapy: ≤24 hour
	Prostate brachytherapy or cryotherapy	AOC: 1st generation cephalosporin AA: Clindamycin Duration of therapy: ≤24 hour
	Transrectal prostate biopsy	AOC: Fluoroquinolone, 1st/2nd/3rd generation cephalosporin AA: TMP-SMX, aminoglycoside (aztreonam) Duration of therapy: ≤24 hour
Upper urinary tract instrumentation	Shock-wave lithotripsy	AOC: Fluoroquinolone, TMP-SMX AA: Aminoglycoside (aztreonam) ± ampicillin, 1st/2nd generation cephalosporin, amoxacillin/clavulanate Duration of therapy: ≤24 hour
	Percutaneous renal surgery	AOC: 1st/2nd generation cephalosporin, aminoglycoside (aztreonam) + metronidazole or clindamycin AA: Ampicillin/sulbactam, fluoroquinolone Duration of therapy: ≤24 hour
	Ureteroscopy	AOC: Fluoroquinolone, TMP-SMX AA: Aminoglycoside (aztreonam) ± ampicillin, 1st/2nd generation cephalosporin, amoxacillin/clavulanate Duration of therapy: ≤24 hour

Continued on next page

Table 7 continued

	Vaginal surgery (includes urethral sling procedures)	AOC: 1st/2nd generation cephalosporin, aminoglycoside (aztreonam) + metronidazole or clindamycin AA: Ampicillin/sulbactam, fluoroquinolone Duration of therapy: ≤24 hour
Open or laparoscopic surgery	Without entering urinary tract	AOC: 1st generation cephalosporin AA: Clindamycin Duration of therapy: single dose
	Involving entry into urinary tract	AOC: 1st/2nd generation cephalosporin, aminoglycoside (aztreonam) + metronidazole or clindamycin AA: Ampicillin/sulbactam, fluoroquinolone Duration of therapy: ≤24 hour
	Involving intestine	AOC: 2nd/3rd generation cephalosporin, aminoglycoside (aztreonam) + metronidazole or clindamycin AA: Ampicillin/sulbactam, ticarcillin/clavulanate, pipercillin/tazobactam, fluoroquinolone Duration of therapy: ≤24 hour
	Involving implanted prosthesis	AOC: Aminoglycoside (aztreonam) + 1st/2nd generation cephalosporin or vancomycin AA: Ampicillin/sulbactam, ticarcillin/clavulanate, pipercillin/tazobactam Duration of therapy: ≤24 hour
Essential Medicine Lists Guidance on surgical antibiotic prophylaxis[53]		
Prostate surgery	Laparoscopic procedure	Cefazolin (or cefuroxime)
Nephrectomy	Laparotomy nephrectomy and partial nephrectomy	Cefazolin (or cefuroxime)
Standard Treatment Guidelines and Essential Medicines List for South Africa[54]		
Nephro-urological surgery	Nephro-urological procedure	Cefazolin

AA: alternative antimicrobial; AOC: antimicrobial of choice; ASHP: American Society of Health System Pharmacist; TMP-SMX: trimethoprim-sulfamethoxazole

4.6. Indian evidence

In a recent study by Sharma AP et al. 2019, single-dose intravenous cefuroxime was administered to patients undergoing clean and clean-contaminated elective major urological surgeries.[58] This study showed that a protocol involving single-dose i.v. cefuroxime was effective in 89.5% (248/277) of patients.[58] The failure rate (41.7%) (Defined as patients with postoperative complications) was higher for the contaminated procedures (OR –6.43; 95% CI 1.51–27.2; p<0.001). Postoperative sepsis with or without shock (16/29, 55.2%) was the most common cause of protocol failure. Fourteen out of the 16 patients who developed sepsis had undergone endourological surgeries. It was suggested that perioperative prophylaxis with cefuroxime is effective for urological surgeries. Similar protocols should be developed and validated at major healthcare centers which can limit the unnecessary use of antibiotics and prevent the emergence of antibiotic resistance.[58] The study concluded that 2^{nd} generation cephalosporins, as cefuroxime, could be a safe and effective choice to prevent SSIs in India.[58] Moreover, data from other studies in India show that cephalosporins, mainly the 2nd and 3rd generation, are commonly used as prophylaxis for general surgeries.[49,59,60]

