SURGICAL ANTIMICROBIAL PROPHYLAXIS

CHI Formulary Development Project

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ASHP	American Society of Health-System Pharmacists
BID	Bis In Die (Twice Per Day)
CABG	Coronary Artery Bypass Graft
CDC	Centers for Disease Control and Prevention
CHI	Council of Health Insurance
CRAB	Carbapenem-Resistant Acinetobacter Baumannii
CRE	Carbapenem-Resistant Enterobacterales
EMA	European Medicines Agency
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESCR-E	Extended-Spectrum Cephalosporin-Resistant Enterobacterales
EUCIC	European Committee on Infection Control
FDA	Food and Drug Administration
FQR-E	Fluoroquinolone-Resistant Enterobacterales
GFR	Glomerular Filtration Rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IDF	Insurance Drug Formulary
IDSA	Infectious Diseases Society of America
IV	Intravenous
KSA	Kingdom of Saudi Arabia
MDR-GNB	Multidrug-Resistant Gram-Negative Bacteria
MRSA	Methicillin-Resistant Staphylococcus Aureus
NICE	National Institute for Health and Care Excellence
PAP	Perioperative Antibiotic Prophylaxis
PO	Per Os (By Mouth)
RCT	Randomized Controlled Trial
SAP	Surgical Antibiotic Prophylaxis
SFDA	Saudi Food and Drug Authority
SHEA	Society for Healthcare Epidemiology of America

SIS	Surgical Infection Society
SSI	Surgical Site Infection
TRUSPB	Transrectal Ultrasound-Guided Prostate Biopsy
VAD	Ventricular Assist Device
WHO	World Health Organization

Executive Summary

Surgical antimicrobial prophylaxis involves the use of antimicrobial medications to prevent infections that may arise from surgical procedures. Surgical site infections (SSIs) affect 0.5% to 3% of surgery patients[1]. A study in Saudi Arabia by Rawabdeh et al. (2016) identified causative organisms for SSIs in a teaching hospital. *Staphylococcus aureus* and *Escherichia coli* were the primary causative organisms, with an incidence rate of 11.4% for surgical site infections among the studied patients[2].

This report compiles all clinical and economic evidence related to surgical antimicrobial prophylaxis according to the relevant sources. The ultimate objective of issuing surgical antimicrobial prophylaxis guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients requiring surgical antimicrobial prophylaxis in Saudi Arabia**.

The focus of the review was on North American and joint European and other international guidelines issued within the last five years. Each guideline recommended a preferred antibiotic, as well as an alternative, to the different types of surgeries. KSA also has its surgical prophylaxis guidelines, which was tackled in this report. The guidelines also emphasize on safety considerations and potential interactions when a patient is subjected to antibiotic therapy. In addition, a recent systematic review and meta-analysis was tackled; showing that there is low evidence for intraoperative redosing of antibiotics for surgical prophylaxis.

Surgical antimicrobial prophylaxis involves a **multidisciplinary approach**, in which **drug therapy is an integral component.** The major goal is to prevent infections that may occur as a result of a surgical procedure. The standard pharmacological interventions include antibiotic therapy that is mainly administered pre-operatively in a timely manner.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of AGHD.

Major recommendations for suggested drug therapies are summarized in the tables below:

Table 1. SFDA-Registered Drugs for Surgical Antimicrobial Prophylaxis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Cephalosporins First Generation: o Cefazolin Second Generation: o Cefoxitin o Cefuroxime Third Generation: o Ceftriaxone o Cefotaxime Fourth Generation: o Cefepime	Recommended Peri-Operative Antibiotic Prophylaxis for Solid Organ Transplant Recipients by Organ: Renal transplantation: First-generation cephalosporin recommended for ≤ 24 hours	**First line**	Strong, low [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
	For patients colonized with a resistant organism, use a third-generation cephalosporin or alternative agent passed on individual susceptibilities and local formulary for ≤ 24 hours.	**First line**	Strong, low [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
	Cefazolin: Cardiac Surgery/ Vascular/ Thoracic, Cardiac Surgery with prosthetic material, Cardiac device insertion (e.g., pacemaker implantation), Gastroduodenal, Biliary Tract, Colorectal, appendectomy, hernia repair, breast) Cesarean delivery, hysterectomy, Head & Neck, Neurosurgery, Orthopedics, Plastic Surgery, Urology.	**Preferred agent**	N/A [Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)]

	Cefoxitin: Urology: Open/laparoscopic involving intestine: (clean-contaminated, e.g., radical cystectomy with ileal conduit)	**Preferred agent**	N/A [Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)]
	Heart transplant with prior VAD: Single first-generation cephalosporin (e.g., cefazolin). Alternative: vancomycin* plus either ceftriaxone 1 g IV or cefepime 2 g IV	**Alternative Agent**	N/A [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
Ertapenem	Ertapenem is recommended at a dose of 1 gram as an alternative agent in antimicrobial prophylaxis.	**Alternative Agent**	N/A Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)
Clindamycin	Alternative agent in Cardiac Surgery/ Vascular/ Thoracic, Cardiac Surgery with prosthetic material, Cardiac device insertion (e.g., pacemaker implantation), Gastroduodenal, Biliary Tract, Colorectal, appendectomy, hernia repair, breast) Cesarean delivery, hysterectomy, Head & Neck. Alternative: Renal	**Alternative Agent**	N/A [Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021) and Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]

	Pancreas, pancreas-kidney transplant.		
Fluoroquinolones: o Ciprofloxacin (1st generation) o Levofloxacin (3rd generation) o Moxifloxacin (4th generation)	Ciprofloxacin: Alternative agent in Urology: Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy) Clean with entry into urinary tract, as well as in gastroduodenal/ colorectal/ biliary/and pancreas-kidney or kidney transplant	**Alternative Agent**	N/A [Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021)]
	Levofloxacin in Biliary Tract Colorectal, appendectomy, urology surgeries, and Heart Transplant.	**Alternative Agent**	N/A [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019) and Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)]
Vancomycin	Alternative agent in cardio-thoracic surgery, neurology MRSA colonization, orthopedic surgery, vascular surgery, liver transplant, pancreas or pancreas-kidney transplant.	**Alternative Agent**	N/A [Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021) and Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious

			Diseases Community of Practice (2019)]
Penicillins: ○ Piperacillin-Tazobactam ○ Ampicillin-Sulbactam ○	Piperacillin-Tazobactam: Preferred agent in liver transplantation.	**Preferred agent**	N/A [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
	Liver transplantation: Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam recommended for up to 24 hours.	**Preferred agent**	Strong, low [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
	Another alternative would be ampicillin-sulbactam or in countries where available intravenously amoxicillin-clavulanate for ≤48 hours; antifungals may be considered based on individual patient risk.	**Alternative Agent**	Strong, high [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)]
	Pancreas and pancreas-kidney transplantation: ampicillin-sulbactam for ≤48 hours and a single dose of fluconazole are recommended.	**Preferred agent**	Strong, low [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious

			Diseases Community of Practice (2019)]
Metronidazole	For appendectomy, obstructed small intestinal and colorectal: add Metronidazole. To be added in Clean – contaminated head/neck surgeries (cancer or other procedure with exception of tonsillectomy and functional endoscopic sinus procedure) and urology surgeries.	**Step Therapy**	N/A [Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021) and University of Toronto's Best Practice in Surgery (BPS) Clinical Practice Guideline for Surgical Site Infection Prevention (2017)]
Gentamicin	Gastroduodenal Cesarean delivery Gynecological (e.g. hysterectomy) Urology: Involving implanted prosthesis. Clean with entry into urinary tract Renal transplant Pancreas, pancreas-kidney transplant	**Alternative Agent**	N/A [Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019) and Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021)]
Gatifloxacin	**Ophthalmic**	**Alternative**	N/A University of Toronto's Best Practice in Surgery (BPS) Clinical Practice Guideline for Surgical Site Infection Prevention (2017)

Table 2. Non-SFDA Registered Drugs for Surgical Antimicrobial Prophylaxis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Aztreonam	Lung or Heart-Lung Transplant	**Alternative**	N/A Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)
	Renal transplantation: Patients with severe cephalosporin allergy should use alternative agents such as a fluoroquinolone or aztreonam.	**Alternative**	weak, low Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)
Tobramycin	Gastroduodenal/esophageal/ distal pancreatic resection Percutaneous endoscopic gastrostomy (PEG) Biliary tract- laparoscopic procedure – High risk emergency, inserting prosthetic device, diabetes, risk of intraoperative gallbladder rupture/conversion to open, age >70	**Alternative**	N/A Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)

	years, ASA ≥3, reintervention within 1-month, acute cholecystitis, obstructive jaundice, CBD stones, nonfunctional GB, pregnancy, immunosuppression. Biliary tract- open procedure Liver resection Clean-contaminated (incision through oral/pharyngeal mucosa) head and neck: cancer surgery and other clean-contaminated procedures with the exception Endoscopic transsphenoidal neurosurgery. Open or Laparoscopic: without entry into bowel/vagina Caesarean section Hysterectomy		

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

1.1.1 Saudi Ministry of Health Antibiotics Surgical Prophylaxis Protocol (2021)

The Saudi Ministry of Health issued a surgical prophylaxis protocol in 2021. No evidence levels of grades of recommendations outlined in this document[3].

Table 3. Antibiotics Surgical Prophylaxis (Saudi Ministry of Health)

Antibiotics Surgical Prophylaxis	
The use of antimicrobial agents for dirty procedures or established infection is classified as treatment of presumed infection, not prophylaxis. The treatment is excluded from this form. ***Consider adding a single dose of gentamicin 5 mg/kg IV if your hospital is facing gram negative bacterial surgical site infection according to local hospital antibiogram.** *For procedures lasting more than 4 hours, or for procedures with more than 1,500 mL blood loss, repeat dose of Cefazolin every 4 hours OR Clindamycin every 6 hours as an alternative agent (in case of allergy or preferred regimen not available)	
Gastroduodenal **Procedures involving entry into the lumen of gastrointestinal tract (bariatric, pancreaticoduodenectomy)** **Procedures without entry into gastrointestinal tract (antireflux, highly selective vagotomy) for high-risk patients** **Laparoscopic procedure: Elective, high risk** **Appendectomy for uncomplicated appendicitis** **Colorectal** **Biliary tract: open procedure** **Small intestine: Non-obstructed or obstructed**	
Preferred regimen: • Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30mg/kg) IV single dose + ***For appendectomy, obstructed small intestinal and colorectal add***	***Alternative agents:*** • Clindamycin 900 mg (children dose: 10 mg/kg) IV within 60 minutes + Ciprofloxacin 400 mg IV (children dose: 10 mg/kg)

• Metronidazole 500 mg (children dose: 15 mg/kg) IV single dose within 60 minutes prior to incision	single dose within 120 minutes prior to incision ***Obstructed small intestinal:*** • Metronidazole 500 mg (children dose: 15 mg/kg) IV single dose within 60 minutes prior to incision + Ciprofloxacin 400 mg IV (children dose: 10 mg/kg) single dose within 120 minutes prior to incision

***Cardiac*:**

- Screen patients for MRSA nasal carriage, if positive eradicate with nasal mupirocin & chlorhexidine body wash for 5 days.
- Coronary artery bypass, Cardiac device insertion procedures (e.g., pacemaker implantation and Ventricular assist devices.

Thoracic

- Noncardiac procedures, including lobectomy, pneumonectomy, lung resection, and thoracotomy.
- Video-assisted thoracoscopic surgery.

Preferred regimen:	***Alternative agents:***
• Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	• Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose within 60 minutes prior to incision • Vancomycin 15 mg/kg (max.2 g) (children dose: 15 mg/kg) IV single dose within 120 minutes prior to incision

Cesarean delivery

Vaginal or abdominal hysterectomy/other obstetric procedure

Preferred regimen:	***Alternative agents:***
• Cefazolin 2 g (if weight ≥120 kg: 3g) IV single dose within 60 minutes prior to incision	• Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose + Gentamicin 5 mg/kg (children dose: 2.5 mg/kg) single dose within 60 minutes prior to incision

Head/ neck

Clean cut procedures: none	
Clean with prosthesis: **(excluding tympanostomy tubes)** ***Preferred regimen:*** • Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	***Clean with prosthesis***: (excludes tympanostomy tubes) ***Alternative agents:*** • Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose within 60 minutes prior to incision
Clean – contaminated: **(cancer or other procedure with exception of tonsillectomy and functional endoscopic sinus procedure)** ***Preferred regimen:*** • Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30mg/kg) IV single dose + Metronidazole 500 mg (children dose:15 mg/kg) IV single dose within 60 minutes prior to incision.	***Clean – contaminated***: (cancer or other procedure with exception of tonsillectomy and functional endoscopic sinus procedure) ***Alternative:*** • Clindamycin 900 mg (children dose: 10mg/kg) IV single dose within 60 minutes prior to incision
Urology	
Preferred regimen: ***Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)*** ***Clean without entry into urinary tract:*** • Cefazolin 2 g (if weight≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision ***Involving implanted prosthesis.*** ***Clean with entry into urinary tract:*** • **Cefazolin 2 g (if weight≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision ± Gentamicin 5 mg/kg (children dose: 2.5 mg/kg) single dose within 60 minutes prior to incision** ***Clean-contaminated:***	***Alternative agents:*** ***Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)*** ***Clean with entry into urinary tract*** ***Clean-contaminated:*** • Ciprofloxacin 400mg (children dose: 10mg/kg) IV single dose within 120 minutes prior to incision ***Clean without entry into urinary tract:*** • Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose within 60 minutes prior to incision • Vancomycin 15 mg/kg (max.2 g) (children dose: 15 mg/kg) IV single dose within 120 minutes prior to incision

• Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose + Metronidazole 500 mg (children dose: 15 mg/kg) IV single dose within 60 minutes prior to incision	***Involving implanted prosthesis:*** • Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose ± gentamicin 5 mg/kg (children dose: 2.5 mg/kg) single dose within 60 minutes prior to incision

Neurosurgery:

Elective craniotomy and cerebrospinal fluid-shunting Procedures

Implantation of intrathecal pumps

***Preferred regimen*:** • Cefazolin 2 g (if weight≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	***Alternative agents***: • Clindamycin 900 mg (children dose: 10 mg/kg) IV single dose within 60 minutes prior to incision ***If MRSA colonization is present:*** • Vancomycin 15 mg/kg (max.2g) (children dose:15 mg/kg) IV single dose within 120 minutes prior to incision

Orthopedic: ***Screen patients for MRSA nasal carriage, if positive eradicate with nasal mupirocin & chlorhexidine body wash for 5 days.**

***Clean operations: hand, knee or foot not involving implantation of foreign materials: none**

Spinal procedures with and without instrumentation

Hip fracture repair.

Implantation of internal fixation devices (e.g., nails, screws, plates, wires)

Total joint replacement

Preferred regimen: • Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	***Alternative agents:*** • Clindamycin 900 mg (children dose: 10 mg/kg) IV for single dose within 60 minutes prior to incision • Vancomycin 15 mg/kg (max.2g) (children dose:15 mg/kg) IV single dose within 120 minutes prior to incision

Vascular

Hernioplasty or herniorrhaphy

MESH Placement

Preferred regimen:	***Alternative***:
• Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	• Clindamycin 900 mg (children dose: 10 mg/kg) IV for single dose within 60 minutes prior to incision. • Vancomycin 15 mg/kg (max.2g) (children dose:15mg/kg) IV single dose within 120 minutes prior to incision

Ophthalmic

- **Topical Moxifloxacin 1 drop every 5–15 minutes for 5 doses.**

Addition of: (OPTIONAL)

- Cefazolin 100 mg by subconjunctival injection OR
- Cefazolin 1–2.5 mg Intracameral

Liver transplantation

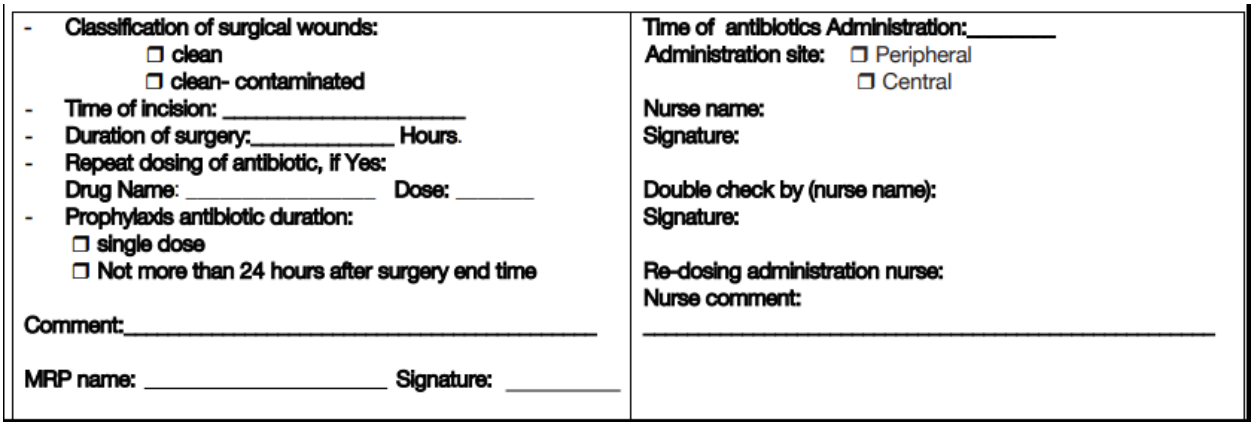
Preferred regimen:	***Alternative:***
• Piperacillin–tazobactam 3.375 g (children > 9 months and ≤ 40 kg: 100mg/kg of penicillin component) IV single dose within 60 minutes prior to incision	• Clindamycin 900 mg (children dose: 10 mg/kg) IV for single dose within 60 minutes prior to incision + Ciprofloxacin 400 mg IV (children dose: 10 mg/kg) single dose within 120 minutes prior to incision • Vancomycin 15 mg/kg (max.2g) (children dose:15mg/kg) IV single dose within 120 minutes prior to incision ++ Ciprofloxacin 400 mg IV (children dose: 10 mg/kg) single dose within 120 minutes prior to incision

Pancreas and pancreas–kidney transplantation

Preferred regimen:	***Alternative***:
• Cefazolin 2 g (if weight ≥120 kg: 3 g) (children dose: 30 mg/kg) IV single dose within 60 minutes prior to incision	• Clindamycin 900 mg (children dose: 10 mg/kg) IV for single dose within 60 minutes prior to incision + Ciprofloxacin 400 mg

	IV (children dose: 10 mg/kg) single dose within 120 minutes prior to incision • Vancomycin 15 mg/kg (max.2g) (children dose: 15mg/kg) IV single dose within 120 minutes prior to incision ++ Ciprofloxacin 400 mg IV (children dose: 10 mg/kg) single dose within 120 minutes prior to incision
Post-operative duration of antimicrobial prophylaxis should be limited to less than 24 hours from surgery end time, regardless of the presence of indwelling catheters, drains or prosthesis.	

The following figure provides a sample documentation form to fill from the Saudi Ministry of Health on the antimicrobial prophylaxis administered to the patient, based on the classification of surgical wound:



- **Classification of surgical wounds:**
  - ❒ clean
  - ❒ clean- contaminated
- **Time of incision:** _____
- **Duration of surgery:**_____ **Hours.**
- **Repeat dosing of antibiotic, if Yes:**
  Drug Name: _____ **Dose:** _____
- **Prophylaxis antibiotic duration:**
  - ❒ single dose
  - ❒ Not more than 24 hours after surgery end time

Comment:_____

MRP name: _____ **Signature:** _____

Time of antibiotics Administration:_____
Administration site: ❒ Peripheral
❒ Central
Nurse name:
Signature:

Double check by (nurse name):
Signature:

Re-dosing administration nurse:
Nurse comment:
_____

Figure 1. *Antimicrobial prophylaxis documentation (retrieved from the Saudi Ministry of Health 2021 antibiotics surgical prophylaxis protocol)*

1.2 North American Guidelines

1.2.1 Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (2019)

There are no evidence levels of grades of recommendations outlined in this document[4]. The following recommendations are provided by the Stanford Health Care on Surgical Antimicrobial Prophylaxis[4]:

Antibiotic selection: refer to table 4 for appropriate antibiotic choices based on the surgical procedure. Consider adding vancomycin or clindamycin for patients known to be carrying MRSA.

Table 4. Preferred Empiric Agent by Surgical Type

Preferred Empiric Agent by Surgical Type		
	Preferred Agent	Beta-lactam allergy
Cardiac Surgery/ Vascular/ Thoracic	Cefazolin	Vancomycin*
Cardiac Surgery with prosthetic material	Cefazolin + vancomycin	Vancomycin*
Cardiac device insertion (e.g., pacemaker implantation)	Cefazolin	Vancomycin*
Gastroduodenal	Cefazolin	Vancomycin* + gentamicin
Biliary Tract	Cefazolin	Metronidazole + Levofloxacin
Colorectal, appendectomy	Cefazolin + metronidazole	Metronidazole + Levofloxacin
Other general surgery (e.g. hernia repair, breast)	Cefazolin	Vancomycin*
Cesarean delivery	Cefazolin	Clindamycin* + gentamicin
Gynecological (e.g. hysterectomy)	Cefazolin	Clindamycin* + gentamicin
Head & Neck	***Clean (incision through skin):*** Cefazolin ***Clean-contaminated:*** • Ear/sinonasal procedure: Cefazolin • Procedures w/ oral mucosa breach: Cefazolin + Metronidazole ***Contaminated***: Cefazolin + metronidazole	Clindamycin
Neurosurgery	Cefazolin	Vancomycin*
Orthopedics	Cefazolin	Vancomycin*
Plastic Surgery	Cefazolin	Vancomycin*

Urology**: These are empiric recommendations when no pre-op urine culture data is available, or cultures were negative.	Cefazolin ***Open/laparoscopic involving intestine:*** (clean-contaminated, e.g., radical cystectomy with ileal conduit): Cefoxitin If prosthetic material involved in urologic procedures, should add one-time dose of gentamicin.	Gentamicin**[a] + Clindamycin**[b] ***Open/laparoscopic*** (clean skin incision, does not involve GU tract): Clindamycin**[b]. ***Open/laparoscopic involving intestine:*** (clean-contaminated, e.g., radical cystectomy with ileal conduit): Metronidazole + Levofloxacin If prosthetic material involved in urologic procedures, should add one-time dose of gentamicin if not already given.
Heart Transplant	Vancomycin + cefazolin ***	Vancomycin + levofloxacin ***
Lung or Heart-Lung Transplant	Vancomycin + cefepime ***	Vancomycin + aztreonam ***
Liver Transplant	Piperacillin/tazobactam***	Vancomycin* or clindamycin + ciprofloxacin***

* Clindamycin can be used as an alternative to vancomycin. Clindamycin and vancomycin are recommended alternative agents to cefazolin for patients with beta-lactam allergies. According to SHC 2018 hospital-wide antibiogram, 79% of MSSA isolates were susceptible to clindamycin, while 100% were susceptible to vancomycin. If practical, we recommend vancomycin as the preferred choice for those with beta-lactam allergies.

