1. Summary statement of the proposal for inclusion, change or deletion

This is a proposal for inclusion of two first generation cephalosporins - Cefazolin and Cephalexin - in the WHO model list of essential medicines. First generation cephalosporins have activity against several Gram positive cocci causing common community acquired infections and a few gram negative bacilli. Drugs from this group are available for oral (Cephalexin) as well as for parenteral (Cefazolin) use. These drugs are licensed for use and widely available in many developing and developed countries.

Inclusion of these drugs in the WHO essential list of medicines with appropriate guidelines for use will help in promoting proper use of these drugs where indicated and in preventing misuse. Including these first generation cephalosporins in the essential drug list will also help in limiting misuse of broader spectrum cephalosporins for indications that can be adequately managed using narrower spectrum drugs. This will help in cutting cost of therapy and in delaying emergence and spread of highly resistant bacteria like the ESBL producing gram negative bacilli.

Therefore it becomes important that these drugs are listed with definite guidelines for their use

2. Name of the focal point in WHO submitting or supporting application

Not applicable.

3. Names of organisations consulted and or supporting the application

Not applicable.

4. International non-propriety name (INN generic name) of the medicine

a. Cephalexin /Cephalexin monohydrate

b. Cefazolin / Cefazolin sodium

5. Formulation proposed for inclusion – including adult and paediatric

Cefazolin – parenteral (injectable) 1gm/vial
Cephalexin - Oral
Capsules – 250mg/capsule and 500mg/capsule
Syrup – powder to be reconstituted with water – 125mg/5ml and 250mg/5ml

6. International availability – sources, if possible manufacturers

Cefazolin – Manufactured and marketed by many in developed and developing countries e.g. Smith Kline Beecham, Fujisawa USA, Dr. Reddy's laboratory
Cephalexin – Capsule and formulation for suspension are also manufactured and marketed by many eg Apothecon, Orchid, Aurobindo Pharma Ltd, Ranbaxy, Barr

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

As individual drugs – oral and parenteral formulations - belonging to first generation cephalosporins

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population

First generation cephalosporins, Cephalexin and Cefazolin have activity against gram-positive bacteria like *Staphylococcus aureus* (irrespective of penicillinase production) and streptococci, which are the most frequent causes of community acquired skin and soft tissue infections. The spectrum is similar to that of penicillin and penicillinase resistant penicillins (e.g. cloxacillin) which have better activity against Streptococci and Methicillin susceptible *S. aureus* (MSSA).These bacteria are also responsible for the vast majority of wound infections following surgery. Cefazolin and Cephalexin also have action against Gram negative bacilli like *E coli,* and Klebsiella spp which commonly cause community acquired urinary tract infections (UTI).

However, bacterial resistance to this group of drugs is on the increase. These drugs have no action on methicillin resistant *Staphylococcus aureus* (MRSA) and are not useful for treating infections due to enterococci. MRSA accounts only for a small

proportion of community acquired infections. On the other hand, about 25% of *E coli,* the single most frequent cause of UTI are resistant to first generation cephalosporins.

Empirical use of antimicrobials will depend on the knowledge of probable bacterial cause of infection and local resistance patterns. Taking into consideration the current knowledge on these two important issues, first generation cephalosporins are mainly used for their activity against gram positive cocci ie for prophylaxis of surgical site infections and in the treatment of skin and soft tissue infections. Details about individual drugs are given below.

Cefazolin

1. This drug is recommended and used widely as antimicrobial prophylaxis [1, 2] in several surgeries performed at primary and secondary level hospitals, like caesarean sections and herniorrhaphy. In addition to the spectrum of activity, pharmacokinetics of this parenteral drug also is advantageous for this indication. Cefazolin prophylaxis is used for

   a. Clean surgeries where there is no inflammation and respiratory, alimentary, genital or urinary tact is not entered. This includes cardiac [3, 4], vascular, neurological and orthopaedic [5] surgeries. Clean surgeries without prosthetics, like breast surgery and herniorrhaphy[6, 7] are also shown to benefit from prophylactic antibiotics. However a recent mataanalyses did not show evidence for the use of prophylaxis in inguinal hernia repair[8]

   b. Clean contaminated surgeries like Caesarian sections[9] to prevent endometritis. For other gynaecological surgeries and surgeries of gastrointestinal tract, biliary tract etc, antibiotics with broader spectrum of activity, may be better. However, cefazolin is also shown to prevent infections in gynaecological surgeries through abdominal route [10, 11] and in gastric surgeries [12, 13].

2. Since first generation cephalosporins have good activity against Gram positive cocci, they can be used instead of penicillin or cloxacillin especially in those with mild and moderate hypersensitivity to penicillin. Cefazolin can be used where parenteral therapy is indicated like moderate to severe infections due MSSA like osteomyelitis, cellulitis, native valve endocarditis, and skin and soft infections[14-16]. Several of these conditions occur frequently in the community and Cefazolin is one of the most frequently used out patient parenteral preparations.

3. In those hypersensitive (mild or moderate) to penicillin, Cefazolin has been recommended as an alternative to prevent infective endocarditis in those undergoing oral procedures [17]and for intrapartum prophylaxis of Group B streptococcal infection [18] These are also situations arising at community level. However, 10% of individuals with penicillin hypersensitivity can also have hypersensitivity to this drug Cefazolin has a longer half-life than other first-generation cephalosporins therefore only fewer daily doses are required.

Cephalexin

Situations where cephalexin is recommended for use is limited. Suspected staphylococcal skin infections [19, 20] requiring systemic antimicrobial therapy is the main indication. It is widely used as an antistaphylococcal agent especially in children[[21]. Alhough other better oral cephalosporins are available for this indication[22], cephalexin is cheaper. As far as emergence of resistance is concerned, the narrower spectrum cephalexin is better for community use as compared to later generations of cephalosporins. Skin and soft tissue infections requiring systemic antimicrobial therapy occur frequently in developing countries.