5. Place of Cephalosporin in Clinical Practice Guidelines

Low incidence of side-effects and better clinical outcomes of cephalosporin make them widely used antibiotics for prophylaxis in general surgeries. The American Society of Health System Pharmacist (ASHP) and Standard Treatment Guidelines of South Africa recommend cephalosporin, alone or in combination with other antibiotics, to prevent SSIs after general surgeries. Cephalosporin is also recommended as an alternative in allergic conditions seen with other antibiotics. Indian Council of Medical Research (ICMR) recommends cephalosporin as a first-line treatment in combination with metronidazole during class III and IV surgeries to prevent SSI. The current place of cephalosporin antibiotics in the clinical practice guidelines is summarized in Tables 5, 6, 7 and 8.

6. Conclusion

Cefuroxime is an effective 2nd generation cephalosporin with a good tolerability and safety profile and is therefore widely recommended by various guidelines as a prophylactic antibiotic for patients undergoing general surgeries. These recommendations are based on clinical and scientific evidence supporting effectiveness of cefuroxime in prevention of postoperative infection across several general surgeries. Cefuroxime has a broad-spectrum antibiotic activity, and pharmacokinetic and pharmacodynamics profile supporting its use in sequential

Table 8: Antimicrobial guidelines recommendations of cephalosporin for surgical antibiotic prophylaxis by Indian Council of Medical Research[57]

Type of surgery	Type of common organisms	Recommendations
Class I/clean surgery	Gram-positive cocci (S. aureus, coagulase negative Staphylococci [CoNS])	None or single perioperative ideal dose of 2 g cefuroxime/cephalexin
Class II/clean-contaminated surgery	Gram-negative bacilli anaerobes S. aureus	1L AOC: Cefazolin or ampicillin sulbactam or ceftriaxone (in patients with acute cholecystitis or acute biliary tract infections) AA: If mixture of gram positive and gram negative is suspected: ceftriaxone only if not extended spectrum betalactamase (ESBL) In ß-lactum allergy: Clindamycin or vancomycin with cefazolin, aztreonam, gentamicin, or single-dose fluoroquinolone
Class III/contaminated surgery	Gram-negative bacilli anaerobes	1L: Cefazolin + metronidazole 2L: Metronidazole + aminoglycoside/fluoroquinolone
Class IV/dirty-infected surgery	Gram-negative bacilli anaerobes may be mixed with gram-positive bacteria	1L: Cefazolin + metronidazole Treatment for infected surgical wounds: Ertapenem + clindamycin + aminoglycoside/aztreonam, or fluoroquinolone + metronidazole + aminoglycoside/ fluoroquinolone
Surgery of intestinal or genitourinary tract	Gram-negative bacilli anaerobes	1L: Piperacillin-tazobactam i.v. 3.375 g every 6 h or 4.5 g every 8 h or imipenem-cilastatin i.v. 500 mg every 6 h 2L (as in case of non-ESBL organisms): Ceftriaxone 1 g every 24 h + metronidazole i.v. 500 mg every 8 h

1L: first line; 2L: second line; AOC: antimicrobial of choice; AA: alternative antimicrobial therapy. It can be administered alone or in combination with other classes of antibiotics based on clinical characteristics of individual patients undergoing general surgeries to reduce the risk of postoperative SSIs, abscess, septicemia, and microbial growth. To conclude, cefuroxime, a 2nd generation cephalosporin is an effective and low-cost alternative in surgical prophylaxis for general surgeries, particularly for patients who need sequential antibiotic therapy in India.

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8. Conflict of Interest

None.

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