**Urology notes:

**a: Ciprofloxacin is a reasonable alternative. However, according to the 2018 SHC antibiogram, more E. coli isolates were susceptible to aminoglycosides than fluoroquinolones.

**b: If there is a significant concern for MRSA, vancomycin should be considered as an alternative to clindamycin. According to the SHC 2018 hospital wide antibiogram, only 55% of MRSA isolates are susceptible to clindamycin, while 100% were susceptible to vancomycin. In addition, clindamycin has limited urinary penetration. However, vancomycin infusion should be started 60-120 minutes prior to incision to allow for complete drug administration.

***In patients with documented infections prior to surgery, prophylaxis should be directed at causative pathogens; consult ID.

Antibiotic dosage: table 5 details dosing and re-dosing recommendations. We advocate for weight-based dosing of cefazolin and vancomycin. Administer cefazolin every 4 hours, clindamycin every 8 hours, and note that vancomycin does not require re-dosing due to its long half-life. It is suggested to consider earlier re-dosing than indicated in cases of excessive intra-operative blood loss (>1500 mL). Aminoglycosides and vancomycin should not be re-dosed in such situations.

Table 5. Dosing and Re-Dosing of Antimicrobial Agents

Dosing and re-dosing of antimicrobial agents			
Antimicrobial	**Recommended Dose**	**Re-dosing (hours)**	**Notes**
Commonly used			
Cefazolin	2 grams > 120 kg = 3 grams	4	
Clindamycin	900 mg	6	
Vancomycin	< 80 kg = 1 gram 80 – 99 kg = 1.25 grams 100 -120 kg = 1.5 grams >120 kg = 2 grams	12	Requires prolonged infusion time, can be given 60-120 minutes prior to incision
Other			
Ampicillin-sulbactam	3 grams	2	
Aztreonam	2 grams	4	
Cefepime	2 grams	4	Renal insufficiency: contact OR pharmacy
Cefotetan	2 grams	6	
Cefoxitin	2 grams	2	
Ceftriaxone	2 grams	N/A	
Cefuroxime	1.5 grams	4	
Ciprofloxacin	400 mg	8	Requires prolonged infusion time, can be given 60-120 minutes prior to incision
Ertapenem	1 gram	N/A	

Gentamicin	5 mg/kg (single dose) If CrCl <20, 2mg/kg (single dose) or consult pharmacy	N/A	
Levofloxacin	500 mg; 750mg if lung transplant	N/A	Requires prolonged infusion time, can be given 60-120 minutes prior to incision
Metronidazole	500 mg	12	
Piperacillin-tazobactam	3.375 grams	2	Renal insufficiency: contact OR pharmacy
Tobramycin	5 mg/kg (single dose) If CrCl <20, 2mg/kg (single dose) or consult pharmacy	N/A	

Timing of pre-operative antibiotics: current guidelines advise administering pre-operative antibiotics <60 minutes before incision. Although recent data supports the efficacy of antibiotics given <30 minutes prior to incision, the guidelines have not revised the timeframe. It is crucial for pre-operative antibiotics to achieve effective tissue concentrations before incision, with a suggested optimal window of ~15–45 minutes before incision. For vancomycin and fluoroquinolones, which require prolonged infusion times, it is recommended to start vancomycin infusion 60-120 minutes before incision due to its long half-life.

Duration of post-operative antibiotics: all patients are suggested to receive < 24 hours of post-operative antibiotics. In numerous procedures, no doses after incision closure are deemed necessary.

Table 6. Post-Operative Dosing

Post-operative dosing	
Antimicrobial	**Recommended Dose** (Many procedures require no post-op doses of antimicrobials. If desired, limit duration to <24 hours post closure.) Refer to solid organ transplant protocols if applicable

Cefazolin	2 grams q8h up to 2 doses or see Transplant Protocols if applicable
Clindamycin	900 mg q8h up to 2 doses
Vancomycin	1 grams q12h up to 1 dose or see Transplant Protocols if applicable
Ampicillin-sulbactam	3 grams q6h up to 3 doses
Aztreonam	2 grams q8h up to 2 doses
Cefepime	Lung transplant: 2g q8h extended infusion (see Transplant Manual for duration)
Cefotetan	2 grams q12h up to 1 dose
Cefoxitin	2 grams q6h up to 3 doses
Ceftriaxone	No post-op doses needed (q24h hour dosing)
Cefuroxime	1.5 grams q8h up to 2 doses
Ciprofloxacin	400 mg q12h up to 1 dose
Gentamicin	No post-op doses needed (q24h hour dosing)
Levofloxacin	No post-op doses needed (q24h hour dosing)
Metronidazole	500 mg q8h up to 2 doses
Piperacillin-tazobactam	3.375g q8h extended infusion up to 2 doses or see Transplant Protocols if applicable
Tobramycin	No post-op doses needed (q24h hour dosing)

1.2.2 Surgical Site Infections: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (2019)

These guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of post-operative SSIs in solid organ transplantation (SOT). The recommendations following the GRADE methodology outlined in Appendix B[5].

- Risk Factors and Preventive Strategies:
    - Transplant centers should assess local prevalence of S. aureus colonization and SSIs and customize nasal decolonization based on individual population risk. In some centers, the heart and lung transplant population might be at higher risk than kidney or pancreas recipients although in other centers, all trans- plant patients might be at increased risk based on the local prevalence of MRSA in the community or the local hospital (strong, moderate).

- Recommended Peri-Operative Antibiotic Prophylaxis for Solid Organ Transplant Recipients by Organ:
    - Renal transplantation
        - First-generation cephalosporin recommended for ≤24 hours (strong, low).
        - For patients colonized with a resistant organism, use a third-generation cephalosporin or alternative agent passed on individual susceptibilities and local formulary for ≤24 hours (strong, low).
        - Patients with severe cephalosporin allergy should use alternative agents such as a fluoroquinolone or aztreonam (weak, low).
        - If the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).
- Pancreas and pancreas-kidney transplantation:
    - Ampicillin-sulbactam for ≤48 hours and a single dose of fluconazole are recommended. Longer durations of fluconazole is recommended for patients with specific risk factors for fungal infection from 7 to up to 14 days (strong, low).
    - If the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target specific pathogens based on the current infection and individual risk factors (strong, moderate).
- Liver transplantation
    - Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam recommended for up to 24 hours (strong, low).
    - Another alternative would be ampicillin-sulbactam or in countries were available intravenously amoxicillin-clavulanate for ≤48 hours; antifungals may be considered based on individual patient risk. (strong, high).
    - The use of selective bowel decontamination prior to liver transplantation is not recommended (strong, low).
    - The use of probiotics is not recommended (strong, low).
    - If the patient is being treated for an active infection at the time of organ transplantation, the antibiotic regimen should be altered to target

specific pathogens based on the current infection and individual risk factors (strong, moderate).

- Intestinal and multivisceral transplantation
    - We recommend using of one of the following regimens (strong, low):
        - vancomycin, cefepime, metronidazole, and fluconazole or
        - vancomycin, piperacillin-tazobactam, and fluconazole or an echinocandin in cases of fluconazole resistance.
    - Typically, antibiotic prophylaxis is advised to be maintained for 48 to 72 hours in most cases. It is strongly recommended to continue prophylaxis until peri-operative complications such as pancreatitis, anastomotic leak, or fistula contaminations have been surgically addressed or resolved (strong, low).
    - In cases where a patient is undergoing organ transplantation while being treated for an active infection, we strongly recommend modifying the antibiotic regimen. The adjustment should be tailored to target specific pathogens based on the ongoing infection and individual risk factors (strong, moderate).
- Heart Transplantation:
    - First-generation cephalosporin alone recommended for up to 24 hours (strong, moderate).
    - For MRSA-colonized patients, use vancomycin plus a first-generation cephalosporin for up to 48 hours (weak, low).
    - Customize antibiotic regimen for patients with active infections at the time of transplantation (strong, moderate).
    - Special Considerations in Heart Transplantation:
        - For patients on VAD suppressive antibiotics, continue post-transplant based on infection severity.
        - Include coverage for prior VAD infection in the peri-operative antibiotic regimen (strong, moderate). Longer duration of prophylaxis is recommended according to the type and severity of pre-HT infection.
        - After explant of the VAD at the time of heart transplant, antimicrobials should be continued in the immediate post-transplant period, with the length of therapy dependent on the severity of infection (strong, very low).

        - If there is no history of VAD infection, we recommend using the standard regimen for heart transplant surgical prophylaxis (strong, moderate).
    - ECMO Bridge to Heart Transplant:
        - Use standard peri-operative prophylaxis if no evidence of active infection or colonization in the ECMO circuit (strong, low).
        - Cover infecting/colonizing organisms if evidence of ECMO circuit infection or colonization (strong, moderate).
        - In individuals with an open chest post-heart transplant, a notable infection risk factor, we advocate customizing peri-operative prophylaxis. This customization should consider individual patient factors, the specific scenario, and the timing of chest closure. The aim is to assess whether an extended duration of antimicrobial therapy is warranted, emphasizing the importance of such individualized approaches (strong, low).
- Lung transplantation
    - It is advised to employ a combination of vancomycin and an anti-Pseudomonal beta-lactam for a duration of 48 to 72 hours (weak, low).
    - If a patient is undergoing organ transplantation while currently being treated for an active infection, we strongly recommend adjusting the antibiotic regimen. This adjustment should be tailored to address specific pathogens based on the ongoing infection and individual risk factors (strong, moderate).
- Customization of Antibiotics based on Unique Circumstances and Recipient and Donor Colonization/ Infection:
    - In individuals experiencing delayed chest closure, it is advisable to adhere to the initial surgical prophylaxis regimen for cardiac or lung transplant. It is recommended to refrain from employing broad-spectrum antibiotics unnecessarily unless clear evidence of an active infection is present (weak, low).
    - Pulmonary pre-transplant colonization:
        - In transplant centers situated in endemic regions with a high incidence of organ transplants in high-risk patients, we suggest a pre-transplant assessment of donor and recipient colonization/infection (weak, low). Given the escalating cases of infections and MDRO colonization, it may be suitable to conduct surveillance of respiratory and rectal anatomical sites in organ

recipients prone to colonization (e.g., those from endemic areas for MDROs or with prior exposure to prolonged or broad-spectrum antibiotics). Infection prevention strategies and targeted antimicrobial stewardship for prophylaxis and treatment should be personalized to each patient and case scenario (weak, low).

- For recipients with an active or previously treated infection or known colonization by multidrug-resistant organisms (e.g., carbapenem-resistant or carbapenemase-producing Gram-negative organisms), we strongly recommend pre- and post-transplant consultation with transplant infectious disease specialists. This facilitates the selection of the most appropriate regimen and duration on an individualized basis (strong, low).
- If a transplant recipient is undergoing treatment for a prior active infection, it is strongly recommended that this treatment be sustained both in the operating room and post-operatively as originally planned (strong, moderate).

- Superficial Incisional SSIS
  - We advise the use of systemic antibiotic treatment following antimicrobial stewardship principles. Adjust the duration based on the individual patient's clinical response (strong, low).
  - Commence empiric treatment with broad-spectrum antibiotics. Ensure coverage for Gram-positive cocci from the skin and anticipated flora at the operation site. Consider local epidemiology, transplant type, colonization status, patient risk factors for challenging pathogens, clinical severity, infection source, and recent infections (Strong, low).
  - Consider first-generation cephalosporin or anti-staphylococcal penicillin for MSSA. Opt for an active antibiotic agent (e.g., vancomycin) in the presence of high MRSA risk factors (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics) (strong, low).
  - Prescribe broad-spectrum agents if the patient exhibits risk factors for MDROs. These factors include pre-transplant colonization, peri-operative prophylaxis, prolonged tracheal intubation, long-term hospitalization, urologic manipulation, kidney-pancreas transplantation, renal replacement therapy post-transplant, post-transplant urinary obstruction, and recurrent UTI (strong, low).
  - Tailor definitive antimicrobial treatment based on the patient's clinical response. Consider Gram stain, wound culture, and sensitivity results (strong, moderate).

    - The role of topical antibiotics and additional agents, such as antiseptics (hydrogen peroxide, povidone-iodine), in managing infected wounds is uncertain and should be avoided (strong, low).

- Deep Incisional SSIS
    - In cases of moderate to severe surgical site infections (SSIs), which may exhibit features like systemic toxicity, significant cellulitis (>2 cm beyond the incision), purulent drainage, fascial dehiscence, and deep drainage, it is recommended to administer antibiotics empirically along with surgical intervention. The initial empirical selection of antibiotics should adhere to the criteria outlined for superficial SSIs (strong, low).
- Organ/Space
    - Source control is crucial for organ/space SSIs, such as mediastinitis, empyema, and intra-abdominal abscess. This necessitates either percutaneous or operative drainage (strong, high). The initial selection of empiric antibiotics in these cases should align with the criteria established for superficial SSIs (strong, low).

The following table provides the recommendations for peri-operative antibiotics by organ transplant type:

Table 7. Recommendations for Peri-Operative Antibiotics by Organ Transplant Type

Organ type	IDSA/ASHP/ SIS/SHEA guidelines	An alternative approach	Intra-op re-dosing	Post-op dosing	PCN-allergic	Duration post-op
Renal	Single first-generation cephalosporin (e.g., cefazolin	Cefazolin 2 g IV	Every 4 h	Cefazolin 2 g q8h	Vancomycin* or clindamycin 900 mg IV plus gentamicin 5 mg/kg IV	≤24 h
Pancreas, pancreas-kidney	Single first-generation cephalosporin (e.g., cefazolin)	Ampicillin-sulbactam 3 g IV plus, fluconazole 400 mg IV	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	Vancomycin* or clindamycin 900 mg IV plus gentamicin 5 mg/kg IV and fluconazole 400 mg IV	Antibacterial ≤48 h, Antifungal ×1 dose, unless high risk in which case ≤14 d
Liver	Third generation cephalosporin plus ampicillin or piperacillin-tazobactam alone	Ampicillin-sulbactam 3g IV ± fluconazole 400 mg IV × 1 or echinocandin or liposomal amphotericin B if high risk for invasive fungal	Every 2 h (fluconazole not re-dosed)	Ampicillin-sulbactam 1.5 g q6h	or echinocandin or liposomal amphotericin B if high risk for invasive fungal infection (duration depends on the individual risk)	and antifungal agent and duration depends on the individual risk

			infection (duration depends on the individual risk)				
Intestinal/ multivisceral		None given	Vancomycin* plus cefepime 2 g IV plus metronidazole 500 mg IV plus fluconazole 400 mg IV or vancomycin* plus, piperacillin-tazobactam 4.5 g IV plus fluconazole 400 mg IV	Every 4 h (fluconazole not re-dosed)	Cefepime 2 g q8h, metronidazole 500 mg q8h, fluconazole 400 mg q24h, piperacillin-tazobactam 4.5 g q6h, Vancomycin per weight/ GFR*	Vancomycin* plus levofloxacin 750 mg IV plus metronidazole 500 mg IV	≤72 h; if infected mesh or fistulas, then extend to 7 d
Heart	With prior VAD	Single first-generation cephalosporin (e.g., cefazolin)	Vancomycin* plus either ceftriaxone 1 g IV or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/ GFR*	Vancomycin* plus levofloxacin 750 mg IV q24h	≤48 h
	Without prior VAD	Single first-generation cephalosporin (e.g., cefazolin)	Vancomycin* plus cefazolin 2 g IV	Every 4 h	Cefazolin 1 g q8h, Vancomycin per weight/ GFR*	Vancomycin* plus levofloxacin 750 mg IV q24h	≤48 h

Lung		Single first-generation cephalosporin (e.g., cefazolin)	Vancomycin* plus third-generation cephalosporin or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/ GFR*	Vancomycin* plus levofloxacin 750 mg IV q24h	≤72 h

All dosing regimens should be modified based on the patient's renal and liver function.

*Vancomycin doses should be calculated based on the patient's weight and renal function.

1.2.3 Centers for Disease Control and Prevention (CDC) Guideline for the Prevention of Surgical Site Infection (2017)

This guideline published by the CDC in 2017 is intended to provide new and updated evidence-based recommendations for the prevention of SSI and should be incorporated into comprehensive surgical quality improvement programs to improve patient safety. Evidence levels and grades of recommendations are outlined in the table below[6]:

Table 8. CDC Recommendation Categories

Recommendation Categories	
Category IA	A strong recommendation supported by high to moderate–quality evidence suggesting net clinical benefits or harm.
Category IB	A strong recommendation supported by low-quality evidence suggesting net clinical benefits or harms or an accepted practice (e.g., aseptic technique) supported by low to very low–quality evidence.
Category IC	A strong recommendation required by state or federal regulation.
Category II	A weak recommendation supported by any quality evidence suggesting a trade-off between clinical benefits and harms.
No recommendation/ unresolved issue	An issue for which there is low to very low–quality evidence with uncertain trade-offs between the benefits and harms or no published evidence on outcomes deemed critical to weighing the risks and benefits of a given intervention.

The following recommendations are provided by the Centers for Disease Control and Prevention on the Prevention of Surgical Site Infection:

- Parenteral Antimicrobial Prophylaxis
    - Administer preoperative antimicrobial agents only when indicated based on published clinical practice guidelines. Time their administration to establish bactericidal concentration in the serum and tissues at incision (Category IB–strong recommendation; accepted practice).

- No further refinement of timing is recommended based on clinical outcomes (No recommendation/unresolved issue).
- Administer appropriate parenteral prophylactic antimicrobial agents before skin incision in all cesarean section procedures (Category IA–strong recommendation; high-quality evidence).
- No randomized controlled trials found to evaluate benefits and harms of weight-adjusted parenteral antimicrobial prophylaxis dosing (No recommendation/unresolved issue).
- Insufficient randomized controlled trial evidence to evaluate benefits and harms of intraoperative redosing of prophylactic antimicrobial agents (No recommendation/unresolved issue).
- In clean and clean-contaminated procedures, do not administer additional prophylactic antimicrobial doses after surgical incision closure, even with a drain (Category IA–strong recommendation; high-quality evidence).

- Non-parenteral Antimicrobial Prophylaxis
  - Uncertain trade-offs for intraoperative antimicrobial irrigation and soaking prosthetic devices (No recommendation/unresolved issue).
  - Do not apply antimicrobial agents to the surgical incision (Category IB–strong recommendation; low-quality evidence).
  - Autologous platelet-rich plasma not necessary to prevent SSI (Category II–weak recommendation; moderate-quality evidence).
  - Consider triclosan-coated sutures with trade-offs between benefits and harms (Category II–weak recommendation; moderate-quality evidence).
  - Randomized controlled trial evidence suggested uncertain trade-offs between the benefits and harms regarding antimicrobial dressings applied to surgical incisions after primary closure in the operating room for the prevention of SSI. (No recommendation/ unresolved issue.)

1.2.4 University of Toronto's Best Practice in Surgery (BPS) Clinical Practice Guideline for Surgical Site Infection Prevention (2017)

The recommendations following the GRADE methodology outlined in Appendix B[7].

The following recommendations are provided by the University of Toronto on Surgical Site Infection prevention:

- Antibiotic Use:
    - Surgical patients universally should be administered appropriate prophylactic antibiotics, excluding specific clean surgical procedures (refer to table below) (Level of evidence: High).
    - Patients reporting antibiotic allergies must undergo an allergy history to identify the causative antibiotic and specify the reaction type. For penicillin cross-reactions, an alternative to beta-lactams is warranted only in cases of severe/anaphylactic reactions (e.g., hives, hypotension, respiratory difficulties) (Level of evidence: Moderate).