Another major advantage is its safety in pregnancy. Because of its activity against *E coli*, it has also been used as one of the alternative antimicrobials in treating UTI in children[23, 24] and in pregnant women[25]. It has been evaluated as oral therapy following parenteral therapy and as oral therapy alone and found to be as effective as other antimicrobials used for treating symptomatic urinary tract infections in pregnancy [26].

Cephalexin is also recommended as prophylaxis for infective endocarditis during oral procedures in persons with penicillin hypersensitivity. Cephalexin is also recommended by some for use in upper respiratory infections including pharyngitis, sinusitis and acute otitis media. Cephalexin is used widely [27] for any type of upper respiratory infections especially in children. The drug has activity on streptococci causing pharyngitis, but there is no evidence on its ability to prevent rheumatic fever. It is not on the current guidelines from western countries, for the treatment of acute otits media

Since the drug has activity against bacteria causing common infections in children like upper respiratory infections including sinusitis and acute otitis media, skin and soft tissue infections and UTI, this drug is widely used in paediatric out patient

practice. The relative absence of adverse effects, availability and palatability of the syrup add to the popularity of this drug. Therefore, although definite evidence based indications for cephalexin is limited, it is widely used for treatment of infections especially in children. Most of its use in developing countries is based on information given by drug 'representatives'.

9. Treatment details (dosage, regimen, duration, reference to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Peak serum levels of **cefazolin** occur within 1—2 hours following an IM dose. It is distributed into most body tissues and fluids including gallbladder; liver; kidney; bone; myocardium; sputum; bile; and pericardial, pleural, and synovial fluids. It does not reach therapeutic levels within the CSF but does cross the placenta. Cefazolin is largely excreted unchanged into the urine. A small percentage is excreted in breast milk.

Adults	**Dose**	**Frequency**
Treatment of infection	0.5 to 1gm	6-8 hrs (max 6gm/ day)*
Surgical prophylaxis	1 gm IV at induction of anaesthesia; after cord clamping for Caesarean section	Can repeat if surgery lasts more than 3 hrs
Children	**Dose**	**Frequency**
Treatment of infection	10 to 15mg/kg (25mg/kg for serious infections)	6-8hrs*
Surgical prophylaxis	25mg/kg (max 1gm) IV at induction of anaesthesia	Can repeat if surgery lasts more than 3 hrs

* Dosage and frequency change based on severity of infection within the ranges shown.

Guidelines

- Guideline for the prevention of surgical site infection, Centre for Disease Control and Prevention, 1999[28] – relevant pages enclosed
- Integrated management of pregnancy and child birth; Managing complications in pregnancy and child birth: a guide for midwives and doctors. WHO,2003 [29]

- Guidelines for the use of prophylactic antibiotics in surgery in Taiwan Infectious Diseases Society of Republic of China; Taiwan Surgical Association 2004[30]
- Clinical guideline on antibiotic prophylaxis for dental patients at risk for infection.American Academy of Pediatric Dentistry (AAPD); 2005[17].
- Practice guidelines for out patient parenteral antimicrobial therapy. Infectious Diseases Society of America - Medical Specialty Society.1997 (revised 2004)[31]
- Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR 2002 [18]
- Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Infectious Diseases Society of America - Medical Specialty Society. 2005 [19]
- ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. American College of Cardiology; 2004[32].

Cephalexin is administered orally, is acid-stable, and rapidly absorbed from the GI tract. Following a 250 or 500 mg oral dose of cephalexin, average peak serum concentrations of 9 or 15—18 mcg/ml, respectively, are achieved within 1 hour and mean serum concentrations decline to 1.6 or 3.4 mcg/ml, respectively, at 3 hours post-dose. Cephalexin is distributed into most body tissues and fluids but does not reach therapeutic levels within the CSF. It crosses the placenta. A small percentage is excreted in breast milk. Cephalexin is also largely excreted unchanged into the urine which leads to high urinary concentrations.

Adult	**Dose**	**Frequency**
Treatment of infection	250-500mg	6hrs (max 4gm per day)
Prophylaxis for UTI	250mg at night	
Children	**Dose**	**Frequency**
Treatment of infection	6.25-12.5 mg/kg	6 hrs
Prophylaxis for UTI	12.5 mg/kg (max 250mg) at night	

Guidelines

- Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources, World Health Organisation, 2005[24]

- Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Infectious Diseases Society of America - Medical Specialty Society. 2005 [19, 23]
- Clinical practice guidelines, use of antibiotics in paediatric care. Ministry of Health, Singapore, 2002 [23]
- Systemic diseases in pregnancy. Finnish Medical Society Duodecim. 2006 [25]

10. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategy, systematic reviews identified, reasons fro selection/exclusion of particular data)

The Cochrane library was searched for reviews and other clinical trials using cefazolin or cephalexin for various indications. A Medline search was also done for studies documenting clinical efficacy.

Evidence available show that antibacterial prophylaxis as compared to placebo, helps in reducing infections following different types of surgery [33-36]. In a review done in 1999 on antibiotic prophylaxis regimens for Caesarean sections, first generation cephalosporins had similar efficacy as ampicillin; OR 1.27 (95% CI 0.84 – 1.93). There was no difference between first and later generations of cephalosporins; OR 1.21 (0.97-1.51). Details of studies included are appended [9].

Antibacterial prophylaxis is useful in preventing infections in surgeries for close fracture fixations[33] as compared to placebo. Cefazolin was used in some of the studies included in the review. Studies included in this review on cefazolin are attached.

Cefazolin is useful in preventing surgical site infections and urinary tract infection after laparoscopic abdominal hysterectomy [10, 11] Effect was similar to that of amoxicillin clavulanic acid combinations. It is also useful as prophylaxis in termination of pregnancy [37]

As a prophylactic agent in gastrectomy, cefazolin was useful in minimising infections [12] and the results were similar to that of ampicillin sulbactam combinations[13].