Table 9. Procedure Specific Recommended Agents and Duration

Procedure Specific Recommended Agents and Duration		
Division	**Recommended Agents**	**B-lactam allergy Recommended Agents**
	Cardiac	
Coronary artery bypass (CABG), valve replacement (+/- CABG), other cardiac procedures	Cefazolin	Vancomycin
Ventricular assist devices, Device insertion (e.g. pacemaker)	Cefazolin	Vancomycin
Cardiac catheterization, Transesophageal echocardiogram	None	None
	General	
Gastroduodenal/esophageal/ distal pancreatic resection	Cefazolin	Vancomycin + Aminoglycoside
Percutaneous endoscopic gastrostomy (PEG)	Cefazolin	Vancomycin + Aminoglycoside
Biliary tract- laparoscopic procedure- Elective low risk	None	None
Biliary tract- laparoscopic procedure – High risk emergency, inserting prosthetic device, diabetes, risk of intraoperative	Cefazolin	Vancomycin + Aminoglycoside

gallbladder rupture/conversion to open, age >70 years, ASA ≥3, reintervention within 1-month, acute cholecystitis, obstructive jaundice, CBD stones, nonfunctional GB, pregnancy, immunosuppression. Biliary tract- open procedure Liver resection		
Colorectal, small bowel, appendectomy Pancreaticoduodenectomy	Cefazolin + Metronidazole If Risk of Gram-Negative Resistance: Add Aminoglycoside	Vancomycin + Aminoglycoside + Metronidazole
Hernia repair- Hernioplasty, herniorrhaphy	Cefazolin	Vancomycin
Low risk anorectal procedures: hemorrhoidectomy, fistulotomy, sphincterotomy	None	None
Thoracic		
Non-cardiac procedures (e.g. lobectomy, pneumonectomy, lung resection, and thoracotomy) Video-assisted thorascopic surgery	Cefazolin	Vancomycin
Thoracentesis or chest tube insertion for non-traumatic indications (e.g. spontaneous pneumothorax) Mediastinoscopy	None	None
Head and Neck		
Clean: no incision through oral/nasal/pharyngeal mucosa (e.g. parotidectomy, thyroidectomy, and	None	None

submandibular gland excision)		
Clean with placement of prosthetic material (excludes tympanostomy tubes)	Cefazolin	Vancomycin + Metronidazole
Clean-contaminated (incision through oral/pharyngeal mucosa): cancer surgery and other clean-contaminated procedures with the exception of tonsillectomy and functional endoscopic sinus procedures	Cefazolin + Metronidazole	Vancomycin + Aminoglycoside + Metronidazole
Neurosurgery		
Elective craniotomy, stereotactic brain biopsy, cerebrospinal fluid-shunting procedures, ICP monitor, external ventricular drain, and implantation of intrathecal pumps	Cefazolin	Vancomycin
Endoscopic transsphenoidal neurosurgery	Cefazolin	Vancomycin + Aminoglycoside (There is minimal data for the best regimen in such patients)
Orthopedic		
Arthroscopy without graft implantation	None	None
Spinal procedures with and without instrumentation, hip fracture repair, Implantation of internal fixation devices (e.g., nails, screws, plates, wires) and total joint replacement	Cefazolin	Vancomycin If emergent surgery precludes the infusion time for vancomycin, clindamycin may be used instead
Urologic		
Prior to stone removal or invasive procedures involving mucosal bleeding/ trauma, obtain urine sample and treat based on culture and sensitivity result.		
Cystoscopy/Shock wave lithotripsy	None	

· no risk factors		
Cystoscopy/Shock wave lithotripsy: • Risk factors: advanced age, immunocompromised, large stone burden, history of pyelonephritis/ infected stone, prolonged catheterization, nephrostomy tubes	If no hospitalization in last year, recent antibiotic use from the class, or other risks for resistance: ciprofloxacin 500mg PO or cefazolin (if no beta-lactam allergy)	
• **Manipulation: Prostatectomy, biopsy, foreign body removal, urethral dilation, stent placement/removal** **Ureteroscopy** **Percutaneous nephrolithotomy** Transrectal prostate biopsy	If risk of Gram-negative resistance: aminoglycoside or Ceftriaxone 1g (if no beta-lactam allergy)	
Percutaneous renal surgery	Cefazolin	Vancomycin
Open or Laparoscopic: **without entry into bowel/vagina** involving manipulation of bowel/vagina	Cefazolin	Vancomycin + Aminoglycoside
	Cefazolin + Metronidazole	Vancomycin + Aminoglycoside + Metronidazole
Vascular		
Brachiocephalic procedures and carotid endarterectomy without prosthetic material Angiography, angioplasty, thrombolysis, vascular stenting	None	None
Arterial surgery Graft placement or repair	Cefazolin	Vancomycin
Plastics		
Clean without risk factors (not breast surgery)	None	None
Clean - high risk • **prosthetic material, skin irradiation, traumatic/crush hand injuries, flap reconstruction, panniculectomy,**	Cefazolin	Vancomycin

injuries requiring amputation/reconstructive limb surgery, injuries involving bone, joint, tendon (except open flexor tendon injuries) or nerve. Clean-contaminated		
Breast surgery	Cefazolin	Vancomycin
Ophthalmic		
	<u>1 drop every 5-15 min for 5 doses:</u> Topical neomycin-polymyxin B-gramicidin or Gatifloxacin or moxifloxacin Optional to add at the end of the procedure: subconjunctival injection cefazolin 100mg or intracameral cefazolin 1-2.5mg or cefuroxime 1 mg	
Obstetrical/Gynecological		
Caesarean section	Cefazolin	Aminoglycoside + Vancomycin
Hysterectomy	Cefazolin	Vancomycin + Aminoglycoside
Therapeutic termination of pregnancy	Doxycycline 100 mg PO 1 hour before procedure, then 200 mg PO post-procedure	

- Antibiotics should be administered to achieve optimal tissue concentrations (refer to table below) (Level of evidence: Moderate).

Table 10. Recommended Dosing and Redosing of Agents for Antimicrobial Prophylaxis

Recommended dosing and re-dosing of antimicrobial prophylaxis			
Agent	**Adult dose**	**Pediatric dose (max dose should not exceed the**	**Intra-operative re-dosing (from initiation of pre-op dose)**

		recommended adult dose)		
Cefazolin	2 g 3 g if weight ≥ 120kg	30mg/kg IV (max dose: 2g)	q4hrs (Max 6g/24hrs) If CrCl < 30 mL/min: q12h Neonates: 6hours	Or Redose antibiotic if intra-op blood loss ≥ 1.5 L
Aminoglycoside[a] Gentamicin or Tobramycin	3 mg/kg[a] (round to nearest 20 mg)	2.5 mg/kg	If CrCl ≥ 60 ml/min: q8h If CrCl < 40-60 ml/min: q12h If CrCl < 40: no re-dose Neonates: 6 hours	
Metronidazole	500 mg	15 mg/kg Neonates <1200g: 7.5mg/kg	q12h Neonates: No repeat doses	
Vancomycin[b,c]	15 mg/kg round to nearest 50mg (max 2g/dose) Administer ≤1g over 60min, > 1g-1.5g over 90min > 1.5g over 120min	15 mg/kg (max dose: 1g)	q12 hrs No redose if CrCl < 30 ml/min Pediatrics: 6 hours Neonates: 10 hours	Do not redose with intra-op blood loss

a. dose based on actual body weight (ABW) unless obese. If ABW >20% above ideal body weight (IBW), use Dosing Weight= IBW + 0.4*(ABW – IBW)
IBW Men: 50kg + 2.3kg (x inches above 60in); IBW Women: 45.5kg + 2.3kg (x inches above 60in)

b. **dose should be based on total body weight.**

c. if tourniquet is used, entire dose should be infused prior to inflation

    - Antibiotics must be given within 60 minutes before surgical incision/tourniquet inflation. Vancomycin and fluoroquinolones, requiring a lengthier infusion time, should be initiated to ensure completion within the 60-minute window (Level of evidence: Low-Moderate).
    - Antibiotics should be re-administered if the procedure duration exceeds two half-lives of the antibiotic or in cases of excessive blood loss (>1.5L in adults), excluding vancomycin (Level of evidence: Very low).
    - Postoperative antibiotic administration is discouraged unless there is an indication other than prophylaxis (Level of evidence: High).
    - Patients with indwelling drains or intravascular catheters do not require additional prophylaxis (Level of evidence: Moderate).
    - In patients colonized with MRSA, vancomycin should be incorporated into the regimen (Level of evidence: Moderate).
    - Patients receiving therapeutic antibiotics preoperatively face an elevated risk of surgical site infections. While the optimal prophylaxis method remains unknown, prophylactic antibiotics should be administered unless the therapeutic antibiotic also provides coverage for SSI prophylaxis. Additionally, these antibiotics should be timed to ensure maximal tissue concentration at incision (Level of evidence: Very low).
- Staphylococcus aureus decolonization
    - Consider Staphylococcus aureus screening with a nasal swab and decolonization for carriers with intranasal mupirocin 2% ointment BID and chlorhexidine-gluconate body wash for 5 days before surgery in cardiac surgery and orthopedic/spinal surgery with hardware insertion (Low level of evidence).
    - For MRSA carriers, contemplate decolonization in collaboration with hospital infection control practitioners or infectious disease consultants (Very low level of evidence).
- Special considerations
    - Antimicrobial-coated sutures may be employed to reduce SSIs (Moderate level of evidence).
    - The local application of vancomycin powder in spine surgery is a subject of controversy, and no strong recommendation can be made based on current evidence (Very low level of evidence).

- While antibiotic-impregnated shunts may be beneficial in reducing central nervous system shunt infections, no strong recommendation can be made based on current evidence (Very low level of evidence).
- Endocarditis prophylaxis is necessary only for patients with specific predisposing cardiac conditions before certain dental procedures (Low level of evidence) and manipulation of the respiratory mucosa (Very low level of evidence).

Figure 2 provides an algorithm on identifying allergic reactions to penicillin:

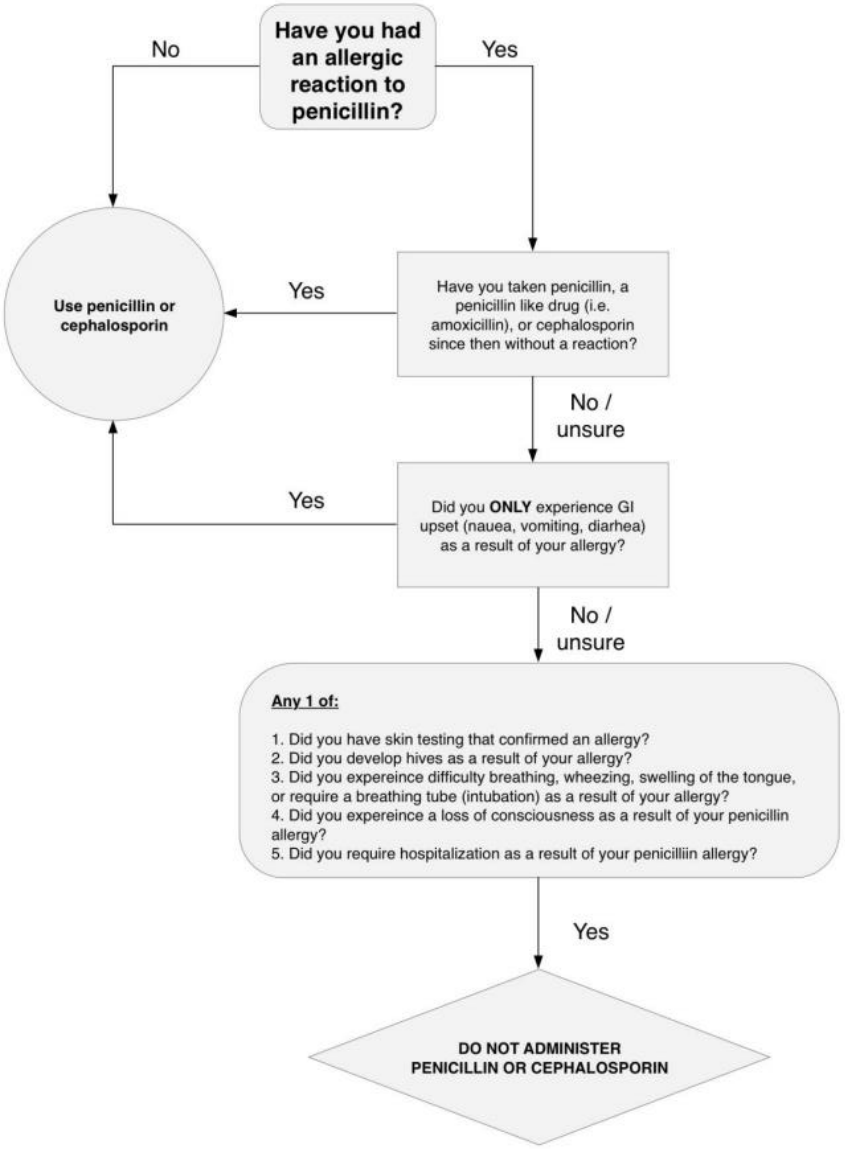


***Figure 2**. Algorithm on identifying allergic reactions to penicillin (retrieved from the University of Toronto 2017 guidelines)*

1.2.5 American Dental Association (ADA) Antibiotic Prophylaxis Prior to Dental Procedures (2022)

No evidence levels or grades of recommendations were outlined[8].

Key Takeaways

- There are currently fewer instances where antibiotic prophylaxis may be necessary before specific dental procedures.
- For individuals with prosthetic joint implants, a January 2015 ADA clinical practice guideline, derived from a 2014 systematic review, advises against routine antibiotic use before dental procedures to prevent prosthetic joint infection.
- The ADA Chairside Guide suggests that for patients with complications related to joint replacement surgery undergoing dental procedures involving gingival manipulation or mucosal incision, the decision to use prophylactic antibiotics should be made in consultation with the patient and orthopedic surgeon. If deemed necessary, the orthopedic surgeon is best positioned to recommend the appropriate antibiotic regimen and, if feasible, prescribe it.
- Regarding infective endocarditis prophylaxis, updated 2021 American Heart Association guidelines advocate premedication for a specific subset of patients, considering scientific evidence that highlights the greater risk of adverse antibiotic reactions compared to the benefits of prophylaxis for many individuals previously eligible for it. Concerns about antibiotic resistance also influenced this decision.
- Infective endocarditis prophylaxis for dental procedures is recommended solely for patients with underlying cardiac conditions carrying the highest risk of adverse outcomes from infective endocarditis. For individuals with these cardiac conditions, prophylaxis is advised for all dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa.

Prevention of Prosthetic Joint Infection

Based on a comprehensive evidence review, the 2015 ADA clinical practice guideline emphasizes that, in general, prophylactic antibiotics are not recommended for patients with prosthetic joint implants before dental procedures to prevent prosthetic joint infection.

An accompanying editorial by Meyer similarly affirms that the new CSA guideline explicitly states that, for the majority of patients, prophylactic antibiotics are unnecessary before dental procedures to prevent prosthetic joint infections. The

guideline acknowledges that patients with prior medical conditions or complications related to joint replacement surgery may require premedication. In cases where medically compromised patients undergo dental procedures involving gingival manipulation or mucosal incision, the consideration of prophylactic antibiotics should be made after consultation with both the patient and orthopedic surgeon. For individuals with serious health conditions, such as immunocompromising diseases, it may be suitable for the orthopedic surgeon to recommend an antibiotic regimen as medically indicated, as outlined in the new chair-side guide.

A commentary published in the February 2017 issue of JADA, authored by ADA-appointed experts, provides guidance on utilizing appropriate use criteria published by the American Academy of Orthopedic Surgeons in January 2017. The commentary encourages dentists to adhere to the 2015 guideline, consult the appropriate use criteria when necessary, and consider the patient's specific needs and preferences when contemplating antibiotic prophylaxis before dental treatment.

Prevention of Infective Endocarditis

Patient Selection

The current infective endocarditis/valvular heart disease guidelines state that use of preventive antibiotics before certain dental procedures is reasonable for patients with:

- prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts;
- prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords;
- a history of infective endocarditis;
- a cardiac transplant[a] with valve regurgitation due to a structurally abnormal valve;
- the following congenital (present from birth) heart disease:[b]
- unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
- any repaired congenital heart defect with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or a prosthetic device

[a] *According to limited data, infective endocarditis appears to be more common in heart transplant recipients than in the general population; the risk of infective endocarditis is highest in the first 6 months after transplant because of endothelial disruption, high-*

intensity immunosuppressive therapy, frequent central venous catheter access, and frequent endomyocardial biopsies.[9]

[b] *Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease.*

Pediatric Patients

Congenital heart disease can indicate that prescription of prophylactic antibiotics may be appropriate for children. It is important to note, however, that when antibiotic prophylaxis is called for due to congenital heart concerns, they should only be considered when the patient has:

- Cyanotic congenital heart disease (birth defects with oxygen levels lower than normal), that has not been fully repaired, including children who have had a surgical shunts and conduits.
- A congenital heart defect that's been completely repaired with prosthetic material or a device for the first six months after the repair procedure.
- Repaired congenital heart disease with residual defects, such as persisting leaks or abnormal flow at or adjacent to a prosthetic patch or prosthetic device.

Antibiotic prophylaxis is not recommended for any other form of congenital heart disease.

Antibiotic Recommendations

- Clindamycin is no longer recommended due to potential severe reactions; alternative antibiotics include cephalexin, azithromycin, clarithromycin, doxycycline, cefazolin, and ceftriaxone.
- Cephalosporins should be avoided in individuals with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

Administration and Dosage

- Prophylactic antibiotics should ideally be given before the dental procedure to reach adequate blood levels.
- If inadvertently not administered before the procedure, the dosage may be given up to 2 hours afterward.
- For patients with consecutive appointments requiring prophylaxis, the regimen should be repeated before each appointment.
- Administration and Dosage:

- Prophylactic antibiotics should ideally be given before the dental procedure to reach adequate blood levels.
- If inadvertently not administered before the procedure, the dosage may be given up to 2 hours afterward.
- For patients with consecutive appointments requiring prophylaxis, the regimen should be repeated before each appointment.

Miscellaneous Indications

- Antibiotic prophylaxis is generally not advised unless specific individuals with extenuating circumstances are identified, and the determination is made by the patient's surgeon or treating physician.
- Guidance provided is that antibiotic prophylaxis is generally unnecessary unless the individual is predisposed to infection, in which case the treating physician may consider prescribing antibiotics.
- Specific conditions, such as artificial joint replacement, may prompt consideration for prophylaxis based on individual factors.

1.3 European Guidelines

1.3.1 ESCMID/EUCIC Clinical Practice guidelines on Perioperative Antibiotic Prophylaxis in Patients Colonized by Multidrug-Resistant Gram-Negative Bacteria Before Surgery (2023)

The aim of the guidelines published jointly by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Committee on Infection Control (EUCIC) is to provide recommendations on perioperative antibiotic prophylaxis (PAP) in adult inpatients who are carriers of multidrug-resistant Gram-negative bacteria (MDR-GNB) before surgery. Recommendations follow the GRADE methodology outlined in Appendix B and are summarized below[9]:

- Extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E)
- Recommendation for screening ESCR-E colonization:
    - We recommend conducting rectal screening to identify ESCR-E carriers before colorectal and liver transplant surgery based on local epidemiology (Conditional, Low).
    - It may be considered good clinical practice to screen all solid organ transplant recipients for ESCR-E before surgery based on local epidemiology (Ungraded good practice statement: Expert opinion).

- Recommendation for targeted perioperative antibiotic prophylaxis (PAP) in patients colonized with ESCR-E before surgery:
    - We conditionally recommend targeted PAP for patients colonized with ESCR-E undergoing colorectal surgery (Conditional, Low).
    - We conditionally recommend targeted PAP for patients colonized with ESCR-E undergoing liver transplant surgery (Conditional, Very Low).
    - Considering targeted PAP for all solid organ transplant recipients who are colonized with ESCR-E before surgery may be considered good clinical practice (Ungraded good practice statement: Expert opinion).
- Carbapenem-resistant Enterobacterales (CRE)
- Recommendation for screening CRE colonization:
    - We suggest implementing rectal screening to identify CRE carriers before liver transplant surgery based on local epidemiology (Conditional, Low).
    - It may be considered good clinical practice to screen all solid organ transplant recipients for CRE before surgery based on local epidemiology (Ungraded good practice statement: Expert opinion).
- Recommendation for targeted PAP in patients colonized with CRE before surgery:
    - There is insufficient evidence for or against targeted PAP for patients colonized with CRE before surgery at the time of writing, and therefore, no recommendation can be issued (No recommendation).
- Carbapenem-resistant Acinetobacter baumannii (CRAB)
- Recommendation for screening CRAB colonization:
    - We conditionally recommend implementing rectal screening to identify CRAB carriers before liver transplant surgery based on local epidemiology (Conditional, Low).
    - It might be considered good clinical practice to screen all solid organ transplant recipients for CRAB before surgery based on local epidemiology (Ungraded good practice statement: Expert opinion).
- Recommendation for targeted PAP in patients colonized with CRAB before surgery:
    - There is insufficient evidence for or against targeted PAP for patients colonized with CRAB before surgery at the time of writing, and therefore, no recommendation can be issued (No recommendation).

- Fluoroquinolone-resistant Enterobacterales (FQR-E)
- Recommendation for screening FQR-E colonization in transrectal ultrasound-guided prostate biopsy (TRUSPB):
    - We recommend rectal screening to identify FQR-E carriers before TRUSPB (Conditional, Moderate).
- Recommendation for targeted PAP in patients colonized with FQR-E before TRUSPB:
    - We suggest the use of targeted PAP for patients colonized with FQR-E before TRUSPB (Conditional, Moderate).
- Recommendation for screening MDR-GNB colonization and targeted PAP in other urologic surgery:
    - Insufficient evidence is available at this time to recommend for or against screening to inform targeted PAP for patients colonized with MDR-GNB before urologic surgery (No recommendation).
- MDR-GNB (ESCR-E, CRE, CRAB) colonization before surgery
- Recommendation on timing for preoperative MDR-GNB screening:
    - For MDR-GNB screening, cultures performed within 3 weeks prior to surgery may be considered (Ungraded good practice statement: Expert opinion)
- Recommendation on duration of PAP in patients colonized with MDR-GNB before surgery:
    - PAP should be discontinued within 24 hours after surgery in patients colonized with MDR-GNB (Strong, Moderate).
    - In transplant surgery other than renal transplant, the extension of PAP duration to 48-72 hours may be considered according to the type of transplant (Ungraded good practice statement: Expert opinion).

1.3.2 National Institute for Health and Care Excellence (NICE) Guideline of the Prevention and Treatment of Surgical Site Infections (2020)

Evidence levels and grades on recommendations are outlined in the table below[10]:

Table 11. NICE Grading Scheme for Recommendations

Grading Scheme for Recommendations			
Level	**Type of evidence**	**Grade**	**Evidence**
1	Evidence obtained from a single randomized controlled trial or a meta-analysis of randomized controlled trials	A	At least 1 randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level 1) without extrapolation
2a	Evidence obtained from at least 1 well-designed controlled study without randomization	B	Well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels 2 or 3); or extrapolated from level 1 evidence
2b	Evidence obtained from at least 1 other well-designed quasi-experimental study	–	–
3	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies	–	–
4	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	C	Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level 4) or extrapolated from level 1 or 2 evidence. This grading indicates that directly applicable clinical studies of good quality are absent or not readily available
4	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	GPP	Recommended good practice based on the clinical experience of the GDG.

The following recommendations are provided by NICE on surgical site infections:

- Antibiotic Prophylaxis
    - Administer antibiotic prophylaxis to patients before clean surgery involving prosthesis or implant placement, clean-contaminated surgery, and contaminated surgery.
    - Avoid routine antibiotic prophylaxis for clean non-prosthetic uncomplicated surgery.
    - Use the local antibiotic formulary, considering potential adverse effects when selecting specific antibiotics for prophylaxis.
    - Consider giving a single intravenous dose of antibiotic prophylaxis at the start of anesthesia. Administer prophylaxis earlier for operations involving a tourniquet.
    - Consider the timing, pharmacokinetics, and necessary infusion time of the antibiotic before administration. Provide a repeat dose if the operation exceeds the antibiotic's half-life.
    - Administer antibiotic treatment (in addition to prophylaxis) for surgery on a dirty or infected wound.
    - Inform patients, whenever possible, before and after the operation if antibiotic prophylaxis is necessary or has been given.

1.4 International Guidelines

1.4.1 World Health Organization (WHO) Global Guidelines on the Prevention of Surgical Site Infection - 2nd Edition (2018)

The recommendations following the GRADE methodology outlined in Appendix B[11].

The following recommendations are provided by the World Health Organization on prevention of surgical site infection:

- Preoperative measures
    - The panel recommends that surgical antibiotic prophylaxis (SAP) should be administered prior to the surgical incision when indicated (depending on the type of operation) (Strong, Low).
    - The panel recommends the administration of SAP within 120 minutes before incision, while considering the half-life of the antibiotic (Strong, Moderate).