For therapy, first generation cephalosporins performed as well as other antibacterials in treating urinary tract infections in pregnancy [38].

Cephalexin has been shown to be effective in treating skin and soft tissue infections[20].

11. Summary of comparative evidence on safety

Adverse reactions are rare with first generation cephalosporins and seldom reported. The important probable adverse reaction is hypersensitivity. About 10% of individuals hypersensitive to penicillin can have hypersensitivity to cephalosporins. Among 781 courses studied, anaphylaxis occurred in 0.26% and rash in 1.92% [31]. Cholestatic hepatitis is also described. [31, 39]. Since these drugs are primarily eliminated through kidneys, dosage needs to be modified in case of renal impairment.

12. Summary of available data on comparative cost and cost effectiveness within the pharmacological class or therapeutic group

As per International Drug Price Indicator Guide, a range of prices are there. Median prices in US $ is shown below.

Cefazolin injectable drug - 1gm 0.7838/vial

Cephalexin

250 mg capsule -	0.044/capsule
500 mg capsule - .	0.0805/ capsule
125mg/ml suspension –	0.007/ml
250mg/ml suspension–	0.0098/ml

Ampicillin		Cefuroxime	
1gm injectable	0.1344/vial	1.5gm injectable	2.7589/vial
250 mg capsule	0.0139/cap	250mg cap	0.2381/cap
250mg/5ml suspension	0.0009/ml		

Cloxacillin		Ceftriaxone	1.1931/vial
1gm injectable	1.025/vial	1 gm injectable	0.6058/vial
250 mg capsule	0.0147cap		
125mg/5ml suspension	0.0037/ml		

Amoxicillin/Clavulanic acid

Injectable (1000 +200mg)		4.9547/ vial
Capsule	250 +125	0.3136

13. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, cost per quality adjusted life years gained, if possible and relevant)

Since the prices vary in different countries, the cost of therapy can vary.

Prophylaxis Cefazolin 1gm Approximately $1

Therapy for 5 days with Cefazolin	Approximately $ 20
Therapy for 5 days with Cephalexin	Approximately $1 – 2

There is an estimated cost benefit of $30 per case if prophylaxis is given for Caesarean section, as compared to no prophylaxis[40].Cost analyses for therapy has shown that Cefazolin is more cost effective compared to Ampicillin Clavulanic acid combinations[13]. Single dose prophylaxis is cost effective[41]

14. Summary of regulatory status

First generation cephalosporins are registered in virtually all WHO member states. Cefazolin and Cephalexin are manufactured in several countries and available in most countries. These belong to category B of risk in pregnancy (animal studies do not show harmful effects, not enough controlled studies in women).

15. Availability of pharmacopoeial standards

First generation cephalosporins are listed in all major pharmacopoeas. USP has monographs on Cefazolin and Cephalexin. European pharmacopoeia has a monograph on cefazolin sodium.

16. Proposed text for the WHO Model Formulary

Cefazolin

A parenteral first generation cephalosporin with good activity against methicillin susceptible *S.aureus* and streptococci.

Injection Cefazolin/Cefazolin sodium 1gm.

Although it can be given IM or IV, IM injections are very painful and better avoided.

Uses

1. Prophylaxis to prevent surgical wound infection in clean/ clean contaminated surgeries like Caesarian sections, abdominal hysterectomy, surgeries for closed fractures etc. The drug has to be present in the tissues at the time of incision and so a single IV injection within 30 min before start of surgery is recommended. A repeat dose is of no use except in prolonged surgeries.
2. Moderate to severe infections of bone, skin and soft tissues suspected to be caused by the above mentioned bacteria and requiring parenteral therapy, as an alternative to penicillin group of drugs. Can be used as an outpatient parenteral drug; but the first dose has to be administered in clinic setting.
3. Therapy of UTI caused by susceptible bacteria. In the current scenario where resistance to this drug is increasing among *E coli*, and can be more than 20% in most

community acquired infections, this drug is better avoided as an empirical choice for treatment of UTI. Because of its safety in pregnancy, this drug may be used based on culture and susceptibility data on individual patient.

4. Other infections like septicaemia, based on culture and susceptibility data.

Contraindications

Proven immediate hypersensitivity to penicillin or carbapenems.

Precautions

Chances of hypersensitive reactions occurring in 10% of individuals with Penicillin hypersensitivity.

The dose has to be reduced in renal impairment.

This drug is not useful if infections where MRSA or enterococci are possibilities as in infections in patients with history of recent hospitalisation, infections following catheterisation, etc.

Dosage

Adults	**Dose**	**Frequency**
Treatment of infection	0.5 to 1gm	6-8 hrs (max 6gm/ day)*
Surgical prophylaxis	1 gm IV at induction of anaesthesia; after cord clamping for Caesarean section	Can repeat if surgery lasts more than 3 hrs
Children	**Dose**	**Frequency**
Treatment of infection	10 to 15mg/kg (25mg/kg for serious infections)	6-8hrs*
Surgical prophylaxis	25mg/kg (max 1gm) IV at induction of anaesthesia	Can repeat if surgery lasts more than 3 hrs

Duration for therapy is about 5 days, but can vary depending on patient characteristics and severity of infection to about 10 days. Clinical response is usually evident within 48 hrs. If there is no response within 48hrs situation has to be re evaluated

Adverse reactions

Adverse reactions are rare. Include rash, anaphylaxis and cholestatic hepatitis.

Confusion can occur following large doses in renal impairment.

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Cephalexin

Cephalexin is an oral first generation cephalosporin with with good activity against methicillin susceptible *S.aureus* and streptococci

Tablets/ capsules 250mg and 500mg

Oral suspensions 125mg/5ml and 250mg/5ml

Uses

1. Skin and soft tissue infections requiring systemic antibiotics, as an alternative to penicillin group of drugs.
2. Therapy of UTI caused by susceptible bacteria. Since more than 20% of *E coli*, causing community acquired infections can be resistant, this drug is better avoided as an empirical choice. Because of its safety in pregnancy, it may be used based on culture and susceptibility data in individual patient.