    - The panel suggests that preoperative oral antibiotics combined with mechanical bowel preparation should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery (Conditional, Moderate).
    - The panel recommends that mechanical bowel preparation alone (without administration of oral antibiotics) should not be used for the purpose of reducing SSI in adult patients undergoing elective colorectal surgery (Strong, Moderate).
- Preoperative and/or intraoperative measures
    - The panel suggests that antibiotic incisional wound irrigation should not be used for the purpose of preventing SSI (Conditional, Low).
- Postoperative measures
    - The panel recommends against the prolongation of SAP after completion of the operation for the purpose of preventing SSI (Strong, Moderate).
    - The panel suggests that preoperative antibiotic prophylaxis should not be continued in the presence of a wound drain for the purpose of preventing SSI (Conditional, Low).
    - The panel suggests removing the wound drain when clinically indicated. No evidence was found to allow making a recommendation on the optimal timing of wound drain removal for the purpose of preventing SSI (Conditional, Very Low).

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2022** for Surgical Antibiotic Prophylaxis.

Table 12. Systematic Review and Meta-Analysis for Surgical Antibiotic Prophylaxis

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Niels Wolfhagen, MD, Y Quirine J. J. Boldingh, MD, Mats de Lange, MD, Marja A. Boermeester, MD, PhD,Y and Stijn W. de Jonge, MD (2022)	Intraoperative Redosing of Surgical Antibiotic Prophylaxis in Addition to Preoperative Prophylaxis Versus Single dose Prophylaxis for the Prevention of Surgical Site Infection[12]	The aim of this study was to determine the effect of preoperative surgical antibiotic prophylaxis (SAP) with additional intraoperative redosing compared to single-dose preoperative surgical antibiotic prophylaxis on the incidence of surgical site infections (SSI).	The primary outcome was (adjusted) OR for SSI after receiving preoperative SAP with additional intraoperative redosing (intervention) compared to a single dose of preoperative SAP (control). Secondary outcomes included SSI related mortality, length of hospital stay, adverse events related to the use of antibiotics such as allergic reactions or Clostridium difficile infections.	2 randomized controlled trials (RCT) and 8 cohort studies comprising 9470 patients were included. Pooled odds ratios for SSI in patients receiving intraoperative redosing compared to those without redosing were 0.47 (95% CI: 0.19–1.16. I^2 = 36%) for RCTs and 0.55 (95% CI: 0.38–0.79, I^2 = 56%) for observational cohorts. There was considerable clinical heterogeneity among antibiotics used and redosing protocols. GRADE-assessment showed overall low certainty of evidence.

Section 2.0 Drug Therapy

A thorough review of the main health technology assessment (HTA) bodies including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), yielded no results for any of the drugs detailed below. This is probably because these medications have been marketed for years, and multiple generics are available. In addition, surgical prophylaxis is usually given as a one-time dose, or, if repeated, is administered for a short period of time, leading to a relatively low cost of treatment.

2.1 Aminoglycosides

2.1.1 Gentamicin

Table 13. Gentamicin Drug Information

SCIENTIFIC NAME GENTAMICIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotic
Drug Sub-class	Aminoglycoside
ATC Code	**J01GB03**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous Use
Dose (Adult) [DDD]*	IV: 5 mg/kg as a single dose within 60 minutes prior to surgical incision; give in combination with other antibiotics (procedure dependent). Note: In cases where extension of prophylaxis is

	warranted postoperatively, total duration should be ≤24 hours. Postoperative prophylaxis is not recommended in clean and clean-contaminated surgeries.
Maximum Daily Dose Adults*	5 mg/kg as a single dose within 60 minutes prior to surgical incision
Dose (pediatrics)	Infants, Children, and Adolescents: IV: 2.5 mg/kg as a single dose; administer within 60 minutes prior to surgical incision with or without other antibiotics (procedure dependent)
Maximum Daily Dose Pediatrics*	2.5 mg/kg as a single dose within 60 minutes prior to surgical incision
Adjustment	**Dosing: Altered Kidney Function: Pediatric IV:** • Parenteral: Note: Gentamicin serum concentrations should be monitored in patients with kidney impairment; following the initial dose, subsequent doses may be determined based on therapeutic monitoring. • Renally adjusted dose recommendations are based on doses of 2.5 mg/kg/dose every 8 hours. • Intermittent hemodialysis: 2 mg/kg/dose; redose as indicated by serum concentration. • Peritoneal dialysis (PD): 2 mg/kg/dose; redose as indicated by serum concentration. • Continuous renal replacement therapy (CRRT): 2 to 2.5 mg/kg/dose every 12 to 24 hours, monitor serum concentrations. **Dosing: Altered Kidney Function: Adult** **Conventional/traditional dosing:**

	• The recommendations are expert opinion derived from Leroy 1978 and based on a usual dosage range of 3 to 5 mg/kg/day. • Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2): • Hemodialysis, intermittent (thrice weekly): Dialyzable (~50%; dependent on filter and duration): Note: Postdialysis concentrations should be drawn ≥2 and up to 4 hours after hemodialysis (HD) to allow for redistribution. • Peritoneal dialysis: IM, IV: Initial: 1 to 3 mg/kg/dose (depending on infection site, severity, and susceptibility of infecting organisms) every 48 to 72 hours based on gentamicin serum concentrations. • CRRT: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, nephrotoxicity) due to drug accumulation is important. • PIRRT (eg, sustained, low efficiency diafiltration): Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate

	drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, nephrotoxicity) due to drug accumulation is important. Dosing below assumes daily use of PIRRT. **Dosing: Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, dosage adjustment is not likely to be necessary (does not undergo hepatic metabolism).
Prescribing edits*	MD, CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Given in combination with other antibiotics (procedure dependent)	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**The following adverse drug reactions are of undefined frequency:** Edema, hypertension, headache, lethargy, myasthenia, numbness, Clostridioides difficile-associated diarrhea, agranulocytosis, anemia, muscle cramps, muscle fatigue, auditory impairment, hearing loss, pulmonary fibrosis, respiratory depression.
Drug Interactions*	X- Agalsidase Alfa X- Amikacin (Systemic) X- Arbekacin X- Ataluren

	X- Bacitracin (Systemic) X- BCG (Intravesical) X- Cholera Vaccine X- CISplatin X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal) X- Foscarnet X- Isepamicin X- Kanamycin X- Mannitol (Systemic) X- Mecamylamine X- Methoxyflurane Depends on Route X- Neomycin (Systemic) X- Netilmicin (Ophthalmic) X- Netilmicin (Systemic) X- Paromomycin X- Plazomicin X- Polymyxin B X- Ribostamycin X- Sisomicin X- Streptomycin X- Tobramycin (Systemic)
Special Population	• Patients with genomic variants in MT-RNR1: Carriers of certain variants in the MT-RNR1 gene (e.g., m.1555A>G) may be at increased risk for aminoglycoside-induced ototoxicity, including potentially significant hearing loss that may be irreversible, even when serum levels are within the normal range. • Pregnancy: [US Boxed Warning]: Aminoglycosides may cause fetal harm if administered to a pregnant woman.
Pregnancy	Gentamicin crosses the placenta. Aminoglycosides may cause fetal harm if administered to a pregnant patient. There are several reports of total irreversible bilateral congenital deafness

	in children whose mothers received another aminoglycoside (streptomycin) during pregnancy. Although serious side effects to the fetus/infant have not been reported following maternal use of all aminoglycosides, a potential for harm exists. Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of gentamicin may be altered.
Lactation	Gentamicin is present in breast milk. The World Health Organization (WHO) considers gentamicin to be compatible with breastfeeding. Infants should be monitored for thrush and diarrhea.
Contraindications	Hypersensitivity to gentamicin, other aminoglycosides, or any component of the formulation.
Monitoring Requirements	Urinalysis, urine output, BUN, serum creatinine, plasma gentamicin levels (as appropriate to dosing method). Test hearing before, during, and after treatment, particularly in those at risk for ototoxicity or who will be receiving prolonged therapy (>2 weeks). Some penicillin derivatives may accelerate the degradation of aminoglycosides in vitro. This may be clinically significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.
Precautions	**Concerns related to adverse effects:** • Hypersensitivity: Cross-sensitivity to other aminoglycosides may occur.

	• Nephrotoxicity: [US Boxed Warning]: May cause nephrotoxicity; usual risk factors include preexisting renal impairment, concomitant nephrotoxic medications, advanced age, and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible. • Neuromuscular blockade and respiratory paralysis: May cause neuromuscular blockade and respiratory paralysis; especially when given soon after anesthesia or neuromuscular blockers. • Neurotoxicity: [US Boxed Warning]: May cause neurotoxicity; usual risk factors include preexisting renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur. • Superinfection: Prolonged use may result in fungal or bacterial superinfection, including Clostridioides difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. **Disease-related concerns:** • Electrolyte abnormalities: Use with caution in patients with hypocalcemia, hypokalemia, or hypomagnesemia.

	• Hearing impairment: Use with caution in patients with preexisting vertigo, tinnitus, or hearing loss. • Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis. • Renal impairment: Use with caution in patients with preexisting renal insufficiency; dosage modification required. **Concurrent drug therapy issues:** • Neurotoxic and/or nephrotoxic drugs: [US Boxed Warning]: Avoid concomitant or sequential use of other neurotoxic and/or nephrotoxic drugs (eg, cisplatin, polymyxin B, colistin, vancomycin, other aminoglycosides). • Potent diuretics: [US Boxed Warning]: Avoid concomitant use with potent diuretics (eg, ethacrynic acid, furosemide) since diuretics themselves may cause ototoxicity and may enhance aminoglycoside toxicity. **Other warnings/precautions:** • Long-term use: Risk of toxicity is increased with extended duration of administration; additional monitoring may be required with long-term use. • Surgical irrigation: May be almost completely systemically absorbed after local irrigation and/or topical application (except to the urinary bladder) during surgical procedures. Consider potential for nephrotoxicity, neuromuscular blockade, ototoxicity, and respiratory paralysis when administering aminoglycosides in this manner.

Black Box Warning	• Toxicity • Pregnancy
REMS*	N/A

Conclusion statement- Gentamicin

Gentamicin is recommended as an alternative agent for gastroduodenal, cesarean delivery, gynecological (e.g. hysterectomy), urological (involving implanted prosthesis) procedures. In addition, it can be used in clean surgeries with entry into urinary tract, renal transplants, and pancreas or pancreas-kidney transplants.

2.2 Cephalosporins

- **First Generation Cephalosporins:** Cefazolin
- **Second Generation Cephalosporins:** Cefoxitin, Cefuroxime
- **Third Generation Cephalosporins:** Ceftriaxone, Cefotaxime
- **Fourth Generation Cephalosporins:** Cefepime

Table 14. Cephalosporins Drug Information

SCIENTIFIC NAME **Cephalosporins (Cefazolin, Cefoxitin, Cefuroxime, Ceftriaxone, Cefotaxime, Cefepime)**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotics
Drug Sub-class	Cephalosporins - **First generation:** Cefazolin - **Second generation:** Cefoxitin, Cefuroxime - **Third generation:** Ceftriaxone, Cefotaxime - **Fourth generation:** Cefepime
ATC Code	- **For Cefazolin:** J01DB04, J01DB08, J01DB09

	- **For Cefoxitin:** J01DC01 - **For Cefuroxime:** J01DC02 - **For Ceftriaxone:** J01DD04 - **For Cefotaxime:** J01DD01 - **For Cefepime:** J01DE01
Pharmacological Class (ASHP)	8:12.06 Cephalosporins
DRUG INFORMATION	
Dosage Form	Powder for injection, powder for solution for injection, powder for solution for injection/infusion, powder and solvent for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	- **Cefazolin: Surgical prophylaxis: IV:** 2 g for patients <120 kg or 3 g for patients ≥120 kg; administer within 60 minutes of surgical incision. Use in combination with metronidazole for procedures requiring anaerobic coverage (eg, colorectal and clean-contaminated head and neck procedures). May repeat dose intraoperatively in 4 hours if procedure is lengthy or if there is excessive blood loss. - **Cefoxitin: Surgical (perioperative) prophylaxis: IV:** 2 g within 60 minutes prior to surgical incision. Doses may be repeated in 2 hours if procedure is lengthy or if there is excessive blood loss. - **Cefuroxime: Surgical prophylaxis (eg, cardiac surgery, head and neck surgery) (alternative agent): IV:** 1.5 g within 60 minutes prior to surgical incision; use in combination with metronidazole

	for select head and neck procedures. Cefuroxime dose may be repeated intraoperatively in 4 hours if procedure is lengthy or if there is excessive blood loss. - **Ceftriaxone: <u>Surgical prophylaxis, colorectal (alternative agent): IV:</u>** 2 g within 60 minutes prior to surgical incision in combination with metronidazole. - **Cefotaxime: <u>Surgical prophylaxis (off-label use): IV:</u>** 1 g within 60 minutes prior to surgical incision. Doses may be repeated in 3 hours if procedure is lengthy or if there is excessive blood loss. - **Cefepime:** ✓ **Intestinal, multivisceral organ transplant: intra-op re-dosing:** Cefepime 2g IV (in addition to other antimicrobials) every 4h, **post-op dosing:** Cefepime 2g IV (in addition to other antimicrobials) every 8h ✓ **Heart transplant: intra-op re-dosing:** Cefepime 2g IV (in addition to other antimicrobials) every 4h, **post-op dosing:** Cefepime 2g IV (in addition to other antimicrobials) every 8h ✓ **Lung transplant:** Cefepime 2g IV (in addition to other antimicrobials) every 4h, **post-op dosing:** Cefepime 2g IV (in addition to other antimicrobials) every 8h

Maximum Daily Dose Adults*	- **Cefazolin:** 12 g/day - **Cefoxitin:** N/A - **Cefuroxime:** N/A - **Cefotaxime:** N/A
Dose (pediatrics)	- **Cefazolin: <u>Surgical prophylaxis: Infants, Children, and Adolescents: IV:</u>** 30 mg/kg within 60 minutes prior to procedure, may repeat in 4 hours for prolonged procedure or excessive blood loss (eg, >1,500 mL in adults) - **Cefoxitin: <u>Infants, Children, and Adolescents: Limited data available in infants <3 months of age: IV:</u>** 40 mg/kg within 60 minutes prior to surgery; may repeat dose in 2 hours for prolonged procedure or excessive blood loss. - **Cefuroxime: <u>Surgical prophylaxis: Children and Adolescents: IV:</u>** 50 mg/kg within 60 minutes prior to incision; may repeat dose in 4 hours if procedure is lengthy or if there is excessive blood loss. - **Ceftriaxone: <u>Surgical prophylaxis: Children and Adolescents: IV:</u>** 50 to 75 mg/kg within 60 minutes prior to the procedure. - **Cefotaxime: <u>Surgical prophylaxis: Children and Adolescents: IV:</u>** 50 mg/kg within 60 minutes prior to surgical incision; may repeat in 3 hours if procedure is lengthy or if there is excessive blood loss. - **Cefepime: <u>Surgical prophylaxis and intra-op dosing: Patients</u>**

	<u>≤50 kg:</u> 50 mg/kg IV every 4h with 2 re-doses[11]
Maximum Daily Dose Pediatrics*	- **Cefazolin: maximum dose dependent upon patient weight:** Weight <120 kg: 2,000 mg/dose; weight ≥120 kg: 3,000 mg/dose. - **Cefoxitin:** 2,000 mg/dose. - **Cefuroxime:** 1,500 mg/dose. - **Ceftriaxone:** 2,000 mg/dose. - **Cefotaxime:** 1,000 mg; a larger maximum dose (2,000 mg) is recommended for patients weighing ≥120 kg or with BMI >30 kg/m^2. - **Cefepime:** 2000mg/dose
Adjustment	- **Cefazolin (Adult):** **<u>Renal Impairment:</u>** **1. Altered kidney function:** ➢ CrCl ≥50 mL/minute: 1 to 2 g every 8 hours. ➢ CrCl 30 to <50 mL/minute: 1 to 2 g every 8 to 12 hours. ➢ CrCl >10 to <30 mL/minute: 500 mg to 1 g every 12 hours (some experts give 2 g every 12 hours for severe infections in patients with CrCl 10 to <30 mL/minute. ➢ CrCl ≤10 mL/minute: 500 mg to 1 g every 24 hours. **2. Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2):** IV: 2 g every 6 hours. **3. Hemodialysis, intermittent (thrice weekly): Dialyzable (45% to 60%):** IV: Daily dosing: 500 mg to 1 g every 24 hours (when scheduled dose falls on a dialysis day, administer after dialysis) or

	Thrice weekly (post dialysis) dosing: 2 g after dialysis 3 times weekly or 20 mg/kg (maximum dose: 2 g) after dialysis 3 times weekly or 2 g after dialysis if next dialysis is expected in 48 hours or 3 g after dialysis if next dialysis is expected in 72 hours. 4. **Peritoneal dialysis: IV:** 500 mg every 12 hours or 1 g every 24 hours. 5. **CRRT:** IV: 2 g loading dose followed by either 1 g every 8 hours or 2 g every 12 hours. 6. **PIRRT (eg, sustained, low-efficiency diafiltration):** IV: 2 g loading dose followed by either 1 g every 8 hours or 2 g every 12 hours. - **Cefazolin (Pediatric):** **Renal Impairment:** 1. **Altered kidney function:** Infants, Children, and Adolescents: IV, IM: - GFR ≥50 mL/minute/1.73 m2: No dosage adjustment necessary. - GFR 30 to <50 mL/minute/1.73 m2: 25 to 30 mg/kg/dose every 12 hours; doses up to 50 mg/kg/dose may be needed for severe infections; maximum dose: 2,000 mg/dose. - GFR 10 to 30 mL/minute/1.73 m2: 25 to 30 mg/kg/dose every 24 hours; doses up to 50 mg/kg/dose may be needed for severe infections; maximum dose: 2,000 mg/dose. - GFR ≤10 mL/minute/1.73 m2: 25 to 30 mg/kg/dose every 48 hours; doses up to 50 mg/kg/dose may

	be needed for severe infections; maximum dose: 2,000 mg/dose. 2. **Hemodialysis, intermittent: Dialyzable: 35% to 65%:** - Infants, Children, and Adolescents: Intermittent dosing (eg, 3 times weekly): IV: 25 to 50 mg/kg/dose after dialysis; maximum dose: 2,000 mg/dose. Note: Children with residual kidney function may require higher or more frequent dosing. 3. **Peritoneal dialysis:** Infants, Children, Adolescents: IV, IM: 25 to 30 mg/kg/dose every 24 to 48 hours; maximum dose: 1,000 mg/dose. 4. **CRRT:** Infants, Children, and Adolescents: IV: 25 to 50 mg/kg/dose IV every 8 to 12 hours. Maximum dose: 2,000 mg/dose. 5. **Augmented renal clearance (ARC): Infants, Children, and Adolescents:** GFR ≥200 mL/minute/1.73 m2: Continuous infusion: 150 mg/kg/day as a continuous infusion; maximum daily dose: 12 g/day. May give an initial loading dose of 30 mg/kg (maximum dose: 2,000 mg/dose) before starting the continuous infusion if rapid attainment of therapeutic drug concentrations is desired (eg, sepsis). Dosing is based on a pharmacokinetic modeling study; additional dosages (eg, lower daily doses, every-6-hour dosing) may be

	appropriate depending on the clinical situation. **<u>Hepatic Impairment (Adult and Pediatric):</u>** There are no dosage adjustments provided in the manufacturer's labeling. - **Cefoxitin (Adult):** **<u>Renal Impairment:</u>** 1. **Altered kidney function: LD:** 1 to 2 g, followed by maintenance dosing according to CrCl. **Maintenance dose:** ➢ CrCl 30 to 50 mL/minute: 1 to 2 g every 8 to 12 hours ➢ CrCl 10 to 29 mL/minute: 1 to 2 g every 12 to 24 hours ➢ CrCl 5 to 9 mL/minute: 0.5 to 1 g every 12 to 24 hours ➢ CrCl <5 mL/minute: 0.5 to 1 g every 24 to 48 hours 2. **Hemodialysis:** Loading dose: 1 to 2 g after each hemodialysis; maintenance dose as noted above based on creatinine clearance. - **Cefoxitin (Pediatric):** **<u>Renal Impairment:</u>** - GFR >50 mL/minute/1.73 m2: No adjustment required. - GFR 30 to 50 mL/minute/1.73 m2: 20 to 40 mg/kg/dose every 8 hours. - GFR 10 to 29 mL/minute/1.73 m2: 20 to 40 mg/kg/dose every 12 hours. - GFR <10 mL/minute/1.73 m2: 20 to 40 mg/kg/dose every 24 hours.

	- Intermittent hemodialysis: Moderately dialyzable (20% to 50%): 20 to 40 mg/kg/dose every 24 hours. - Peritoneal dialysis (PD): 20 to 40 mg/kg/dose every 24 hours. - Continuous renal replacement therapy (CRRT): 20 to 40 mg/kg/dose every 8 hours. **Hepatic Impairment (Adult and Pediatric):** There are no dosage adjustments provided in the manufacturer's labeling. - **Cefuroxime (Adult):** **Renal Impairment:** **1. Altered kidney function:** ➢ CrCl: ≥30 mL/min: - If usual recommended dose is 750 mg to 1.5 g every 8 hours: No dosage adjustment necessary. - If usual recommended dose is 250 to 500 mg every 12 hours: No dosage adjustment necessary. ➢ CrCl: 10 to 30 mL/min: - If usual recommended dose is 750 mg to 1.5 g every 8 hours: 750 mg to 1.5 g every 12 hours. - If usual recommended dose is 250 to 500 mg every 12 hours: 250 mg every 12 hours (preferred) or 250 to 500 mg every 24 hours. ➢ CrCl: <10 mL/min: - If usual recommended dose is 750 mg to 1.5 g every 8 hours: 750 mg to 1.5 g every 24 hours. - If usual recommended dose is 250 to 500 mg every 12 hours:

	250 mg every 24 hours (preferred) or 250 to 500 mg every 48 hours. 2. **Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2):** - Extended infusion: IV: 1.5 g infused over 3 hours every 6 hours. - Continuous infusion: IV: 1.5 g loading dose, followed by 6 g infused over 24 hours every 24 hours. 3. **Hemodialysis, intermittent (thrice weekly): Dialyzable (enhances plasma clearance by at least 30%):** IV, Oral: Dose as for patients with CrCl <10 mL/minute; when scheduled dose falls on a dialysis day, administer after dialysis. 4. **Peritoneal dialysis:** IV, Oral: Dose as for patients with CrCl <10 mL/minute. 5. **CRRT:** IV: 1.5 g every 12 hours. 6. **PIRRT (e.g., sustained, low efficiency diafiltration):** IV: 1.5 g every 12 hours. - **Cefuroxime (Pediatric):** **<u>Renal Impairment:</u>** 1. **Altered kidney function:** IV: If usual recommended dose is 75 to 150 mg/kg/day divided every 8 hours; Usual dose: 25 to 50 mg/kg/dose every 8 hours - GFR: ≥30 mL/minute/1.73 m2: No dosage adjustment necessary.

	- GFR: 10 to 29 mL/minute/1.73 m2: 25 to 50 mg/kg/dose every 12 hours. - GFR: <10 mL/minute/1.73 m2: 25 to 50 mg/kg/dose every 12 hours. - Intermittent hemodialysis: 25 to 50 mg/kg/dose every 24 hours; administer after dialysis on dialysis days. - Peritoneal dialysis (PD): 25 to 50 mg/kg/dose every 24 hours. 2. **CRRT: Infants, Children, and Adolescents**: IV: 25 to 50 mg/kg/dose every 8 hours; intervals of every 12 to 18 hours have also been suggested depending on effluent flow rate. **Hepatic Impairment (Adult and Pediatric):** There are no dosage adjustments provided in the manufacturer's labeling. - **Ceftriaxone (Adult):** **Renal Impairment:** 1. **Altered kidney impairment: IM, IV:** - CrCl >15 mL/minute: No dosage adjustment necessary. - CrCl <15 mL/minute: No dosage adjustment necessary. Use of >2 g/day has not been studied and should be done with close monitoring, especially in patients with concurrent hepatic dysfunction (decreased biliary excretion). 2. **Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2): IV:** CrCl ≥150 mL/minute (empiric therapy or organism with minimum

	inhibitory concentration [MIC] = 2): 2 g twice daily. 3. **Hemodialysis, intermittent (thrice weekly): IM, IV:** Poorly dialyzed; no dosage adjustment necessary. Use of >2 g/day has not been studied and should be done with close monitoring, especially in patients with concurrent hepatic dysfunction (decreased biliary excretion). Alternatively, 2 g thrice weekly post dialysis achieves pharmacodynamic goals when the MIC ≤1 mcg/mL. 4. **Peritoneal dialysis: IM, IV:** Poorly dialyzed; no dosage adjustment necessary. Use of >2 g/day has not been studied and should be done with close monitoring, especially in patients with concurrent hepatic dysfunction (decreased biliary excretion) 5. **CRRT: IM, IV:** No dosage adjustment necessary. 6. **PIRRT (eg, sustained, low efficiency hemodiafiltration): IM, IV:** No dosage adjustment necessary. **Hepatic Impairment:** Child-Turcotte-Pugh class A through C: No dosage adjustment necessary. - **Ceftriaxone (Pediatric):** **Renal Impairment:** - No dosage adjustment is generally necessary in renal impairment; Note: If concurrent renal and hepatic dysfunction, a reduced maximum daily dose should be considered; in adults a

	maximum daily dose ≤2,000 mg/day is suggested. - Not dialyzable; no supplemental dose is necessary following hemodialysis or peritoneal dialysis; patients with concomitant hepatic dysfunction must be monitored closely for safety and efficacy. **Hepatic Impairment:** No adjustment is generally necessary in hepatic impairment; Note: If concurrent renal and hepatic dysfunction, a reduced maximum daily dose should be considered; in adults a maximum daily dose ≤2,000 mg/day is suggested. - **Cefotaxime (Adult):** **Renal Impairment:** **1. Altered kidney function:** ➢ CrCl: >50 mL/min: - If the usual indication-specific dose is 1 to 2 g every 8 hours: No dosage adjustment necessary. - If the usual indication-specific dose is 1 to 2 g every 6 hours: No dosage adjustment necessary. - If the usual indication-specific dose is 2 g every 4 hours: No dosage adjustment necessary. ➢ CrCl: >10 to 50 mL/min: - If the usual indication-specific dose is 1 to 2 g every 8 hours: 1 to 2 g every 12 hours. - If the usual indication-specific dose is 1 to 2 g every 6 hours: 1 to 2 g every 8 hours. - If the usual indication-specific dose is 2 g every 4 hours: 2 g every 6 to 8 hours.

	➢ CrCl: ≤10 mL/minute: - If the usual indication-specific dose is 1 to 2 g every 8 hours: 1 to 2 g every 24 hours. - If the usual indication-specific dose is 1 to 2 g every 6 hours: 1 to 2 g every 12 hours. - If the usual indication-specific dose is 2 g every 4 hours: 2 g every 12 hours. ➢ Hemodialysis, intermittent (thrice weekly): - If the usual indication-specific dose is 1 to 2 g every 8 hours: 1 to 2 g every 24 hours. - If the usual indication-specific dose is 1 to 2 g every 6 hours: 1 to 2 g every 12 hours. - If the usual indication-specific dose is 2 g every 4 hours: 2 g every 12 hours. ➢ Peritoneal dialysis: - If the usual indication-specific dose is 1 to 2 g every 8 hours: 1 to 2 g every 24 hours. - If the usual indication-specific dose is 1 to 2 g every 6 hours: 1 to 2 g every 12 hours. - If the usual indication-specific dose is 2 g every 4 hours: 2 g every 12 hours. **2. CRRT: IV:** Dose as for CrCl >10 to 50 mL/minute. **3. PIRRT (eg, sustained, low-efficiency diafiltration): IV:** - PIRRT days: Dose as for CrCl >10 to 50 mL/minute (on PIRRT days, when feasible administer one of the scheduled doses after the PIRRT session).

	- Non-PIRRT days: Dose as for CrCl ≤10 mL/minute. - **Cefotaxime (Pediatric):** **<u>Renal Impairment:</u>** **1. Altered kidney function: Infants, Children, and Adolescents: The following adjustments have been recommended. Note:** Renally adjusted dose recommendations are based on doses of 100 to 200 mg/kg/day divided every 8 hours. - GFR 30 to 50 mL/minute/1.73 m2: 35 to 70 mg/kg/dose every 8 to 12 hours. - GFR 10 to 29 mL/minute/1.73 m2: 35 to 70 mg/kg/dose every 12 hours. - GFR <10 mL/minute/1.73 m2: 35 to 70 mg/kg/dose every 24 hours. - Intermittent hemodialysis: 35 to 70 mg/kg/dose every 24 hours. - Peritoneal dialysis (PD): 35 to 70 mg/kg/dose every 24 hours. - CRRT: 35 to 70 mg/kg/dose every 12 hours. **<u>Hepatic Impairment (Adult and Pediatric):</u>** There are no dosage adjustments provided in the manufacturer's labeling. - **Cefepime (Adult):** **<u>Renal Impairment:</u>** **1. Altered kidney function:** ➢ CrCl: >60 mL/min: - If the usual recommended dose is 1 g every 12 hours: No dosage adjustment necessary.

	- If the usual recommended dose is 2 g every 12 hours: No dosage adjustment necessary. - If the usual recommended dose is 1 g every 6 hours: No dosage adjustment necessary. - If the usual recommended dose is 2 g every 8 hours: No dosage adjustment necessary. ➢ CrCl: 30 to 60 mL/min: - If the usual recommended dose is 1 g every 12 hours: 1 g every 24 hours. - If the usual recommended dose is 2 g every 12 hours: 1 g every 12 hours. - If the usual recommended dose is 1 g every 6 hours: o CrCl 50 to 60 mL/minute: No dosage adjustment necessary. o CrCl 30 to 49 mL/minute: 1 g every 8 hours. - If the usual recommended dose is 2 g every 8 hours: 2 g every 12 hours. ➢ CrCl: 11 to 29 mL/min: - If the usual recommended dose is 1 g every 12 hours: 500 mg every 24 hours. - If the usual recommended dose is 2 g every 12 hours: 1 g every 24 hours. - If the usual recommended dose is 1 g every 6 hours: 1 g every 12 hours. - If the usual recommended dose is 2 g every 8 hours: 1 g every 12 hours or 2 g every 24 hours. ➢ CrCl: < 11 mL/min:

	- If the usual recommended dose is 1 g every 12 hours: 250 mg every 24 hours. - If the usual recommended dose is 2 g every 12 hours: 500 mg every 24 hours. - If the usual recommended dose is 1 g every 6 hours: 1 g every 24 hours. - If the usual recommended dose is 2 g every 8 hours: 1 g every 24 hours. - **Cefepime (Pediatric):** **<u>Renal Impairment:</u>** **1. Altered kidney function:** ➢ CrCl: 30 to 60 mL/minute/1.73 m2: - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 1,000 mg/dose: 50 mg/kg/dose every 24 hours; maximum dose: 1,000 mg/dose. - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 2,000 mg/dose: 50 mg/kg/dose every 24 hours; maximum dose: 2,000 mg/dose. - If the recommended dose is 50 mg/kg/dose every 8 hours; maximum dose: 2,000 mg/dose: 50 mg/kg/dose every 12 hours; maximum dose: 2,000 mg/dose. ➢ CrCl: 11 to 29 mL/minute/1.73 m2: - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 1,000 mg/dose: 25 mg/kg/dose every 24 hours; maximum dose: 500 mg/dose. - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 2,000 mg/dose:

	25 to 50 mg/kg/dose every 24 hours; maximum dose: 1,000 mg/dose. - If the recommended dose is 50 mg/kg/dose every 8 hours; maximum dose: 2,000 mg/dose: 50 mg/kg/dose every 24 hours; maximum dose: 2,000 mg/dose. ➢ CrCl: <11 mL/minute/1.73 m2: - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 1,000 mg/dose: 25 mg/kg/dose every 24 hours; maximum dose: 250 mg/dose. - If the recommended dose is 50 mg/kg/dose every 12 hours; maximum dose: 2,000 mg/dose: 25 to 50 mg/kg/dose every 24 hours; maximum dose: 500 mg/dose. - If the recommended dose is 50 mg/kg/dose every 8 hours; maximum dose: 2,000 mg/dose: 25 to 50 mg/kg/dose every 24 hours; maximum dose: 1,000 mg/dose. **2. Hemodialysis, intermittent:** Dialyzable (based on adult studies: 70% to 85% reduction in serum concentration from a 3.5- to 4-hour hemodialysis treatment with high flux filters: Infants, Children, and Adolescents: IV or via dialysis circuit return line: - Intermittent (posthemodialysis) dosing: 50 mg/kg/dose following dialysis; maximum dose: 2,000 mg/dose.

	- Daily dosing (when scheduled dose falls on a dialysis day, administer after dialysis): Initial (day 1): 50 mg/kg (maximum dose: 1,000 mg/dose) followed by 12.5 to 25 mg/kg/dose once daily. 3. **Peritoneal dialysis (manual or automated):** Infants, Children, and Adolescents: IV, IM: 25 to 50 mg/kg/dose every 48 hours. Usual maximum dose: 1,000 mg/dose; in severe infections or for bacteria with elevated MICs, 2,000 mg/dose maximum may be considered. Alternatively, 25 to 50 mg/kg/dose every 24 hours may be considered for severe infections (eg, septic shock). 4. **CRRT:** Infants, Children, Adolescents: IV: 50 mg/kg/dose (maximum dose: 2,000 mg/dose) every 8 to 12 hours. **Hepatic Impairment (Adult and Pediatric):** IV: 50 mg/kg/dose (maximum dose: 2,000 mg/dose) every 8 to 12 hours.
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common:** - Diarrhea, nausea, vomiting, positive direct Coombs test (Cefepime) **Most serious:** - Increase in hepatic enzymes, Increased blood urea nitrogen, thrombocytopenia. - Clostridioides difficile infection (Cefazolin, ceftriaxone, cefepime), hemolytic anemia (cefazolin, ceftriaxone), Hypersensitivity (immediate and delayed) (cefazolin, ceftriaxone, cefepime), neurotoxicity (cefazolin, cefepime), ceftriaxone-calcium precipitation, kernicterus (ceftriaxone).
Drug Interactions*	**Category X:** • BCG (Intravesical) • Cholera Vaccine • Fecal Microbiota (Live) (Oral) • Fecal Microbiota (Live) (Rectal) • Histamine H2 Receptor Antagonists (Cefuroxime only) • Inhibitors of the Proton Pump (PPIs and PCABs) (Cefuroxime only)
Special Population	- **Cefazolin:** N/A - **Cefoxitin:** o Children: In pediatric patients ≥3 months of age, higher doses have been associated with an increased incidence of eosinophilia and elevated AST. o Older adult: This drug is known to be substantially excreted by the kidney,

	and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function; use care in dose selection and monitor renal function. - **Cefuroxime:** N/A - **Ceftriaxone:** o Neonates: Use extreme caution in neonates due to risk of hyperbilirubinemia, particularly in premature infants (contraindicated in hyperbilirubinemic neonates and neonates <41 weeks postmenstrual age). - **Cefotaxime:** N/A - **Cefepime:** o Older adult: Serious adverse reactions have occurred in elderly patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of encephalopathy, myoclonus, and seizures.
Pregnancy	All the previously mentioned cephalosporins cross the placenta. Based on available data, cephalosporin antibiotics are generally considered compatible for use during pregnancy. - **Cefazolin** is recommended as an alternative antibiotic for group B streptococcus (GBS) prophylaxis in pregnant patients who are

	penicillin allergic and at low risk for anaphylaxis. - **Cefoxitin** is one of the antibiotics recommended for prophylactic use prior to cesarean delivery. - **Cefuroxime** is one of the antibiotics effective for prophylactic use prior to cesarean delivery (ACOG 2018). Cefuroxime is used for the treatment of Lyme disease. - **Ceftriaxone** is recommended for use in pregnant patients for the treatment of gonococcal infections, Lyme disease, and may be used in certain situations prior to vaginal delivery in patients at high risk for endocarditis. - **Cefotaxime** is approved for use in women undergoing cesarean section. - When an antibiotic is needed for the treatment of maternal infection, **cefepime** can be considered. However, other, more well-studied cephalosporins are preferred for use in pregnancy.
Lactation	All the previously mentioned cephalosporins are present in breast milk. Cephalosporins are generally considered acceptable for use in breastfeeding women. In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora. Monitor infants for GI disturbances, such as thrush or diarrhea. According to the manufacturer, the decision to breastfeed during therapy

	should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	- **Cefazolin, cefuroxime and cefepime:** Immediate hypersensitivity (eg, anaphylaxis, serious skin reactions) to the antibiotic itself, other cephalosporin antibiotics, penicillins, other beta-lactams, or any component of the formulation. - **Ceftriaxone:** Hypersensitivity to ceftriaxone, any component of the formulation, or other cephalosporins; **do not use in hyperbilirubinemic neonates**, particularly those who are premature since ceftriaxone is reported to displace bilirubin from albumin binding sites; concomitant use with intravenous calcium-containing solutions/products in neonates (≤28 days); IV use of ceftriaxone solutions containing lidocaine. - **Cefoxitin and cefotaxime:** Hypersensitivity to the antibiotic itself, any component of the formulation, or other cephalosporins.
Monitoring Requirements	- **Cefazolin:** Renal function, hepatic function, CBC, signs of anaphylaxis during first dose. - **Cefoxitin:** Monitor renal function periodically when used in combination with other nephrotoxic drugs; prothrombin time. Observe for signs and

	symptoms of anaphylaxis during first dose. CBC with prolonged use. - **Cefuroxime:** Monitor renal, hepatic, and hematologic function periodically with prolonged therapy. Monitor prothrombin time in patients at risk of prolongation during cephalosporin therapy (nutritionally-deficient, prolonged treatment, renal or hepatic disease). Observe for signs and symptoms of anaphylaxis during first dose. - **Ceftriaxone:** Prothrombin time/INR. Observe for signs and symptoms of anaphylaxis. Test-of-cure 7 to 14 days after initial treatment of pharyngeal gonorrhea. - **Cefotaxime:** Observe for signs and symptoms of anaphylaxis during first dose; CBC with differential (especially with long courses [>10 days]); renal function. - **Cefepime:** Monitor renal function. Observe for signs and symptoms of anaphylaxis during first dose.
Precautions	***Concerns related to adverse effects:*** - **Elevated INR (Cefazolin, cefuroxime, ceftriaxone, cefepime):** May be associated with increased INR, especially in nutritionally deficient patients, prolonged treatment, hepatic or renal disease. - **Superinfection (Cefazolin, cefoxitin, cefuroxime, ceftriaxone, cefotaxime,**

	cefepime): Prolonged use may result in fungal or bacterial superinfection. - **Hypersensitivity (Cefoxitin, cefuroxime)**: Serious and occasionally severe or fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam drugs. Before initiating therapy, carefully investigate previous penicillin, cephalosporin, or other allergen hypersensitivity. Use caution if given to a patient with a penicillin or other beta-lactam allergy because cross sensitivity among beta-lactam antibacterial drugs has been established. If an allergic reaction occurs, discontinue and institute appropriate therapy. - **Arrhythmia (Cefotaxime):** A potentially life-threatening arrhythmia has been reported in patients who received a rapid (<1 minute) bolus injection via central venous catheter. - **Granulocytopenia (Cefotaxime):** Granulocytopenia and more rarely agranulocytosis may develop during prolonged treatment (>10 days). - **Penicillin allergy (Cefotaxime):** Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). - **Tissue inflammation (Cefotaxime):** Minimize tissue

	inflammation by changing infusion sites when needed. ***Disease-related concerns:*** - **Gastrointestinal disease (Cefazolin, cefoxitin, cefuroxime, cefotaxime):** Use with caution in patients with a history of gastrointestinal disease, particularly colitis. - **Renal impairment (Cefazolin, cefoxitin, cefuroxime, cefotaxime):** Use with caution in patients with renal impairment; dosage adjustment required. - **Seizure disorders (Cefazolin, cefoxitin, cefuroxime, cefepime):** Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures. - **Renal/hepatic impairment (concurrent) (Ceftriaxone):** Use with caution in patients with concurrent hepatic dysfunction (impaired biliary excretion) and severe kidney disease; dosing adjustments may be recommended.
Black Box Warning	**N/A**
REMS*	**N/A**

Conclusion Statement- Cephalosporins

Cephalosporins are recommended for Peri-Operative Antibiotic Prophylaxis for Solid Organ Transplant. A first-generation cephalosporin is recommended for ≤ 24 hours as first line in renal transplantation. For patients colonized with a resistant organism, use a third-generation cephalosporin or alternative agent passed on individual susceptibilities and local formulary for ≤ 24 hours as first line. Cefazolin is particularly recommended for Cardiac Surgery/ Vascular/ Thoracic, Cardiac Surgery with prosthetic material, Cardiac device insertion (e.g., pacemaker implantation),

Gastroduodenal, Biliary Tract, Colorectal, appendectomy, hernia repair, breast), Cesarean delivery, hysterectomy, Head & Neck, Neurosurgery, Orthopedics, Plastic Surgery, Urology. Cefoxitin is the preferred agent for Urology: Open/laparoscopic involving intestine: (clean-contaminated, e.g., radical cystectomy with ileal conduit) surgeries. Single first-generation cephalosporin (e.g., cefazolin) is recommended for heart transplant with prior VAD.

2.3 Clindamycin

Table 15. Clindamycin Drug Information

SCIENTIFIC NAME **Clindamycin**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotic
Drug Sub-class	Lincosamide
ATC Code	J01FF01
Pharmacological Class (ASHP)	8:12.28.20 Lincomycins
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Surgical prophylaxis (in combination with other appropriate agents when coverage for MRSA is indicated or for gram-positive coverage in patients unable to tolerate cephalosporins) (off-label use): IV:** 900 mg started within 60 minutes prior to initial surgical incision. Clindamycin doses may be repeated intraoperatively at 6-hour intervals if the procedure is lengthy or if there is excessive blood loss. In cases where an extension of prophylaxis is warranted

	postoperatively, total duration should be ≤24 hours. For clean and clean-contaminated procedures, continued prophylactic antibiotics beyond surgical incision closure is not recommended, even in the presence of a drain.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**Surgical prophylaxis: Children and Adolescents: IV:** 10 mg/kg within 30 to 60 minutes prior to procedure; may repeat dose in 6 hours for prolonged procedure or excessive blood loss.
Maximum Daily Dose Pediatrics*	900 mg/dose
Adjustment	**Adult** **Renal Impairment:** - **Mild to severe impairment:** No dosage adjustment necessary. - **Hemodialysis, intermittent (thrice weekly):** Poorly dialyzed; no supplemental dose or dosage adjustment necessary. - **Peritoneal dialysis:** Poorly dialyzed; no dosage adjustment necessary. - **CRRT:** No dosage adjustment necessary. - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary. **Hepatic impairment:** - **Mild impairment:** There are no dosage adjustments provided in the manufacturer's labeling. - **Moderate to severe impairment:** There are no dosage adjustments provided in the manufacturer's labeling. In studies of patients with moderate or severe liver disease, half-life is prolonged; however, when administered on

	an every-8-hour schedule, accumulation should rarely occur. In severe liver disease, use caution and monitor liver enzymes periodically during therapy. **Pediatric** **<u>Renal Impairment:</u>** - **Mild to severe impairment:** No dosage adjustment necessary. - **Hemodialysis, intermittent (thrice weekly):** Poorly dialyzed; based on adult information, no supplemental dose or dosage adjustment necessary. - **Peritoneal dialysis:** Poorly dialyzed; based on adult information, no supplemental dose or dosage adjustment necessary. - **CRRT:** Based on adult information, no dosage adjustment necessary. **<u>Hepatic Impairment:</u>** No adjustment required. Use caution with severe hepatic impairment.
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Frequency not defined:** - Dermatologic: Urticaria, vesiculobullous dermatitis. - Gastrointestinal: Abdominal pain, nausea, vomiting. **Most serious:** Antibiotic-associated (non-Clostridioides difficile) diarrhea, clostridioides difficile infection, hypersensitivity reactions (immediate and delayed), hypotension (following rapid IV administration), thrombophlebitis (IV), Stevens-Johnson syndrome, toxic epidermal necrolysis, Agranulocytosis , eosinophilia (transient), neutropenia (transient), pancytopenia, thrombocytopenia.
Drug Interactions*	**Category X:** • BCG (Intravesical) • Cholera Vaccine • Fecal Microbiota (Live) (Oral) • Fecal Microbiota (Live) (Rectal) • Fexinidazole • Fusidic Acid (Systemic) • Mecamylamine
Special Population	Atopic patients: Use with caution in atopic patients. Older adult: A subgroup of older patients with associated severe illness may tolerate diarrhea less well. Monitor carefully for changes in bowel frequency.
Pregnancy	Clindamycin crosses the placenta and can be detected in the cord blood and fetal tissue. Clindamycin injection contains benzyl alcohol, which may also cross the placenta. Clindamycin pharmacokinetics are not affected by pregnancy.