Note

Although it is effective against streptococci causing pharyngitis, there is insufficient data on its ability to prevent rheumatic fever/carditis. For proven acute otitis media, first generation cephalosporins are not currently recommended. Cephalexin is not useful for other upper respiratory infections.

There is no evidence to recommend prophylactic use of cephalexin, following trauma.

Contraindications

Proven immediate hypersensitivity to penicillin or carbapenems.

Precautions

Chances of hypersensitive reactions occurring in 10% of individuals with Penicillin hypersensitivity. The dose has to be reduced in renal impairment. This drug is not useful in infections with MRSA or enterococci.

Dosage

Adult	**Dose**	**Frequency**
Treatment of infection	250-500mg	6hrs (max 4gm per day)
Prophylaxis for UTI	250mg at night	
Children	**Dose**	**Frequency**
Treatment of infection	6.25-12.5 mg/kg	6 hrs
Prophylaxis for UTI	12.5 mg/kg (max 250mg) at night	

Duration for therapy is about 5 days, but can vary depending on patient characteristics and severity of infection to about 10 days. Clinical response is usually evident within 48 hrs. If there is no response within 48hrs situation has to be re evaluated

Adverse reactions

Adverse reactions are rare. Include rash, anaphylaxis. Cholestatic hepatitis is a possibility. Confusion can follow large doses in patients with renal impairment

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9.

TABLE 7
SURGICAL WOUND CLASSIFICATION

Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.

Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.

Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Garner JS[1] and Simmons BP[1]

Four principles must be followed to maximize the benefits of AMP:

- Use an AMP agent for all operations or classes of operations in which its use has been shown to reduce SSI rates based on evidence from clinical trials or for those operations after which incisional or organ/space SSI would represent a catastrophe.[266,268,269,282-284]
- Use an AMP agent that is safe, inexpensive, and bactericidal with an in vitro spectrum that covers the most probable intraoperative contaminants for the operation.
- Time the infusion of the initial dose of antimicrobial agent so that a bactericidal concentration of the drug is established in serum and tissues by the time the skin is incised.[285]
- Maintain therapeutic levels of the antimicrobial agent in both serum and tissues throughout the operation and until, at most, a few hours after the incision is closed in the operating room.[179,266-268,282,284,286] Because clotted blood is present in all surgical wounds, therapeutic serum levels of AMP agents are logically important in addition to therapeutic tissue levels. Fibrin-enmeshed bacteria may be resistant to phagocytosis or to contact with antimicrobial agents that diffuse from the wound space.

Table 4 summarizes typical SSI pathogens according to operation type and cites studies that establish AMP efficacy for these operations. A simple way to organize AMP indications is based on using the surgical wound classification scheme shown in Table 7, which employs descriptive case features to *postoperatively* grade the degree of intraoperative microbial contamination. A surgeon makes the decision to use AMP by anticipating *preoperatively* the surgical wound class for a given operation.

AMP is indicated for all operations that entail entry into a hollow viscus under controlled conditions. The most frequent SSI pathogens for such clean-contaminated operations are listed in Table 4. Certain clean-contaminated operations, such as elective colon resection, low anterior resection of the rectum, and abdominoperineal resection of the rectum, also require an additional preoperative protective maneuver called "preparation of the colon," to empty the bowel of its contents and to reduce the levels of live microorganisms.[200,239,256,268,284,287] This maneuver includes the administration of enemas and cathartic agents followed by the oral administration of nonabsorbable antimicrobial agents in divided doses the day before the operation.[200,268,289]

AMP is sometimes indicated for operations that entail incisions through normal tissue and in which no viscus is entered and no inflammation or infection is encountered. Two well-recognized AMP indications for such clean operations are: (1) when any intravascular prosthetic material or a prosthetic joint will be inserted, and (2) for any operation in which an incisional or organ/space SSI would pose catastrophic risk. Examples are all cardiac operations, including cardiac pacemaker placement,[290] vascular operations involving prosthetic arterial graft placement at any site or the revascularization of the lower extremity, and most neurosurgical operations (Table 4). Some have advocated use of AMP during all operations on the breast.[80,242,264]

By definition, AMP is not indicated for an operation classified in Table 7 as contaminated or dirty. In such operations, patients are frequently receiving therapeutic antimicrobial agents perioperatively for established infections.

Cephalosporins are the most thoroughly studied AMP agents.[284] These drugs are effective against many gram-positive and gram-negative microorganisms. They also share the features of demonstrated safety, acceptable pharmacokinetics, and a reasonable cost per dose.[242] In particular, cefazolin is widely used and generally viewed as the AMP agent of first choice for clean operations.[266] If a patient is unable to receive a cephalosporin because of penicillin allergy, an alternative for gram-positive bacterial coverage is either clindamycin or vancomycin.

Cefazolin provides adequate coverage for many clean-contaminated operations,[268,291] but AMP for operations on the distal intestinal tract mandates use of an agent such as cefoxitin (or some other second-generation cephalosporin) that provides anaerobic coverage. If a patient cannot safely receive a cephalosporin because of allergy, a reasonable alternative for gram-negative cover-