	Clindamycin is recommended for use in pregnant patients for the prophylaxis of group B streptococcal disease in newborns (alternative option for patients at high risk for anaphylaxis to penicillin [or whose risk is unknown], and who have GBS susceptible to clindamycin); prophylaxis and treatment of *Toxoplasma gondii* encephalitis (alternative therapy), or treatment of *Pneumocystis pneumonia* (PCP) (alternative therapy); bacterial vaginosis; anthrax; or malaria. Clindamycin is also one of the antibiotics recommended for prophylactic use prior to cesarean delivery and may be used in certain situations prior to vaginal delivery in patients at high risk for endocarditis.
Lactation	Clindamycin is present in breast milk. In general, breastfeeding is considered acceptable when the RID is <10%. The manufacturer reports that clindamycin breast milk concentrations range from <0.5 to 3.8 mcg/mL following doses of 150 mg orally to 600 mg IV. In general, antibiotics that are present in breast milk may cause non–dose-related modification of bowel flora. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother; alternative agents may be preferred. Clindamycin is an alternative antibiotic for the empiric treatment of bacterial mastitis in patients who are breastfeeding. Antibiotic use may be considered when symptoms are

	present for >24 hours and have not responded to conservative measures, or the patient has symptoms such as fever or tachycardia. Consider a milk culture if symptoms do not improve after 48 hours of antibiotic therapy. The diagnosis of mastitis does not require interruption of breastfeeding.
Contraindications	Hypersensitivity to clindamycin, lincomycin, or any component of the formulation. Canadian labeling: Additional contraindications (not in US labeling): Oral clindamycin: Infants <30 days of age.
Monitoring Requirements	Observe for changes in bowel frequency. Monitor for colitis and resolution of symptoms. In severe liver disease monitor liver function tests periodically; consider monitoring renal function periodically in patients with renal impairment or taking nephrotoxic medications; during prolonged therapy monitor CBC, liver, and renal function tests periodically.
Precautions	**Concerns related to adverse effects:** • Renal toxicity: Acute kidney injury has been reported; discontinue treatment if clindamycin-induced acute kidney injury is suspected and no other etiology is identified. • Superinfection: Use may result in overgrowth of nonsusceptible organisms, particularly yeast. Should superinfection occur, appropriate measures should be taken as indicated by the clinical situation. **Disease-related concerns:**

	• GI disease: Use with caution in patients with a history of GI disease, particularly colitis. • Hepatic impairment: Use with caution in patients with moderate to severe liver disease, however, when administered at every-8-hour intervals, drug accumulation is rare. Monitor hepatic enzymes periodically as dosage adjustments may be necessary in patients with severe liver disease. • Renal impairment: Use with caution in patients with renal impairment; acute kidney injury may occur, especially if patient is taking other nephrotoxins concurrently. **Other warnings/precautions:** • Administration (IV): Do not inject IV undiluted as a bolus. Product should be diluted in compatible fluid and infused over 10 to 60 minutes. • Appropriate use: Not appropriate for use in the treatment of meningitis due to inadequate penetration into the CSF.
Black Box Warning	**Colitis**
REMS*	**N/A**

Conclusion Statement- Clindamycin

Clindamycin is recommended as an alternative agent in Cardiac Surgery/ Vascular/ Thoracic, Cardiac Surgery with prosthetic material, Cardiac device insertion (e.g., pacemaker implantation), gastroduodenal, Biliary Tract, Colorectal, appendectomy, hernia repair, breast), Cesarean delivery, hysterectomy, Head & Neck surgeries. It is also an alternative in renal, pancreas, and pancreas-kidney transplant.

2.4 Fluoroquinolones

- 2nd generation: Ciprofloxacin
- 3rd generation: Levofloxacin
- 4th generation: Moxifloxacin

Table 16. Fluoroquinolones Drug Information

SCIENTIFIC NAME **Fluoroquinolones (Ciprofloxacin, levofloxacin, moxifloxacin)**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotics
Drug Sub-class	Fluoroquinolones
ATC Code	• **Ciprofloxacin:** J01MA02, S02AA15 • **Levofloxacin:** J01MA12, S01AE05 • **Moxifloxacin:** J01MA14, S01AE07
Pharmacological Class (ASHP)	8:12.18 Quinolones
DRUG INFORMATION	
Dosage Form	Solution, Solution for infusion, Intravenous infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	• **Ciprofloxacin: Surgical prophylaxis (off-label use): IV (alternative agent):** 400 mg within 120 minutes prior to surgical incision. Note: Use in combination with other appropriate agents may be warranted (procedure-dependent). • **Levofloxacin: Surgical (preoperative) prophylaxis**

	<u>(alternative agent) (off-label use): IV:</u> 500 mg beginning 120 minutes prior to initial surgical incision; use in combination with other appropriate agents may be warranted (procedure dependent). Note: Postoperative prophylaxis is not recommended for clean and clean-contaminated surgeries. • **Moxifloxacin: <u>Surgical prophylaxis (alternative agent for hysterectomy or pelvic reconstruction procedures in patients who cannot receive beta-lactams) (off-label use): IV:</u>** 400 mg within 120 minutes prior to surgical incision in combination with other appropriate antibiotics.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	• **Ciprofloxacin: <u>Surgical prophylaxis: Children and Adolescents: IV:</u>** 10 mg/kg as a single dose within 120 minutes prior to surgical incision. • **Levofloxacin: <u>Surgical prophylaxis: Children and Adolescents: IV:</u>** 10 mg/kg as a single dose 120 minutes prior to procedure. Note: While fluoroquinolones have been associated with an increased risk of tendinopathy/tendon rupture in all ages, use of these agents for single-dose prophylaxis is generally safe. • **Moxifloxacin: <u>Surgical (perioperative) prophylaxis</u>**

	<u>(alternative agent): Limited data available:</u> **<u>Children and Adolescents: IV:</u>** 10 mg/kg within 120 minutes prior to surgical incision
Maximum Daily Dose Pediatrics*	• **Ciprofloxacin:** 400 mg/dose. • **Levofloxacin:** 500 mg/dose • **Moxifloxacin:** 400 mg/dose.
Adjustment	• **Ciprofloxacin (Adult):** **<u>Renal Impairment:</u>** **1. Altered kidney function** ➢ CrCl: >50 to <130 mL/min: 400 mg every 8 to 12 hours. ➢ CrCl: 30 to 50 mL/min: 400 mg every 8 to 12 hours. ➢ CrCl: > 30 mL/min: 200 to 400 mg every 12 to 24 hours. ➢ Hemodialysis, intermittent (thrice weekly): 200 to 400 mg every 24 hours. ➢ Peritoneal dialysis: 200 to 400 mg every 24 hours. **2. Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2): IV:** 400 mg every 8 hours when organism minimum inhibitory concentration (MIC) ≤0.125 mg/L. Monte Carlo simulations suggest a dose of 600 mg every 8 hours may be required to achieve pharmacodynamic goals for organisms with MICs >0.125 mg/L; monitor closely, especially with prolonged courses, or utilize another agent. **3. CRRT: IV:** 200 to 400 mg every 8 to 12 hours.

4. **PIRRT (eg, sustained, low-efficiency diafiltration): IV:** 400 mg every 12 hours assuming MIC susceptibility breakpoint ≤0.5 mg/L.

Hepatic Impairment:

- Initial or dose titration in patients with preexisting liver cirrhosis or dosage adjustment in patients with chronic, worsening hepatic function during treatment: Child-Turcotte-Pugh class A through C: IV, Oral: No dosage adjustment necessary.
- Acute worsening of hepatic function (eg, requiring hospitalization): No dosage adjustment necessary; however, consider discontinuation of ciprofloxacin therapy in patients with suspected ciprofloxacin-induced liver injury unless the benefits outweigh the risks.

- **Ciprofloxacin (Pediatric):**

Infants, Children, and Adolescents:
IV, Oral (immediate release): There are no dosage adjustments provided in the manufacturer's labeling; however, the following guidelines have been used by some clinicians:

- GFR ≥30 mL/minute/1.73 m2: No dosage adjustment necessary.
- GFR 10 to 29 mL/minute/1.73 m2: 10 to 15 mg/kg/dose every 18 hours.
- GFR <10 mL/minute/1.73 m2: 10 to 15 mg/kg/dose every 24 hours.

	➢ Hemodialysis/peritoneal dialysis (PD) (after dialysis on dialysis days): Minimally dialyzable (<10%): 10 to 15 mg/kg/dose every 24 hours. ➢ CRRT: 10 to 15 mg/kg/dose every 12 hours. **Hepatic Impairment:** There are no dosage adjustments provided in manufacturer's labeling; use with caution in severe impairment. ➢ **Levofloxacin (Adult):** **Renal Impairment:** **1. Altered Kidney function:** ➢ CrCl: >50 mL/min: - If usual recommended dose is 250 mg every 24 hours: No dosage adjustment necessary. - If usual recommended dose is 500 mg every 24 hours: No dosage adjustment necessary. - If usual recommended dose is 750 mg every 24 hours: No dosage adjustment necessary. ➢ CrCl: 20 to <50 mL/min: - If usual recommended dose is 250 mg every 24 hours: No dosage adjustment necessary. - If usual recommended dose is 500 mg every 24 hours: 500 mg initial dose, then 250 mg every 24 hours. - If usual recommended dose is 750 mg every 24 hours: 750 mg every 48 hours. ➢ CrCl: <20 mL/min: - If usual recommended dose is 250 mg every 24 hours: 250 mg

	every 48 hours (except for uncomplicated UTI, where no dosage adjustment is required). - If usual recommended dose is 500 mg every 24 hours: 500 mg initial dose, then 250 mg every 48 hours. - If usual recommended dose is 750 mg every 24 hours: 750 mg initial dose, then 500 mg every 48 hours. ➢ Hemodialysis, intermittent (thrice weekly): Dialyzable (21% [4-hour dialysis session utilizing high-flux dialyzers]): - If usual recommended dose is 250 mg every 24 hours: 250 mg every 48 hours. - If usual recommended dose is 500 mg every 24 hours: 500 mg initial dose, then either 250 mg every 48 hours or 125 mg every 24 hours (if daily dosing improves adherence. - If usual recommended dose is 750 mg every 24 hours: 750 mg initial dose, then either 500 mg every 48 hours or 250 mg every 24 hours (if daily dosing improves adherence. ➢ Peritoneal dialysis: - If usual recommended dose is 250 mg every 24 hours: 250 mg every 48 hours. - If usual recommended dose is 500 mg every 24 hours: 500 mg initial dose, then either 250 mg every 48 hours or 125 mg every 24 hours (if daily dosing improves adherence).

	- If usual recommended dose is 750 mg every 24 hours: 750 mg initial dose, then either 500 mg every 48 hours or 250 mg every 24 hours (if daily dosing improves adherence) **2. Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2):** Oral, IV: 750 mg loading dose followed by 500 mg every 12 hours or 1 g every 24 hours. **3. CRRT:** - If usual recommended dose is 250mg every 24 hours: no dosage adjustment necessary - If usual recommended dose is 500mg every 24 hours: 500 mg initial dose, then 250 mg every 24 hours or 500 mg every 48 hours - If usual recommended dose is 750 mg every 24 hours: 750 mg initial dose, then 500mg every 24 hours or 750mg every 48 hours. - **Dose adjustment in PIRRT** - If usual recommended dose is 250mg every 24 hours: no dosage adjustment necessary - If usual recommended dose is 500mg every 24 hours: 500 mg initial dose, then 250 mg every 24 hours (after PIRRT treatment when possible) - If usual recommended dose is 750 mg every 24 hours: 750mg every 48 hours (after PIRRT treatment when possible) - **<u>Hepatic Impairment: Adult</u>** - IV, Oral: There are no dosage adjustments provided in the manufacturer's labeling (has not

	been studied). However, dosage adjustment unlikely due to limited hepatic metabolism. - **Altered Kidney Function: Pediatric** - **Infants, Children, and Adolescents**: IV, Oral: The following adjustments have been recommended (Ref). Note: Renally adjusted dose recommendations are based on doses of 5 to 10 mg/kg/dose every 12 hours in ages ≤5 years and 5 to 10 mg/kg/dose every 24 hours in ages >5 years. - GFR ≥30 mL/minute/1.73 m2: No adjustment necessary - GFR 10 to 29 mL/minute/1.73 m2: 5 to 10 mg/kg/dose every 24 hours - GFR <10 mL/minute/1.73 m2: 5 to 10 mg/kg/dose every 48 hours - Intermittent hemodialysis: 5 to 10 mg/kg/dose every 48 hours; not removed by hemodialysis; supplemental levofloxacin doses are not required - Peritoneal dialysis (PD): 5 to 10 mg/kg/dose every 48 hours; not removed by peritoneal dialysis; supplemental levofloxacin doses are not required - Continuous renal replacement therapy (CRRT): 10 mg/kg/dose every 24 hours - **Dosing: Hepatic Impairment:** Pediatric - There are no dosage adjustments provided in the manufacturer's labeling; has not been studied; however, dosage adjustment

	unlikely to be necessary due to limited hepatic metabolism. **Moxifloxacin** - **Altered Kidney Function**: No dosage adjustment necessary for any degree of kidney dysfunction. - Hemodialysis, intermittent (thrice weekly): Poorly dialyzed: No supplemental dose or dosage adjustment necessary. - Peritoneal dialysis: Poorly dialyzed: No dosage adjustment necessary - CRRT: No dosage adjustment necessary - PIRRT (eg, sustained, low-efficiency diafiltration): No dosage adjustment necessary - **Dosing: Hepatic Impairment: Adult** - No dosage adjustment necessary; however, use with caution in this patient population secondary to the risk of QT prolongation. - **Altered Kidney Function: Pediatric** - Infants, Children, and Adolescents: There are no pediatric specific recommendations. Based on experience in adult patients, no dosage adjustment necessary. Poorly dialyzed (<10%); no supplemental dose or dosage adjustment necessary, including patients on intermittent hemodialysis, peritoneal dialysis, or continuous renal replacement therapy (eg, CVVHD). - **Dosing: Hepatic Impairment: Pediatric**

	- Infants, Children, and Adolescents: There are no pediatric specific recommendations. Based on experience in adult patients, no dosage adjustment necessary; however, use with caution; metabolic disturbances associated with hepatic insufficiency may lead to QT prolongation.
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Aortic aneurysm/aortic dissection Arthropathy/arthralgia CNS effects/neuroexcitation Clostridioides difficile infection Glucose regulation/dysglycemia Hepatotoxicity Hypersensitivity reactions (immediate and delayed) Myasthenia gravis Peripheral neuropathy Phototoxicity/photoallergy QT prolongation Tendinopathy/tendon rupture
Drug Interactions*	X- Aminolevulinic Acid (Systemic) X- BCG (Intravesical)

	X- Cholera Vaccine X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal) X- Nadifloxacin X- Pimozide X- Strontium Ranelate Depends on Route
Special Population	• **Older adult:** Adverse effects (eg, tendon rupture, QT changes) may be increased in elderly patients. • **G6PD deficiency:** Hemolytic reactions may (rarely) occur with fluoroquinolone use in patients with G6PD deficiency. • **Ciprofloxacin in Pediatric:** Adverse effects, including those related to joints and/or surrounding tissues, are increased in pediatric patients and therefore, ciprofloxacin should not be considered as drug of choice in children (exception is anthrax treatment). • **Levofloxacin in Pediatric:** Safety of use in pediatric patients for >14 days of therapy has not been studied; increased incidence of musculoskeletal disorders (eg, arthralgia, tendon rupture) has been observed in children. • **Appropriate use Moxifloxacin**: [US Boxed Warning]: Reserve use of moxifloxacin for treatment of acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis for patients who have no alternative treatment options because of the risk of disabling and potentially serious adverse reactions (eg, tendinopathy and

	tendon rupture, peripheral neuropathy, CNS effects). **Older Adult Considerations** Ciprofloxacin should not be used as first-line therapy unless the culture and sensitivity findings show resistance to usual therapy. The interactions with caffeine and theophylline can result in serious toxicity in the elderly. Adjust dose for renal function. **Ciprofloxacin/Levofloxacin in elderly:** The risk of torsade de pointes and tendon inflammation and/or rupture associated with the concomitant use of corticosteroids and quinolones is increased in the elderly population.
Pregnancy	**Ciprofloxacin** crosses the placenta and produces measurable concentrations in the amniotic fluid and cord serum. **Levofloxacin** crosses the placenta and can be detected in the amniotic fluid and cord blood. Based on available data, an increased risk of major birth defects, miscarriage, or other adverse fetal and maternal outcomes have not been observed following ciprofloxacin/levofloxacin use during pregnancy. **Moxifloxacin** crosses the placenta**.**
Lactation	**Ciprofloxacin** is present in breast milk. There is a case report of perforated pseudomembranous colitis in a breastfeeding infant whose mother was taking ciprofloxacin (Harmon 1992). In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora. Monitor infants for GI disturbances, such as thrush or diarrhea. **Levofloxacin** is present in breast milk. For indications other than anthrax, the

	manufacturer does not recommend use of levofloxacin in breastfeeding patients during therapy or for 2 days after the last levofloxacin dose due to concerns of potential serious adverse reactions; alternatively, lactating patients can pump and discard breast milk during therapy and for 2 days after the last levofloxacin dose. It is not known if **moxifloxacin** is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Use of fluoroquinolone antibiotics should be avoided if alternative agents are available
Contraindications	Hypersensitivity to **ciprofloxacin**, any component of the formulation, or other quinolones; concurrent administration of tizanidine. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in the US labeling): Concurrent administration of agomelatine. **Levofloxacin:** Hypersensitivity to levofloxacin, any component of the formulation, or other quinolones. Canadian labeling: Additional contraindications (not in US labeling): History of tendinopathy or tendon rupture associated with use of any quinolone antimicrobial agent.

	Hypersensitivity to **moxifloxacin**, other quinolone antibiotics, or any component of the formulation.
Monitoring Requirements	**Ciprofloxacin**: CBC, renal and hepatic function during prolonged therapy, altered mental status, signs and symptoms of tendinopathy (tendon pain, swelling, inflammation, or rupture) or peripheral neuropathy; signs and symptoms of disordered glucose regulation (especially in patients with diabetes mellitus); rash; signs and symptoms of hypersensitivity reaction. **Levofloxacin:** Evaluation of organ system functions (renal, hepatic, and hematopoietic) is recommended periodically during therapy; the possibility of crystalluria should be assessed; WBC and signs of infection, altered mental status, signs and symptoms of tendinopathy (tendon pain, swelling, inflammation, or rupture) or peripheral neuropathy; signs and symptoms of disordered glucose regulation (especially in patients with diabetes mellitus); rash; signs and symptoms of hypersensitivity reaction. **Moxifloxacin:** WBC, signs of infection, signs/symptoms of disordered glucose regulation, ECG in patients with liver cirrhosis.
Precautions	**Ciprofloxacin:** • Concerns related to adverse effects: • Crystalluria: Rarely, crystalluria has occurred; urine alkalinity may increase the risk. Ensure adequate hydration during therapy. • Superinfection: Prolonged use may result in fungal or bacterial superinfection.

	• Disease-related concerns: • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. • Syphilis: Since ciprofloxacin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later. **Levofloxacin**: • Concerns related to adverse effects: • Superinfection: Prolonged use may result in fungal or bacterial superinfection. • Disease-related concerns: • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. • Dosage form specific issues: • Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse (AAP ["Inactive" 1997]; CDC 1982); some data suggests that benzoate displaces bilirubin from protein binding sites (Ahlfors 2001); avoid

	or use dosage forms containing benzyl alcohol with caution in neonates. **Moxifloxacin**: • Concerns related to adverse effects: Altered cardiac conduction: Fluoroquinolones may prolong QTc interval; avoid use in patients with known QTc prolongation, ventricular arrhythmias including torsades de pointes, proarrhythmic conditions (eg, clinically significant bradycardia, acute myocardial ischemia), uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants). • Aortic aneurysm and dissection: Fluoroquinolones have been associated with aortic aneurysm ruptures or dissection within 2 months following use, particularly in elderly patients. Fluoroquinolones should not be used in patients with a known history of aortic aneurysm or those at increased risk, including patients with peripheral atherosclerotic vascular diseases, hypertension, genetic disorders involving blood vessel changes (eg, Marfan syndrome, Ehlers-Danlos syndrome), and elderly patients, unless no other

	treatment options are available. Longer treatment duration (eg, >14 days) may increase risk (Lee 2018). • Glucose regulation: Fluoroquinolones have been associated with disturbances in glucose regulation, including hyperglycemia and hypoglycemia. These events have occurred most often in elderly patients or patients receiving concomitant oral hypoglycemic agents or insulin. Severe cases of hypoglycemia, including coma and death, have been reported. Diabetic patients should be monitored closely for signs/symptoms of disordered glucose regulation. Discontinue if a hypoglycemic reaction occurs and immediately initiate appropriate therapy. • Hepatotoxicity: Fulminant hepatitis potentially leading to liver failure (including fatalities) has been reported with use; patients should be advised to discontinue treatment and promptly report signs/ symptoms of hepatitis (eg, abdominal pain, jaundice, dark urine, pale stools). • Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose,

	or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise. • Photosensitivity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may rarely cause moderate to severe phototoxicity reactions. Discontinue use if phototoxicity occurs. • Serious adverse reactions: [US Boxed Warning]: Fluoroquinolones are associated with disabling and potentially irreversible serious adverse reactions that may occur together, including tendinopathy and tendon rupture, peripheral neuropathy, and CNS effects. Discontinue immediately and avoid use of fluoroquinolones in patients who experience any of these serious adverse reactions. Patients of any age or without pre-existing risk factors have experienced these reactions; may occur within hours to weeks after initiation.

	• CNS effects: Fluoroquinolones have been associated with an increased risk of CNS effects including seizures, increased intracranial pressure (including pseudotumor cerebri), lightheadedness, dizziness, and tremors. May occur following the first dose; discontinue immediately and avoid further use of fluoroquinolones in patients who experience these reactions. Use with caution in patients with known or suspected CNS disorder, or risk factors that may predispose to seizures or lower the seizure threshold. • Peripheral neuropathy: Fluoroquinolones have been associated with an increased risk of peripheral neuropathy; may occur soon after initiation of therapy and may be irreversible; discontinue if symptoms of sensory or sensorimotor neuropathy occur. Avoid use in patients who have previously experienced peripheral neuropathy. • Psychiatric reactions: Fluoroquinolones have been associated with an increased risk of psychiatric reactions, including toxic psychosis, hallucinations, or paranoia; may also cause nervousness, agitation, delirium, attention disturbances, insomnia, anxiety, nightmares, memory impairment, confusion, depression, and suicidal thoughts

	or actions. Use with caution in patients with a history of or risk factor for depression. Reactions may occur following the first dose; discontinue if reaction occurs and institute appropriate therapy. • Tendinopathy/tendon rupture: Fluoroquinolones have been associated with an increased risk of tendinopathy and tendon rupture in all ages; risk may be increased with concurrent corticosteroids, solid organ transplant recipients, and in patients >60 years of age, but has also occurred in patients without these risk factors. Rupture of the Achilles tendon has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps, hand) have also been reported. Inflammation and rupture may occur bilaterally. Cases have been reported within hours or days of initiation, and up to several months after discontinuation of therapy. Strenuous physical activity, renal failure, and previous tendon disorders may be independent risk factor for tendon rupture. Discontinue at first sign of tendon pain, swelling, inflammation or rupture. Avoid use in patients with a history of tendon disorders or who have experienced tendinopathy or tendon rupture. • Superinfection: Prolonged use may result in fungal or bacterial

	superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. • Disease-related concerns: • Cardiovascular disease: Use with caution in patients with significant bradycardia or acute myocardial ischemia. • Diabetes: Use with caution in patients with diabetes mellitus; glucose regulation may be altered. • Hepatic impairment: Use with caution in patients with mild, moderate, or severe hepatic impairment or liver cirrhosis; may increase the risk of QT prolongation. • Myasthenia gravis: [US Boxed Warning]: May exacerbate muscle weakness related to myasthenia gravis; avoid use in patients with known history of myasthenia gravis. Cases of severe exacerbations, including the need for ventilatory support, and deaths have been reported. • Renal impairment: Use with caution in patients with renal failure; may increase risk of tendon rupture. • Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture. • Reserve use of moxifloxacin for treatment of acute bacterial sinusitis or acute bacterial

	exacerbation of chronic bronchitis for patients who have no alternative treatment options because of the risk of disabling and potentially serious adverse reactions (eg, tendinopathy and tendon rupture, peripheral neuropathy, CNS effects).
Black Box Warning	Ciprofloxacin/Levofloxacin/Moxifloxacin: - Serious adverse reactions - Exacerbation of myasthenia gravis
REMS*	**N/A**

Conclusion Statement- Fluoroquinolones

Ciprofloxacin is recommended as an alternative agent in Urology: Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy) Clean with entry into urinary tract, as well as in gastroduodenal/ colorectal/ biliary/and pancreas-kidney or kidney transplant. Levofloxacin is recommended as an alternative agent in Biliary Tract Colorectal, appendectomy, urology surgeries, and Heart Transplant.

2.5 Glycopeptides

2.5.1 Vancomycin

Table 17. Vancomycin Drug Information

SCIENTIFIC NAME Vancomycin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	**Glycopeptide**
Drug Sub-class	
ATC Code	**J01XA01**

	A07AA09
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for infusion Lyophilizate for solution for injection Powder for solution for infusion Powder for concentrate for solution for infusion Powder for solution for injection/infusion Injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	IV: 15 mg/kg (usual maximum: 2 g/dose initially started within 60 to 120 minutes prior to initial surgical incision. Vancomycin doses may be repeated intraoperatively in 2 half-lives (approximately 8 to 12 hours in patients with normal renal function) if procedure is lengthy or if there is excessive blood loss (Ref). In cases where an extension of prophylaxis is warranted postoperatively, total duration should be ≤24 hours (Ref). Postoperative prophylaxis is not recommended in clean and clean-contaminated surgeries.
Maximum Daily Dose Adults*	**2 g/dose initially**
Dose (pediatrics)	Infants, Children, and Adolescents: IV: 15 mg/kg/dose within 120 minutes prior to surgical incision. May be administered in combination with other antibiotics depending upon the surgical procedure
Maximum Daily Dose Pediatrics*	**15 mg/kg/dose within 120 minutes prior to surgical incision**

Adjustment

Vancomycin Initial Dose Adjustments in Altered Kidney Function

CrCl (mL/minute)	Suggested loading dose (when applicable) [a]	Suggested initial maintenance dose	Suggested dosing interval
[a]Loading doses recommended in critically ill patients with suspected/documented serious MRSA infections. A loading dose of up to 35 mg/kg may be considered in critically ill patients with sepsis. Obese patients usually require 20 to 25 mg/kg loading doses. Maximum recommended loading dose is 3 g (ASHP/IDSA/PIDS/SIDP [Rybak 2020]). [b]Monitor vancomycin serum concentrations more frequently, especially early on in therapy, to achieve target concentrations as these patients may have unstable or less predictable drug clearance. Care should be taken not to administer maintenance doses when serum concentrations remain >20 mg/L (Golightly 2013; expert opinion).			
>90 to <130	25 to 30 mg/kg	15 to 20 mg/kg	8 to 12 hours
50 to 90	20 to 25 mg/kg	15 to 20 mg/kg	12 hours
15 to <50	20 to 25 mg/kg	10 to 15 mg/kg	24 hours
<15[b]	20 to 25 mg/kg	10 to 15 mg/kg	48 to 72 hours

Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2): An 8- to 24-hour measured urinary CrCl is necessary to identify these patients.

Intermittent infusion: Loading dose (when applicable): 25 to 35 mg/kg followed by 15 to 20 mg/kg every 8 hours depending on degree of augmented kidney function; some patients may require more frequent dosing (eg, 15 mg/kg every 6 hours) to attain target concentrations; utilize frequent serum concentration monitoring.

Continuous infusion:

Loading dose: Administer an appropriate loading dose (eg, 15 to 20 mg/kg) (Ref); higher loading doses (eg, 25 mg/kg) have been used in some protocols and may vary based on population studied; also refer to institution-specific policies and procedures.

Maintenance dose: 40 to 60 mg/kg/day depending on degree of augmented kidney function with frequent serum concentration monitoring; adjust to achieve a target steady state concentration of 20 to 25 mg/L.

Hemodialysis, intermittent (thrice weekly): Dialyzable (25% to 40% depending on dialyzer permeability).

Vancomycin Dosing Depending on Dose Timing and Dialyzer Permeability[a]

Dose timing and dialyzer permeability	Vancomycin dose[b]
Dose given after dialysis ends	
Low permeability (low flux)	Loading dose: 25 mg/kg Maintenance dose: 7.5 mg/kg[c]

[a]ASHP/IDSA/PIDS/SIDP [Rybak 2020]

[b]Initial recommended loading/maintenance doses. The optimal pharmacokinetic/pharmacodynamic target in this population is unknown, but targeting predialysis concentrations of 15 to 20 mg/L are likely to achieve AUCs of 400 to 600 mg·hour/L (ASHP/IDSA/PIDS/SIDP [Rybak 2020]; Crew 2015). Predialysis serum concentrations should be obtained no less than weekly and should determine subsequent dosing (ASHP/IDSA/PIDS/SIDP [Rybak 2020]).

[c]Thrice-weekly dose administration. Typically, patients may require ~25% larger doses for the 3-day interdialytic period (eg, Friday to Monday) to maintain sufficient vancomycin exposure on the third day.

High permeability (high flux)	Loading dose: 25 mg/kg Maintenance dose: 10 mg/kg[c]
Dose given during last hours of dialysis (intradialytic)	
Low permeability (low flux)	Loading dose: 30 mg/kg Maintenance dose: 7.5 to 10 mg/kg[c]
High permeability (high flux)	Loading dose: 35 mg/kg Maintenance dose: 10 to 15 mg/kg[c]

Peritoneal dialysis:

Loading dose: 20 to 25 mg/kg. A vancomycin serum concentration should be obtained ~48 to 72 hours after the loading dose, and subsequent doses (usually 10 to 15 mg/kg) should be administered based on attainment of goal serum concentrations. Doses may vary based on infection site and severity, as well as the presence or absence of residual renal function. Some experts use maintenance doses of up to 20 mg/kg/dose.

CRRT: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Close monitoring of response and adverse reactions due to drug accumulation is important.

Loading dose: 20 to 25 mg/kg followed by 7.5 to 10 mg/kg every 12 hours with more frequent serum concentration monitoring. In patients with suspected or confirmed serious MRSA infections,

	dose adjustments should be made based on AUC monitoring occurring in the first 24 to 48 hours of therapy. **PIRRT** (eg, sustained, low-efficiency diafiltration): Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Close monitoring of response and adverse reactions due to drug accumulation is important. Loading dose (administer even if PIRRT is occurring): 20 to 25 mg/kg, followed by 15 mg/kg after each PIRRT session ends (or during the final 60 to 90 minutes of the session) with more frequent serum concentration monitoring. In patients with suspected or confirmed serious MRSA infections, dose adjustments should be made based on AUC monitoring occurring in the first 24 to 48 hours of therapy. **Hepatic Impairment: Adult** Oral: There are no dosage adjustments provided in the manufacturer's labeling. However, dosage adjustment unlikely due to low systemic absorption. IV: There are no dosage adjustments provided in the manufacturer's labeling. However, degrees of hepatic dysfunction do not affect the pharmacokinetics of vancomycin. **Obesity: Adult** **Example of dosing regimen:** **Class 1, 2, or 3 obesity (BMI ≥30 kg/m2):** Loading dose: Note: Consider utilizing a loading dose when rapid attainment of target concentrations is necessary (eg, sepsis, documented/suspected methicillin-resistant S. aureus infection) .

	Initial: IV: 20 to 25 mg/kg using actual body weight; maximum loading dose: 3 g. After administration of the loading dose, initiate maintenance dose at the next dosing interval. In critically ill patients, may consider loading doses of 20 to 35 mg/kg using actual body weight; maximum loading dose: 3 g. Maintenance dose: IV: Use actual body weight and the following clearance (CL) equations to calculate a maintenance dose; empiric maintenance doses >4.5 g/day are unlikely to be necessary. Note: If vancomycin therapy is continued, individualize vancomycin dose using early Bayesian approach (ie, 2 serum concentrations within first 24 to 48 hours) to achieve target AUC. 1. Calculate estimated vancomycin CL (Ref). Estimate CL (L/hour): 9.656 – [0.078 × age] – [2.009 × SCr] + [0.04 × actual body weight0.75] + [1.09 × sex]. Where adult age is in years; SCr is serum creatinine in mg/dL; actual body weight in kg scaled to an exponent of 0.75; and sex is 1 if male and 0 if female. 2. Calculate empiric vancomycin maintenance regimen. Estimate daily dose (rounded to nearest 250 mg): Estimated CL (L/hour) × 500 mg•hour/L. Where 500 mg•hour/L is the mid-range AUC target selected for a minimum inhibitory concentration (MIC) of 1 mg/L. When the vancomycin CL is estimated to be ≤3 L/hour, administer the dose every 24 hours or divide the daily dose every 12 hours. If CL is estimated to be >3 L/hour, divide the daily dose and administer every 6 to 12 hours.

	Altered Kidney Function: Pediatric **IV**: Note: Vancomycin levels should be monitored in patients with any renal impairment: Infants, Children, and Adolescents: The following adjustments have been recommended: Note: Renally-adjusted dose recommendations are based on intravenous doses of 10 mg/kg/dose every 6 hours or 15 mg/kg/dose every 8 hours. GFR 30 to 50 mL/minute/1.73 m2: 10 mg/kg/dose every 12 hours. GFR 10 to 29 mL/minute/1.73 m2: 10 mg/kg/dose every 18 to 24 hours. GFR <10 mL/minute/1.73 m2: 10 mg/kg/dose; redose based on serum concentrations. Intermittent hemodialysis: 10 mg/kg/dose; redose based on serum concentrations. Peritoneal dialysis (PD): 10 mg/kg/dose; redose based on serum concentrations. Continuous renal replacement therapy (CRRT): 10 mg/kg/dose every 12 to 24 hours; monitor serum concentrations. **Dosing: Hepatic Impairment: Pediatric** IV: There are no dosage adjustments provided in the manufacturer's labeling; however, degrees of hepatic dysfunction do not affect the pharmacokinetics of vancomycin
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	

ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Anaphylaxis Clostridioides difficile infection Drug-induced immune thrombocytopenia Hypersensitivity reactions (delayed) Nephrotoxicity Neutropenia/pancytopenia Ototoxicity Vancomycin infusion reaction
Drug Interactions*	X- BCG (Intravesical) X- Cholera Vaccine X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal)
Special Population	**Older Adult Considerations** As a result of age-related changes in renal function and volume of distribution, accumulation and toxicity are a risk in the elderly with IV administration. Careful monitoring and dosing adjustment is necessary.
Pregnancy	Vancomycin crosses the placenta and can be detected in fetal serum, amniotic fluid, and cord blood. Adverse fetal effects, including sensorineural hearing loss or nephrotoxicity, have not been reported following maternal use during the second or third trimesters of pregnancy. The pharmacokinetics of vancomycin may be altered during pregnancy and pregnant patients may need a higher dose of vancomycin. Maternal half-life is unchanged, but the volume of distribution and the total plasma clearance may be increased. Individualization of therapy through serum concentration monitoring may

	be warranted. The formulation of vancomycin injection containing the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA) has caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during the first or second trimesters of pregnancy, use other available formulations of vancomycin.
Lactation	Vancomycin is present in breast milk following IV administration. Vancomycin exhibits minimal oral absorption; therefore, the amount available to pass into the milk would be limited following oral administration and unlikely to provide clinically relevant exposure to an infant exposed via breast milk. In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora. Monitor infants for GI disturbances, such as thrush or diarrhea.
Contraindications	Hypersensitivity to vancomycin or any component of the formulation.
Monitoring Requirements	Periodic renal function tests, CBC, pregnancy test prior to use for formulation containing PEG 400 and NADA excipients, serial auditory function testing may be helpful to minimize risk of ototoxicity, serum trough vancomycin concentrations in select patients (eg, aggressive dosing, life-threatening infection, seriously ill, unstable renal function, concurrent nephrotoxins, prolonged courses). AUC monitoring: Frequency of AUC monitoring should be based on clinical judgement; frequent or daily monitoring may be appropriate for

	hemodynamically unstable patients; hemodynamically stable patients may only require once-weekly monitoring. Trough monitoring: Hemodynamically stable patients: Draw trough concentrations at least once weekly. Hemodynamically unstable patients: Draw trough concentrations more frequently or in some instances daily. Prolonged courses (>3 to 5 days): Draw at least one steady-state trough concentration; repeat as clinically appropriate. Note: Drawing >1 trough concentration prior to the fourth dose for short course (<3 days) or lower intensity dosing (target trough concentrations <15 mg/L) is not recommended. For patients with uncomplicated skin and soft tissue infections who are not obese and have normal renal function, serum trough monitoring is generally not needed.
Precautions	Concerns related to adverse effects: • Extravasation and thrombophlebitis: IV vancomycin is an irritant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. Pain, tenderness, and necrosis may occur with extravasation. If thrombophlebitis occurs, slow infusion rates, dilute solution (eg, 2.5 to 5 g/L) and rotate infusion sites. • Superinfection: Prolonged use may result in fungal or bacterial superinfection. Disease-related concerns: • Inflammatory bowel disease: Clinically significant serum concentrations have been reported

	in patients with inflammatory disorders of the intestinal mucosa who have taken oral vancomycin (multiple doses) for the treatment of C. difficile-associated diarrhea. Although use may be warranted, the risk for adverse reactions may be higher in this situation; consider monitoring serum trough concentrations in patients with renal insufficiency, severe colitis, and a prolonged course. • Renal impairment: Use with caution in patients with renal impairment or those receiving other nephrotoxic drugs; dosage modification required and close monitoring is recommended in patients with preexisting renal impairment and those at high risk for renal impairment. Accumulation may occur after multiple oral doses of vancomycin in patients with renal impairment; consider monitoring serum concentrations in this circumstance. Other warnings/precautions: • Appropriate use: Oral vancomycin is only indicated for the treatment of CDI or enterocolitis due to S. aureus and is not effective for systemic infections; parenteral vancomycin is not effective for the treatment of enterocolitis. • Intraocular administration (off-label route): Hemorrhagic occlusive retinal vasculitis (HORV), including permanent visual loss, has been reported in patients receiving intracameral or intravitreal

	administration of vancomycin during or after cataract surgery. • Intraperitoneal administration (off-label route): Use caution when administering intraperitoneally (IP); in some continuous ambulatory peritoneal dialysis (CAPD) patients, chemical peritonitis (cloudy dialysate, fever, severe abdominal pain) has occurred. Symptoms are self-limited and usually clear after vancomycin discontinuation.
Black Box Warning	**Risk of embryo-fetal toxicity due to excipients**
REMS*	**N/A**

Conclusion Statement- Vancomycin

Vancomycin is recommended as an alternative agent in cardio-thoracic surgery, neurology MRSA colonization, orthopedic surgery, vascular surgery, liver transplant, pancreas, or pancreas-kidney transplant.

2.6 Carbapenems

2.6.1 Ertapenem

Table 18. Ertapenem Drug Information

SCIENTIFIC NAME Ertapenem	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	Z29.9
Drug Class	Antibiotic
Drug Sub-class	Carbapenem
ATC Code	**J01DH03**
Pharmacological Class (ASHP)	**N/A**
DRUG INFORMATION	
Dosage Form	**Powder for concentrate for solution for infusion**
Route of Administration	Intravenous Use
Dose (Adult) [DDD]*	1 g within 60 minutes prior to surgical incision. Note: Postoperative prophylaxis is not recommended in clean and clean-contaminated surgeries. Some experts recommend against using ertapenem for surgical prophylaxis out of concern for inducing resistance.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**Children and Adolescents: IV: 15 mg/kg within 60 minutes prior to surgical incision.**
Maximum Daily Dose Pediatrics*	**1,000 mg/dose**
Adjustment	**Altered kidney function: IM, IV:** • CrCl >30 mL/minute: No dosage adjustment necessary.

	• CrCl ≤30 mL/minute: 500 mg once daily. • Hemodialysis, intermittent (thrice weekly): • Daily dosing: IM, IV: 500 mg once daily. When scheduled dose falls on a hemodialysis day, administer at least 6 hours prior to hemodialysis or wait until after hemodialysis; however, if the dose is given within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is required following hemodialysis. • Three times weekly (post hemodialysis) dosing: IM, IV: 500 mg or 1 g 3 times weekly after hemodialysis on hemodialysis days. • Note: Consider patient-specific factors such as body weight, infection severity, and residual kidney function when deciding between doses. • Peritoneal dialysis: IM, IV: 500 mg once daily. • CRRT: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations were developed through Monte Carlo simulation only and based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection), organism minimum inhibitory concentration (MIC), and residual kidney function. Close monitoring of response and adverse reactions (eg, neurotoxicity) due to drug accumulation is important.

	• IM, IV: 1 g once daily. • PIRRT (eg, sustained, low-efficiency diafiltration): Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on daily treatments with 4 to 5 L/hour (Ref) or 10 L/hour (Burkhardt 2009) of dialysate/ultrafiltrate flow rate for each 8- to 10-hour session. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection), organism MIC, and residual kidney function. Close monitoring of response and adverse reactions (eg, neurotoxicity) due to drug accumulation is important. • IM, IV: 500 mg initially, then 500 mg post each PIRRT session or 1 g once daily. **Dosing: Hepatic Impairment: Adult** Adjustments cannot be recommended (lack of experience and research in this patient population). **Altered Kidney Function: Pediatric** There are no pediatric specific recommendations; based on experience in adult patients, dosage adjustment suggested. **Dosing: Hepatic Impairment: Pediatric** There are no dosage adjustments provided in the manufacturer's labeling; has not be adequately studied.
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	

PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	Clostridioides difficile infection CNS effects Hypersensitivity reactions (immediate and delayed)
Drug Interactions*	X- BCG (Intravesical) X- Cholera Vaccine X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal) X- Probenecid X- Taurursodiol
Special Population	**Older adult:** Lower doses (based upon renal function) are often required in the elderly.
Pregnancy	Ertapenem is approved for the treatment of postpartum endomyometritis, septic abortion, and postsurgical infections. Ertapenem may be considered for use as an alternative antibiotic in the treatment of intraamniotic infection.
Lactation	Ertapenem is present in breast milk. The relative infant dose (RID) of ertapenem is <1% when calculated using the highest breast milk concentration located and compared to a weight-adjusted maternal dose of 1 g/day. In general, breastfeeding is considered acceptable when the RID of a medication is <10%. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant

	exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora. Monitor infants for GI disturbances, such as thrush or diarrhea
Contraindications	Known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams; known hypersensitivity to local anesthetics of the amide type due to the use of lidocaine as a diluent (IM use only).
Monitoring Requirements	Periodic renal, hepatic, and hematopoietic assessment during prolonged therapy; neurological assessment.
Precautions	**Disease-related concerns:** • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate to severe renal dysfunction. Increased seizure risk has been reported in patients with renal dysfunction. **Concurrent drug therapy issues:** • Valproic acid and derivatives: Carbapenems, including ertapenem, may decrease the serum concentration of divalproex sodium/valproic acid increasing the risk of breakthrough seizures. Concurrent use of carbapenem antibiotics with divalproex sodium/valproic acid is generally not recommended. Alternative antimicrobial agents should be considered, but if a concurrent

	carbapenem is necessary, consider additional antiseizure medication. ***Other warnings/precautions:*** • IM administration: Doses for IM administration are mixed with lidocaine; consult Lidocaine (Systemic) information for associated Warnings/Precautions.
Black Box Warning	**N/A**
REMS*	**N/A**

Conclusion Statement- Ertapenem

Ertapenem is recommended at a dose of 1 gram as an alternative agent in antimicrobial prophylaxis.