OPERATIONS, LIKELY SURGICAL SITE INFECTION (SSI) PATHOGENS, AND REFERENCES ON USE OF ANTIMICROBIAL PROPHYLAXIS*

Operations	Likely Pathogens†
Placement of all grafts, prostheses, or implants	*Staphylococcus aureus*; coagulase-negative staphylococci
Cardiac	*S. aureus;* coagulase-negative staphylococci
Neurosurgery	*S. aureus;* coagulase-negative staphylococci
Breast	*S. aureus;* coagulase-negative staphylococci
Ophthalmic	*S. aureus;* coagulase-negative staphylococci; streptococci; gram-negative bacilli
Limited data; however, commonly used in procedures such as anterior segment resection, vitrectomy, and scleral buckles	
Orthopedic	*S. aureus;* coagulase-negative staphylococci; gram-negative bacilli
Total joint replacement	
Closed fractures/use of nails, bone plates, other internal fixation devices	
Functional repair without implant/device	
Trauma	
Noncardiac thoracic	*S. aureus;* coagulase-negative staphylococci; *Streptococcus pneumoniae;* gram-negative bacilli
Thoracic (lobectomy, pneumonectomy, wedge resection, other noncardiac mediastinal procedures)	
Closed tube thoracostomy	
Vascular	*S. aureus;* coagulase-negative staphylococci
Appendectomy	Gram-negative bacilli; anaerobes
Biliary tract	Gram-negative bacilli; anaerobes
Colorectal	Gram-negative bacilli; anaerobes
Gastroduodenal	Gram-negative bacilli; streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)
Head and neck (major procedures with incision through oropharyngeal mucosa)	*S. aureus;* streptococci; oropharyngeal anaerobes (e.g., peptostreptococci)
Obstetric and gynecologic	Gram-negative bacilli; enterococci; group B streptococci; anaerobes
Urologic	Gram-negative bacilli
May not be beneficial if urine is sterile	

Studies using Cefazolin as prophylaxis in Caesarian sections [1]

Study	Methods	Participants	Interventions	Outcome	Notes
Carlson 1990	Randomized double-blind study	All women undergoing nonelective C/S. Exclusion criteria: drug allergy, antibiotics within the last 14 days, clinical evidence of infection	Group 1: Cefazolin 2 g iv after cord clamped, N=192. Group 2: Cefotetan 2 g iv after cord clamped, N=185.	Febrile morbidity post-operatively: Group 1: 43/192 vs Group 2: 40/185. Endometritis: Group 1: 37/192 vs Group 2: 39/185. Wound infection: Group 1: 3/192 vs Group 2: 3/185. UTI : Group 1: 6/192 vs Group 2: 12/185 Sepsis: Group 1: 2/192 vs Group 2: 1/185.	Country: U.S
Donnenfeld 1986	States randomized, details not provided	All women in labor undergoing C/S Exclusion: drug allergy, antibiotic therapy for other indications, those with evidence of infection.	Group 1: 1 g iv cefazolin after cord clamped and two further doses of 1 g iv at 8 hour intervals (n=51). Group 2: 1 g cefazolin in 500 cc NS, irrigation (n=49).	Endometritis : Group 1: 15/51 vs Group 2: 18/49.	. Country: U.S.
Duff 1987	Randomized double blind trial. Intention to treat analysis.	All women undergoing non-elective C/S . Exclusion criteria: drug allergy, antibiotic therapy within 14 days	Group 1: cefazolin 1 g after cord clamped (n=96). Group 2: cefonicid 1 g after cord clamped (n=103).	No wound infections. Febrile morbidity; Group 1: 18/96 vs Group 2: 15/103. Endometritis: Group 1: 19/96 vs Group 2: 13/103. Sepsis;Group 1: 1/96 vs Group 2: 0/103. UTI; Group 1: 3/96 vs Group 2: 3/103.	Hospital stay (mean): Group 1: 4.4 days vs Group 2: 4.2 days. Country: U.S.
Faro 1990	Randomized	Women for C/S in	Control group: Cefazolin 1g	Endometritis:	Country: U.S.

	trial. Intention to treat analysis	labor >2 hours, afebrile, no antibiotic therapy in previous 7 days. Exclusion: drug allergy N=1580.	iv x 3 doses (first after cord clamped) 9 other groups (all single dose iv after cord clamped): Group 1(cefazolin 1g/n=217), Group 2 (cephazolin 2g/n=161), Group 3 (ceftizoxime 1g/n=145), Group 4 (cefonicid 1g/n=147), Group 5 (cefotetan 1g/n=148), Group 6 (cefoxitin 1g/n=155), Group 7 (cefoxitin 2g/n=162), Group 8 (ampicillin 2g/n=148) and Group 9 (piperacillin 4 g/n=155).	Control: 32/142 vs Group 1: 44/217 vs Group 2: 17/161 vs Group 3:24/155 vs Group 4: 27/162 vs Group 5: 9/148 vs Group 6: 26/145 vs Group 7: 22/146 vs Group 8: 19/148 vs Group 9: 13/155.	
Fugere 1983	Randomized double-blind, control trial.	Women undergoing non-elective C/S in labor Exclusion: mebranes intact, antibiotic therapy in last 48 hours, drug allergy temperature >38 in last 24 h, ROM >36 h.	Group 1: Cefoxitin, 2 g iv after cord clamped and repeat dose x2 q6h (n=30). Group 2: Cefazolin 1 g iv after cord clamped and repeat dose x2 q6h (n=30).	Endometritis: Group 1: 1/30 vs Group 2: 1/30. Wound Infection: Group 1: 0/30 vs Group 2: 2/30. No UTI or febrile morbidity recorded	Language: French. Country: Canada

Hager 1991 Women undergoing C/S Inclusion: age >18, no d Exclusic disease.	Prospective, randomized, double-blind. Not intention to treat, cannot convert	Women undergoing C/S. Inclusion: age >18, no drug allergy, in labor or ROM present. Exclusion: elective C/S, current antibiotic therapy, chronic renal or hepatic disease	Group 1: Cefazolin 1 g iv after cord clamped (N=63). Group 2: Cefoxitin 2 g iv after cord clamped (N=66). Group 3: Cefotaxime 1 g iv after cord clamped (N=60).	Endometritis:Group 1: 4/63 vs Group 2: 9/66 vs Group 3: 5/60. UTI: Group 1: 1/63 vs Group 2: 0/66 vs Group 3: 0/60. Bacteremia :Group 1: 2/63 vs Group 2: 1/63 vs Group 3: 0/60.	Country US
Jakobi 188 Gr	Randomized study. Intention to treat analysis	100 women requiring C/S Exclusion: elective C/S, ROM < 3h, 2 or fewer vaginal exams, temperature >38, drug allergy ROM >24 hours	Group 1: Cefazolin 1 g iv after cord clamped (n=50). Group 2: Cefazolin 1 g iv after cord clamped and two additional same doses at 8 and 16 hours post-operation (n=50)	Febrile morbidity: Group 1: 9/50 vs Group 2:6/50. Endometritis : Group 1: 3/50 vs Group 2: 4/50. UTI : Group 1: 4/50 vs Group 2: 0/50. Wound infection: Group 1: 0/50 vs Group 2: 1/50.	Country Israel
Louie 1982	Randomized, double-blind, placebo control.	All women for non-elective C/S. Inclusion: active labor with ROM, afebrile, no drug	Group 1: Ampicillin 1 g iv after cord clamped and 2 further doses at 6 and 12 hours post-operation (N=60). Group 2: Cefazolin 1 g iv	Endometritis: Group 1: 2/60 vs Group 2: 3/70 vs Group 3: 4/58. UTI: Group 1: 2/60 vs Group 2: 3/70 vs Group 3: 1/58. Wound Infection: Group 1: 2/60 vs Group	Country Canada

	Intention to treat	allergy, no antibiotic therapy in last 14 days.	after cord clamped and 2 further doses at 6 and 12 hours post-operation (N=70). Group 3: Cefotaxime 1 g iv after cord clamped and 2 further doses at 6 and 12 hours post-operation (N=58).	2: 1/70 vs Group 3: 1/58. Febrile morbidity Group 1: 6/60 vs Group 2: 5/70 vs Group 3: 5/58.	
Mathelier 1992	Subjects alternately assigned to treatment groups. Intention to treat.	Women for C/S. Indigent population. Exclusion: IAI, evidence of other infection.	Group 1: Cefazolin 2 g iv after cord clamped and saline irrigation of abdomen (N=154). Group 2: Cefazolin 1 g iv after cord clamped and cefazolin 1 g in 500 cc NS, by irrigation (N=154).	Endometritis and wound infection (grouped together in their analysis - unable to separate):Group 1: 13/154 vs Group 2: 2/154. UTI Group 1: 1/154 vs Group 2: 2/154.	Country: U.S.
Peterson 1990	Randomized, double-blind. Intention to treat	Women undergoing non-elective C/S Exclusion: drug allergy, patient on antibiotics, those with evidence of infection, those requiring SBE prophylaxis	Group 1: Cefazolin 2g iv after cord clamped (N=47). Group 2: Cefamandole 2 g iv after cord clamped (N=59). Group 3: Cefazolin 2 g in 1 L NS by lavage (N=47). Group 4: Cefamandole 2 g in 1 L NS by lavage (N=54).	Endometritis : Group 1: 6/47 vs Group 2: 6/59 vs Group 3: 5/47 vs Group 4: 5/54. Wound infection: Group 1: 0/47 vs Group 2: 2/59 vs Group 3: 0/47 vs Group 4: 0/54. UTI (>10 exp 5 orgs/mL): Group 1: 0/47 vs Group 2: 1/59 vs Group 3: 1/47 vs Group 4: 1/54.	Data from the lavage arms have been compared with the systemic arms. Country: U.S.
Stiver 1983	Randomized double-blind, placebo-control trial.	All women undergoing non-elective C/S	Group 1: Cefoxitin 2g iv after cord clamped (N=124). Group 2: Cefazolin1g iv after cord clamped (N=119).	Endometritis; Group 1: 5/124 vs Group 2: 3/119. Wound infection; Group 1: 2/124 vs Group 2: 4/119. Septic Shock: Group 1: 0/124 vs Group 2: 1/119.	Country: Canada

Orthopaedic surgeries [2]

Study	**Jones 1987 B**
Methods	RCT. Location: Prepaid medical care program, Oregon, USA. Recruitment period: 1984-1985 Adequacy of concealment of assigned allocation: B Intention to treat analysis: 2 Blinding of outcome assessors: 1 Comparability of treatment groups at entry: 1 (see notes) Use of placebo: 1 Definition of inclusion and exclusion criteria: 2 Assessment of wound infection: 2 Duration of surveillance: 1 Losses to follow up: 122 of 1036 (12%).
Participants	914 in study of which a subgroup of 58 who had undergone fracture surgery were analysed for this review. No demographic details for the fracture subgroup. Inclusion criteria: Main analysis:undergoing elective surgery in a range of specialties. Subgroup- undergoing open reduction and fixation of fracture. Exclusion criteria: Concurrent antibiotic treatment, history of hypersensitivity to cephalosporins or penicillins, pregnancy, preoperative urinary tract infection, renal or hepatic disease.
Interventions	a. Cefazolin 1g by intravenous injection at onset of anaesthesia, and 8 hourly for 24 hrs. b. Cefoxitin 2g by intravenous injection at onset of anaesthesia and 6 hourly for 24 hrs. c. Cefotaxime 1g by intravenous injection at onset of anaesthesia (with second dose if operation time exceeded 2 hours)
Outcomes	1. Wound infection. (defined as drainage of purulent material from the wound) within 30 days of operation.

Notes	Demographic data available only for the whole group, but wound infection data for a fracture fixation subgroup.

Study	**Buckley 1990**
Methods	RCT. Location: University Hospital, Canada. Recruitment period: 1985-1988. Adequacy of concealment of assigned allocation: A Intention to treat analysis: 1 Blinding of outcome assessors: 1 Comparability of treatment groups at entry: 2 Use of placebo: 3 Definition of inclusion and exclusion criteria: 3 Assessment of wound infection: 2 Duration of surveillance: 2 Losses to follow up: 40/352 (12%)
Participants	312 analysed (female 225, male 87, mean age 77 years). Inclusion criteria: undergoing hip fracture surgery. Exclusion criteria - Cephalosporin allergy, pathologic fracture, previous surgery on fractured hip, antibiotic treatment with other agent, more than 7 days in hospital pre-op.
Interventions	a. Cefazolin 2g iv induction; 1g 6 hourly iv 3 more doses b. Cefazolin 2g iv induction; placebo (saline) 6 hourly iv 3 doses c. Placebo (saline) iv induction; placebo (saline) 6 hourly iv 3 doses

Outcomes	1. Deep wound infection 2. Superficial wound infection
Study	**Nelson 1983**
Methods	CCT. (Quasi-randomised by last digit of hospital number: odd or even). Location: University Hospital, USA. Recruitment period: Not described. Adequacy of concealment of assigned allocation: C Intention to treat analysis: 1 Blinding of outcome assessors: 1 Comparability of treatment groups at entry: 1 Use of placebo: 1 Definition of inclusion and exclusion criteria: 1 Assessment of wound infection: 2 Duration of surveillance: 3 Losses to follow up: 6 / 358 (2%).
Participants	103 men and women undergoing hip fracture surgery analysed. Subgroup within a larger study which also included a further 255 joint replacement patients. No demographic details provided. Inclusion criteria: undergoing hip fracture surgery Exclusion criteria: none described
Interventions	a. Intravenous antibiotics for 24 hours (either nafcillin or cefazolin 500mg 6 hourly, choice being surgeon dependent) b. Intravenous antibiotics (same agent and dose as in group a) or three days intravenously, and for a subsequent 4 days orally.
Outcome	Deep wound infection

Urinary tract infections studies [3]

Study	**Charleston 1996**
Methods	Allocation by a coin-flip table established at the beginning of the study.
Participants	Women admitted for antepartum pyelonephritis, with an estimated average gestational age of 22 weeks at admission. The groups were well matched for age, race and temperature. Inclusion criteria: admission oral temperature of 38°C or greater, costovertebral angle tenderness, and a positive urine culture with 100,000 colony forming units/ml. Exclusion criteria: evidence of renal abscess, a prior episode of pyelonephritis during the index pregnancy, and women not exhibiting all the inclusion criteria.
Interventions	Both groups received intravenous cephazoline only or cephazolin plus gentamicin or cephazoline plus other antibiotic or ampicillin plus gentamicin or other antibiotic (the initial antibiotic regimen was determinated by the attending physician). In addition, the study group (n = 36) received nitrofurantoin 100 mg q.i.d. to complete 10 days of antibiotic therapy (intravenous followed by oral therapy). The control group (n = 31) received no further oral antibiotic therapy. No long term suppressive therapy was used in any of the patients. Women were removed from the study at the time of any positive urine culture or episode of recurrent pyelonephritis.
Outcomes	Cure rates (intravenous antibiotics plus nitrofurantoin 34/36, intravenous antibiotics only 27/31); recurrent infection (intravenous antibiotics plus nitrofurantoin 6/36, intravenous antibiotics only 3/31).
Notes	Charleston, North Carolina, USA. August 1990 to December 1994. Women were from a lower socioeconomic clinic population with about 1/3 of the women enrolled in the study not returning for their 2-week culture check (9 women in the no oral therapy group and 8 women in the oral therapy group). Authors considered that this fact would call into question the compliance of women in the oral antibiotic treatment group, and that some of the early recurrent infections in the oral therapy group could represent women who were non-compliant in completing their course of nitrofurantoin. However, the number of enrolled women that did not return was similar in both groups.

Study	Florida 1995
Methods	Allocation by a computer-generated randomization schedule. The randomization schedule was kept in the hospital pharmacy and was not accessible to the clinicians.
Participants	All women admitted to the hospital with clinical signs and symptoms of acute pyelonephritis. The diagnosis was made in febrile women (temperature >= 100.4°F), who met any two of the following criteria: (1) chills, (2) costovertebral angle tenderness, (3) urinalysis showing bacteria and white blood cells. Exclusion criteria: history of an acute allergic reaction to cephalosporins or penicillins and recent use of antibiotics.
Interventions	Study group (n = 90): Three doses, one being ceftriaxone, 1 g IV every day; the other two doses were placebo solutions of normal saline solution. Control group (n = 88): cephazolin, 2 g IV every 8 hours. IV treatment was continued until the woman was afebrile (temperature < 100.4°F) for at least 48 hours. Women who failed to respond completely (with resolving clinical signs and symptoms) within 3 days received IV gentamicin (120 mg bolus and 1.5 mg/kg maintenance every 8 hours) in addition to the original antibiotics. Once afebrile, with complete clinical resolution, patients were discharged on a 10-day course of an oral antibiotic consistent with isolated sensitivity findings. Most women received 500 mg of either cephalexin or cephradine four times daily.
Outcomes	Cure rates (ceftriaxone 87/90, cefazolin 83/88); recurrent pyelonephritis (ceftriaxone 3/62, cephazolin 4/60); preterm delivery (ceftriaxone 9/90, cephazolin 8/88); antibiotic change required (ceftriazone 3/90, cephazolin 5/88); birthweight less than 2500 g (ceftriaxone 8/90, cephazolin 5/88); intrauterine growth retardation (ceftriaxone 4/90, cephazolin 5/88).
Notes	Florida, USA. October 1990 through December 1992. University Medical Center of Jacksonville, University of Florida's urban

campus. Obstetric patients are cared by resident physicians in obstetrics and gynecology and nurse-midwives supervised by a full-time faculty obstetrician-gynecologist. The authors consider that although a test of cure was not performed in 17% of study patients, this should not have influenced their findings, because the randomization produced similar treatment groups in all measured respects. They also comment that the mean total cost for ceftriaxone (a single 1 g dose) was 3202 USD less than that for cephazolin (2 g intravenous every 8 hours).

Study	**Los Angeles 1995**
Methods	Allocation by a table of random numbers with random permuted blocks, with a block size of six. Indicator cards in sealed, opaque, sequentially numbered envelopes kept by the principal investigator who was not involved in the randomization. Once a patient consented, the resident in the emergency room telephoned the principal investigator.
Participants	Pregnant women with an estimated gestational age of less than 24 weeks, had one or more symptoms or signs of upper urinary tract infection (temperature greater than 38.4°C, flank pain, or costovertebral angle tenderness), and had a urinalysis suspicious for urinary tract infection. Exclusion criteria: clinical signs of sepsis, respiratory insufficiency, an initial temperature greater than 39.8°C, blood pressure less than 90/50, pulse greater than 140 beats per minute (sustained), creatinine greater than 1.4 mg/dL, white blood cell count greater than 20 per 10^9/L, a known allergy to cephalosporins, a history of anaphylactic reaction to penicillins, inability to tolerate oral intake, inability to follow instructions, or serious underlying medical illness, including a known renal or urological problem, and subjects who had received antibiotic therapy within two weeks of presentation.
Interventions	Outpatients (study group) (n = 60) received ceftriaxone 1 g IM in the emergency room during the observation period. A home health nurse evaluated the patients 18-36 hours after discharge and administered a second injection of ceftriaxone 1 g. Participants then completed a 10-day course of oral cephalexin, 500 mg four times a day. Inpatients (control group) (n = 60) received 1 g IV every 8 hours until they were afebrile for 48 hours. All the participants received acetaminophen, cooling measures, and IV fluids

	while hospitalized. Antibiotic therapy was changed for women with a worsening clinical picture or for those whose did not have clinically improvement at 72 hours.
Outcomes	Cure rates (colony counts in urine of less than 100,000 colonies/mL) (outpatients 57/60, inpatients 53/60); recurrent pyelonephritis (inpatients 3/60, outpatients 3/60); preterm delivery (outpatients 0/60, inpatients 1/60); need for change antibiotic (outpatients 0/60, inpatients 6/60); incidence of prolonged pyrexia (outpatients 0/60, inpatients 4/60).
Notes	Los Angeles, California, USA. April 1991 to July 1993. Authors educated participants who were candidates for outpatient treatment about pyelonephritis and instructed them on the warning signs of septic shock and respiratory insufficiency. The education was continued by visiting nurses who followed up the patients for the first 3 days after discharge. Authors conclude that the majority of patients with pyelonephritis in early pregnancy may be candidates for outpatient therapy.

Study	**Los Angeles 1998**
Methods	Allocation by a computer-generated random table. Assignments were placed in opaque, sealed envelopes. After a participant gave informed consent, the next envelope was opened to determine the treatment allocation.
Participants	Pregnant women recruited from the emergency department of the hospital earlier than 24 weeks' gestation. Inclusion criteria: one or more symptoms of urinary tract infection (temperature at least 100.4°F, flank pain, costovertebral angle tenderness) and urinalysis suspicious for urinary tract infection (seven to ten white blood cells per high-powered field, 20 bacteria per high-powered field, white blood cell casts, positive nitrites on urinary dipstick). Exclusion criteria: women with history of allergy to the antibiotics being studied, had received antibiotic treatment within 2 weeks of enrollment, recurrent pyelonephritis, medical or other concurrent conditions that precluded enrollment, obvious sepsis, history of substance abuse or concurrent incarceration, nonviable or unwanted pregnancies, threatened abortion, inability to follow up because of geographic restrictions, or refusal to participate in the study.

Interventions	Three groups: First group (n = 62): 2 g ampicillin IV every 4 hours and gentamicin 1.75 mg/kg IV every 8 hours after an initial dose of 2 mg/kg IV gentamicin. Second group (n = 58): 1 g IV cephazolin every 8 hours. Third group (n = 59): two 1 g doses of ceftriaxone IM 24 hours apart, followed by 500 mg of oral cephalexin every 6 hours. All subjects received antibiotics and were hospitalized until they were afebrile for 48 hours. At discharge, all women were given 10-day course of cephalexin 500 mg four times a day. Subjects then were given nitrofurantoin 100 mg to take once a day for the remainder of their pregnancy and 6 weeks postpartum. Women who failed to demonstrate significant improvement after 72 hours of therapy were reassessed. Decisions to change antimicrobial agents were made on individual basis.
Outcomes	Cure rates (ampicillin plus gentamicin 58/62, cephazolin 55/58, ceftriaxone 1/59); recurrent pyelonephritis (ampicillin plus gentamicin 3/57, cephazolin 4/50, ceftriaxone 3/52); preterm delivery (ampicillin plus gentamicin 3/57, cephazolin 5/50, ceftriaxone 3/52); NICU admission (ampicillin plus gentamicin 9/57, cephazolin 11/50, ceftriaxone 12/52); antibiotic change required (ampicillin plus gentamicin 0/62, cephazolin 2/58, ceftriaxone 4/59); incidence of prolonged pyrexia (ampicillin plus gentamicin 6/62, cephazolin 4/58, ceftriaxone 6/59).
Notes	Los Angeles, California, USA. October 1994 through May 1997. 189 participants (88.8%) returned for follow-up examination. Urine cultures were obtained from 149 of these subjects. Authors concluded that IM ceftriaxone is as effective as IV ampicillin-gentamicin and IV cephazolin in treating pyelonephritis in pregnancy before 24 weeks' gestation. The costs for the antibiotics would be 150.00 USD for ampicillin-gentamicin and 75.00 USD for both cephazolin and ceftriaxone, but ceftriaxone can be given intramuscularly on an outpatient basis, and it could translate into substantial cost savings. Authors also noticed a low rate of preterm birth (6.9%) compared with the institutional and national rates (about 11%).

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