2.7 Penicillins: Piperacillin-Tazobactam, Ampicillin-Sulbactam

Table 19. Penicillins Drug Information

SCIENTIFIC NAME **Piperacillin-tazobactam, Ampicillin-sulbactam**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes Piperacillin-Tazobactam No Ampicillin Sulbactam
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotic
Drug Sub-class	Penicillin
ATC Code	**J01CR05, J01CR01**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	**Powder for solution for infusion** **powder for solution for injection**
Route of Administration	Intravenous use Intramuscular and intravenous use Parenteral use

Dose (Adult) [DDD]*	Pip-tazo: 3.375 g IV single dose within 60 minutes prior to incision[3] Ampicillin-Sulbactam: 3 g within 60 minutes prior to surgical incision. Doses may be repeated in 2 hours if procedure is lengthy or if there is excessive blood loss. Note: Consider local susceptibility patterns prior to use. In cases in which extension of prophylaxis is warranted postoperatively, total duration should be ≤24 hours. Postoperative prophylaxis is not recommended in clean and clean-contaminated surgeries.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**Pip-Tazo:** **Infants 2 to 9 months: IV:** 80 mg piperacillin/kg within 60 minutes prior to surgical incision; may repeat in 2 hours for prolonged procedure or excessive blood loss (eg, >1,500 mL in adults). **Infants >9 months, Children, and Adolescents weighing ≤40 kg:** IV: 100 mg piperacillin/kg within 60 minutes prior to surgical incision; may repeat in 2 hours for prolonged procedure or excessive blood loss (eg, >1,500 mL in adults). Maximum dose: 3,000 mg piperacillin/dose. **Adolescents weighing >40 kg:** IV: 3,000 mg piperacillin within 60 minutes prior to surgical incision; may repeat in 2 hours for prolonged procedure or excessive blood loss (eg, >1,500 mL in adults) **Ampicillin-Sulbactam:** Children and Adolescents: IV: 50 mg ampicillin/kg/dose within 60 minutes prior to procedure; may repeat in 2 hours if lengthy procedure or excessive

<table>
<tr><td></td><td>blood loss; maximum dose: 2,000 mg ampicillin/dose.</td></tr>
<tr><td>Maximum Daily Dose Pediatrics*</td><td>3,000 mg piperacillin/dose
2,000 mg ampicillin/dose.</td></tr>
<tr><td>Adjustment</td><td><u>PIPERACILLIN-TAZOBACTAM:</u>
Altered kidney function: IV:
Piperacillin/Tazobactam Dosage Adjustments in
<table>
<tr><th></th><th colspan="2">Traditional infusion method (c minutes)</th></tr>
<tr><th>CrCl (mL/minute)</th><th>If the usual recommended dose is 3.375 g every 6 hours</th><th>If the usual recommen dose is 4.5 6 hours</th></tr>
<tr><td colspan="3">[a]Choose the usual recommended dose based on ir severity (see adult dosing), then choose the adjuste corresponding to the patient's CrCl.
[b]Patel 2010; Thabit 2017; expert opinion; manufactu</td></tr>
<tr><td>100 to <130</td><td>Extended infusion preferred</td><td>Extended ir preferred</td></tr>
<tr><td>40 to <100 (usual recommended dose)</td><td>3.375 g every 6 hours</td><td>4.5 g every (</td></tr>
<tr><td>20 to <40</td><td>2.25 g every 6 hours</td><td>4.5 g every 8 hours or 3.3 every 6 hou</td></tr>
<tr><td><20</td><td>2.25 g every 8 hours</td><td>4.5 g every 1 hours or 2.2 every 6 hou</td></tr>
</table>
Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m2): An 8 to 24 hour measured urinary creatinine clearance is necessary to identify these patients.
CrCl 130 to <170 mL/minute: IV: 4.5 g every 6 hours infused over 3 hours or Loading dose: 4.5 g, followed immediately by a daily continuous infusion of 18 g over 24 hours.</td></tr>
</table>

	CrCl ≥170 mL/minute: IV: Loading dose: 4.5 g, followed immediately by a daily continuous infusion of 22.5 g over 24 hours. **Hemodialysis, intermittent (thrice weekly): Dialyzable (30% to 40%): IV:** 4.5 g every 12 hours or 2.25 g every 8 hours; administration of scheduled doses after hemodialysis on dialysis days is preferred but not required. **Peritoneal dialysis: Dialyzable (6% of piperacillin, 21% of tazobactam):** IV: 4.5 g every 12 hours or 2.25 g every 8 hours. **CRRT:** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations assume high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (~1,500 to 3,000 mL/hour), unless otherwise noted. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions due to drug accumulation is important. **CVVH/CVVHD/CVVHDF:** Note: Given piperacillin/tazobactam's favorable safety profile, some experts recommend initiating therapy with relatively high doses (especially in critically ill patients). Dose should be adjusted during CRRT interruptions as ongoing dosing may lead to accumulation and potential increased risk of toxicity.**IV: 4**.5 g every 8 hours (Ref) or 4.5 g loading dose followed by 2.25 g every 6 hours .

Continuous IV infusion: 4.5 g loading dose followed immediately by a 9 g over 24 hours daily maintenance dose.

PIRRT (eg, sustained low-efficiency diafiltration): Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection). Close monitoring of response and adverse reactions due to drug accumulation is important.

IV: Sustained low-efficiency dialysis (8-hour daily sessions with blood flow rate 200 mL/minute and effluent flow rate 300 mL/minute): 3.375 g every 8 hours.

Extended high-volume hemofiltration (10-hour sessions with blood flow rate 200 mL/minute and effluent flow rate >500 mL/minute): 4.5 g every 8 hours.

Dosing: Hepatic Impairment: Adult

No dosage adjustment necessary.

Infants, Children, and Adolescents: IV:

Piperacillin/Tazobactam Dosage Adjustments in Function[a, b, c]

	Traditional infusion method (over 30 m

[a] Choose usual recommended dose based on indic severity (see "Dosing: Pediatric"), then choose the a that column corresponding to the patient's eGFR.

[b] Maximum dose: 4,000 mg/dose.

[c] When targeting pathogens with elevated minima concentrations (MICs), consider dose needed for n addition to severity and site of infection; consider n concentrations if available.

[d] For dose recommendations >400 mg/kg/day, use assessment of risks and benefits) to make patient- adjustment if kidney function is altered; consider t monitoring if available.

	If the usual recommended dose is 200 to 300 mg/kg/**day**		If the usual recommended dose is 300 to 400 mg/kg/**day**[d]		If the recom ded d 300 t mg/k
eGFR	Usual dose: 67 to 100 mg piperacillin/ kg/dose every 8 hours	Usual dose: 50 to 75 mg piperacillin/ kg/dose every 6 hours	Usual dose: 100 to 133 mg piperacillin/ kg/dose every 8 hours	Usual dose: 75 to 100 mg piperacillin/ kg/dose every 6 hours	Usua 100 m piper kg/do infus 3 to 4 every hours
≥40 mL/minute/1.73 m^2 (usual recommended dose)	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary	No dosage adjustment necessary	No do adjus neces
20 to <40 mL/minute/1.73 m^2	45 to 70 mg piperacillin/ kg/dose every 8 hours	35 to 50 mg piperacillin/ kg/dose every 6 hours	70 to 90 mg piperacillin/ kg/dose every 8 hours	50 to 70 mg piperacillin/ kg/dose every 6 hours	70 m piper kg/do infus 3 to 4 every hours
<20 mL/minute/1.73 m^2	45 to 70 mg piperacillin/ kg/dose every 12 hours	35 to 50 mg piperacillin/ kg/dose every 8 hours	70 to 90 mg piperacillin/ kg/dose every 12 hours	50 to 70 mg piperacillin/ kg/dose every 8 hours	70 m piper kg/do infus 3 to 4 every hours

Hemodialysis, intermittent: Dialyzable: 30% to 40% of administered drug removed by dialysis.

Infants, Children, and Adolescents: IV: 50 to 100 mg piperacillin/kg/dose every 12 hours; administer scheduled doses after hemodialysis on dialysis days if possible

Peritoneal dialysis: Dialyzable: ~6% piperacillin and 21% tazobactam.

	Infants, Children, and Adolescents: IV: 50 to 100 mg piperacillin/kg/dose every 12 hours **CRRT:** **Note:** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and ultrafiltration rates of 68 mL/kg/hour unless otherwise noted; flow rates vary widely in pediatric patients. Appropriate dosing requires consideration of drug penetration to site of infection, MIC of bacteria, and severity of illness. Close monitoring of response and adverse reactions due to drug accumulation (eg, neurotoxicity) is important. Due to minimal data in pediatric patients receiving CRRT, consider monitoring serum concentrations (eg, trough concentration) if available. Children and Adolescents: *Intermittent infusion*: IV: 100 mg piperacillin/kg/dose every 8 hours *Continuous infusion*: IV: 200 mg piperacillin/kg/dose infused over 24 hrs. **Augmented renal clearance:** **Note:** Augmented renal clearance (ARC) is a condition that occurs in certain critically ill patients without organ dysfunction and with normal serum creatinine concentrations that results in increased drug elimination. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients. When available, consider utilizing extended infusion due to higher probability of attaining pharmacodynamic targets. Children and Adolescents: GFR ≥130 mL/minute/1.73 m^2:

	Traditional or extended infusion: IV: 100 mg piperacillin/kg/dose every 6 hours; infuse over 3 to 4 hours if possible. *Continuous infusion*: IV: Loading dose: 100 mg piperacillin/kg infused over 30 minutes, followed by 400 mg/kg/dose infused over 24 hours. **Dosing: Hepatic Impairment: Pediatric** Infants ≥2 months, Children, and Adolescents: No dosing adjustment necessary. **<u>AMPICILLIN-SULBACTAM:</u>** **Altered kidney function**: **IV:** **Note:** Estimation of renal function for the purpose of drug dosing should be done using the Cockcroft-Gault formula. Dosage recommendations are expressed as grams of **ampicillin/sulbactam** combination CrCl ≥30 mL/minute: No dosage adjustment necessary. CrCl 15 to 29 mL/minute: 1.5 to 3 g every 12 hours. CrCl 5 to 14 mL/minute: 1.5 to 3 g every 24 hours. **Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m^2):** Augmented renal clearance (ARC) is a condition that occurs in certain critically-ill patients without organ dysfunction and with normal serum creatinine concentrations. Young patients (<55 years of age) admitted post trauma or major surgery are at highest risk for ARC, as well as those with sepsis, burns, or hematologic malignancies. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients

	IV: 1.5 to 3 g every 4 to 6 hours (expert opinion). **Hemodialysis, intermittent (thrice weekly):** Dialyzable (39% to 63%) **IV:** 1.5 to 3 g every 12 to 24 hours; administer after dialysis when scheduled dose falls on dialysis days **Peritoneal dialysis: IV:** 1.5 g every 12 hours or 3 g every 24 hours **CRRT:** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, neurotoxicity) due to drug accumulation is important. CVVH/CVVHD/CVVHDF: **IV:** 3 g every 8 to 12 hours **PIRRT (eg, sustained, low-efficiency diafiltration):** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, neurotoxicity) due to drug accumulation is important. **IV:** Initial: 3 g followed by 1.5 to 3 g every 8 to 12 hours. Where possible, give one dose after PIRRT session **Dosing: Hepatic Impairment: Adult**

	There is no dosage adjustment provided in the manufacturer's labeling. **Children and Adolescents: IV:** CrCl ≥30 mL/minute/1.73 m^2: No dosage adjustment required. CrCl 15 to 29 mL/minute/1.73 m^2: Administer every 12 hours. CrCl 5 to 14 mL/minute/1.73 m^2: Administer every 24 hours. **Dosing: Hepatic Impairment: Pediatric** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	Piperacillin-Tazobactam: AGE
AGE (Age Edit): Piperacillin-Tazobactam: Not for infants <2 months	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Pip-Tazo:** Clostridioides difficile infection Drug-induced immune thrombocytopenia Hematologic effects Hypersensitivity reactions (delayed) Hypersensitivity reactions (immediate) Nephrotoxicity Neurotoxicity **Amp-Sulbactam:** Pain at injection site, thrombophlebitis, Diarrhea, Lymphocytosis (atypical), mucous membrane bleeding, candidiasis, chest pain, edema, fatigue
Drug Interactions*	X- BCG (Intravesical)

	X- Cholera Vaccine X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal)
Special Population	**Older Adult Considerations** Has not been studied exclusively in the elderly. Adjust dose for renal function.
Pregnancy	**Piperacillin and tazobactam** cross the placenta. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of piperacillin/tazobactam may be altered. Both **ampicillin and sulbactam** cross the placenta. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of ampicillin/sulbactam may be altered. As a class, penicillin antibiotics are widely used in pregnant women. Based on available data, penicillin antibiotics are generally considered compatible for use during pregnancy.
Lactation	**Piperacillin** is present in breast milk; information for tazobactam is not available. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Piperacillin/tazobactam is considered compatible with breastfeeding in women when used for the treatment of airway diseases, such as cystic fibrosis. Bioavailability is expected to be low if ingested orally (eg, via breast milk); however, intestinal absorption may be increased in neonates. In general, antibiotics that are present in breast milk may cause non-dose-related modification of bowel flora.

	Monitor infants for GI disturbances, such as thrush and diarrhea. **Ampicillin and sulbactam** are present in breast milk. A review article notes the exposure of ampicillin and sulbactam to a breastfeeding infant would be ~1% to 2% of a typical adult dose. The manufacturer recommends that caution be used if administering to breastfeeding patients. Ampicillin is considered compatible with breastfeeding when used in usual recommended doses. In general, antibiotics that are present in breast milk may cause nondose-related modification of bowel flora. Monitor infants for GI disturbances.
Contraindications	Hypersensitivity to **penicillin's**, cephalosporins, beta-lactamase inhibitors, or any component of the formulation. Hypersensitivity (eg, anaphylaxis or Stevens-Johnson syndrome) to **ampicillin, sulbactam**, or to other beta-lactam antibacterial drugs (eg, penicillins, cephalosporins), or any component of the formulations; history of cholestatic jaundice or hepatic dysfunction associated with ampicillin/sulbactam
Monitoring Requirements	**Pip-Tazo**: Creatinine, BUN, hematologic parameters (especially with prolonged [≥21 days] use; eg, CBC with differential, PT, PTT), serum electrolytes, LFTs, urinalysis; signs of bleeding; monitor for signs of anaphylaxis during first dose, if a skin rash develops monitor closely, CNS effects. **Amp-Sulb**: With prolonged therapy, monitor hematologic, renal, and hepatic function; monitor for signs of

	anaphylaxis during first dose. In patients with preexisting hepatic impairment, monitor hepatic function at regular intervals.
Precautions	**Pip-Tazo:** **Concerns related to adverse effects:** · Electrolyte abnormalities: Sodium content (2.8 mEq per gram of piperacillin) should be considered in patients requiring sodium restriction. Assess electrolytes periodically in patients with low potassium reserves. · Superinfection: Use may result in fungal or bacterial superinfection. **Disease-related concerns:** · Renal impairment: Use with caution in patients with renal impairment or in hemodialysis patients. Dosage adjustment recommended. **Amp-Sulbactam:** Concerns related to adverse effects: • Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity or a history of sensitivity to multiple allergens. Patients with a history of penicillin hypersensitivity have experienced severe reactions when treated with cephalosporins. Before initiating therapy, carefully investigate previous penicillin, cephalosporin, or other allergen hypersensitivity. If an allergic reaction occurs, discontinue and institute appropriate therapy. • Hepatic dysfunction: Hepatitis and cholestatic jaundice have been

	reported (including fatalities). Toxicity is usually reversible. Monitor hepatic function at regular intervals in patients with hepatic impairment. • Rash: Appearance of a rash should be carefully evaluated to differentiate a nonallergic ampicillin rash from a hypersensitivity reaction; rash occurs in 5% to 10% of children and is a generalized dull red, maculopapular rash, generally appearing 3-14 days after the start of therapy. It normally begins on the trunk and spreads over most of the body. It may be most intense at pressure areas, elbows, and knees. • Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Disease-related concerns: • Hepatic impairment: Hepatotoxicity has been reported. Monitor hepatic function at regular intervals in patients with hepatic impairment. • Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibacterials are not recommended in these patients. • Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.
Black Box Warning	**N/A**
REMS*	**N/A**

Conclusion Statement- Penicillins

Piperacillin-Tazobactam is the preferred agent in liver transplantation. Third-generation cephalosporin plus ampicillin or piperacillin-tazobactam are preferred and recommended for up to 24 hours. Another alternative would be ampicillin-sulbactam or intravenous amoxicillin-clavulanate for ≤48 hours. In pancreas and pancreas-kidney transplantation: ampicillin-sulbactam for ≤48 hours is recommended as a preferred agent.

2.8 Nitroimidazoles

2.8.1 Metronidazole

Table 20. Metronidazole Drug Information

SCIENTIFIC NAME METRONIDAZOLE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	Z29.9
Drug Class	Antibiotic
Drug Sub-class	Antiprotozoal, Nitroimidazole
ATC Code	**J01XD01** **P01AB01**
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution Solution for infusion Film-coated tablet Suspension Tablet
Route of Administration	Intravenous use Oral use
Dose (Adult) [DDD]*	**IV:** 500 mg within 60 minutes prior to surgical incision in combination with other antibiotics. Considered a

	recommended agent for select procedures involving the GI tract, urologic tract, or head and neck **Oral:** Colorectal surgical prophylaxis (off-label use): 1 g every 3 to 4 hours for 3 doses with additional oral antibiotics, starting after mechanical bowel preparation the evening before a morning surgery and followed by an appropriate IV antibiotic prophylaxis regimen. **Uterine evacuation (induced abortion or pregnancy loss) (alternative agent) (off-label use):** 500 mg as a single dose 1 hour prior to uterine aspiration; may be administered up to 12 hours before the procedure. Note: The optimal dosing regimen has not been established; various protocols are in use.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**Children and Adolescents:** IV: 15 mg/kg as a single dose 30 to 60 minutes prior to procedure; maximum dose: 500 mg/dose. **Surgical prophylaxis, colorectal:** **Children and Adolescents:** Oral: 15 mg/kg/dose every 3 to 4 hours for 3 doses, starting after mechanical bowel preparation the afternoon and evening before the procedure, with or without additional oral antibiotics and with an appropriate IV antibiotic prophylaxis regimen; maximum dose: 1,000 mg/dose
Maximum Daily Dose Pediatrics*	IV: 500 mg/dose PO: 1,000 mg/dose
Adjustment	**Altered kidney function:** **IV, Oral:** **CrCl ≥10 mL/minute:** No dosage adjustment necessary; however,

	monitor closely for adverse effects due to accumulation of metabolites in patients with more severe impairment (CrCl <30 mL/minute), particularly with prolonged courses of therapy. **CrCl <10 mL/minute:** No dosage adjustment necessary; however, monitor closely for adverse effects due to accumulation of metabolites, particularly with prolonged courses of therapy. A dose of 500 mg every 12 hours may be adequate to achieve therapeutic plasma levels for nonsevere non-Clostridioides difficile infections. **Hemodialysis, intermittent (thrice weekly):** Dialyzable (42% to 65% metronidazole and hydroxyl and acetic acid metabolites): **IV, Oral: Usual dose:** 500 mg every 8 to 12 hours. Note: Larger doses may be utilized depending on clinical indication, but with close monitoring for adverse effects, particularly if the treatment course is >1 to 2 weeks in duration. On dialysis days, administer after dialysis. If administration cannot be separated from hemodialysis, consider supplemental dose following hemodialysis. **Peritoneal dialysis: Minimally dialyzed (10% removal with single long dwell:** IV, Oral: No dosage adjustment necessary. Monitor for adverse effects due to metabolite accumulation, particularly if the treatment course is >1 to 2 weeks in duration. **CRRT: IV, Oral:** No dosage adjustment necessary. **PIRRT (eg, sustained, low-efficiency diafiltration):**

	IV, Oral: No dosage adjustment necessary. On PIRRT days, administer after PIRRT session. If administration cannot be separated from PIRRT, consider supplemental dose following completion of PIRRT session. **Dosing: Hepatic Impairment: Adult** **The hepatic dosing** Note: Metronidazole clearance is decreased, and elimination half-life is prolonged in patients with cirrhosis. Prolonged use or total cumulative dose may result in accumulation that has been linked to neurotoxicity and encephalopathy, which may be irreversible. Metronidazole-induced encephalopathy can usually be confirmed (~90% of cases) through MRI (eg, T2 weighted/coronal fluid-attenuated inversion recovery sequences demonstrating symmetric lesions of the dendritic nuclei). Close monitoring is warranted for early recognition of metronidazole-induced encephalopathy in patients with cirrhosis. Hepatic impairment prior to treatment initiation: Single-dose regimens (eg, 2 g once) do not require dose adjustment. Child-Turcotte-Pugh class A and B: No dosage adjustment necessary. Child-Turcotte-Pugh class C: Oral, IV: Capsules: Amebiasis: 375 mg 3 times daily. Trichomoniasis: 375 mg once daily. Injection, tablets: If usual recommended frequency is every 12 hours: No adjustment necessary. If usual recommended frequency is every 6 to 8 hours: Maintain dose but

	reduce frequency to every 12 hours. For example, if usual recommended dose is 500 mg every 6 hours, then reduce to 500 mg every 12 hours. Oral suspension: Reduce dose by 50% Infants, Children, and Adolescents: Manufacturer's labeling: • Mild, moderate, or severe impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, decreased renal function does not alter the single-dose pharmacokinetics. • ESRD requiring dialysis: Metronidazole metabolites may accumulate; monitor for adverse events; accumulated metabolites may be rapidly removed by dialysis. • Intermittent hemodialysis (IHD): If administration cannot be separated from hemodialysis, consider supplemental dose following hemodialysis. • Peritoneal dialysis (PD): No dosage adjustment necessary. • Alternate dosing: Others have used the following adjustments. Note: Renally adjusted dose recommendations are based on doses of 15 to 30 mg/kg/day divided every 6 to 8 hours. • GFR ≥10 mL/minute/1.73 m2: No adjustment required. • GFR <10 mL/minute/1.73 m2: 4 mg/kg/dose every 6 hours. • Intermittent hemodialysis (IHD): Extensively removed by hemodialysis: 4 mg/kg/dose every 6 hours.

	• Peritoneal dialysis (PD): Extensively removed by peritoneal dialysis: 4 mg/kg/dose every 6 hours. • Continuous renal replacement therapy (CRRT): No adjustment required. **Dosing: Hepatic Impairment: Pediatric Infants, Children, and Adolescents:** Mild or moderate impairment: No dosage adjustment necessary; use with caution and monitor for adverse events. Severe impairment: Reduce dose by 50%. Based on experience in adult patients, the dosing interval may be prolonged while maintaining the usual individual dose (eg, administration of the usual dose but scheduling it every 12 hours instead of every 6).
Prescribing edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a surgeon or infectious disease specialist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	CNS effects Disulfiram-like reaction
Drug Interactions*	X- Alcohol (Ethyl) X- BCG (Intravesical) X- Carbocisteine Depends on Dosage Form X- Cholera Vaccine X- DiazePAM Depends on Dosage Form X- Digoxin Depends on Dosage Form

	X- Dimethindene (Systemic) Depends on Dosage Form X- Disulfiram X- DroNABinol Depends on Dosage Form X- Etomidate Depends on Dosage Form X- Fecal Microbiota (Live) (Oral) X- Fecal Microbiota (Live) (Rectal) X- LORazepam Depends on Dosage Form X- Mebendazole X- PENTobarbital Depends on Dosage Form X- Ritonavir Depends on Dosage Form X- Sulfamethoxazole Depends on Dosage Form
Special Population	Older Adult Considerations: Adjust dose based on renal function.
Pregnancy	Metronidazole crosses the placenta. Cleft lip with or without cleft palate has been reported following first trimester exposure to metronidazole; however, most studies have not shown an increased risk of congenital anomalies or other adverse events to the fetus following maternal use during pregnancy. Because metronidazole was carcinogenic in some animal species, concern has been raised whether metronidazole should be used during pregnancy. Available studies have not shown an increased risk of infant cancer following metronidazole exposure during pregnancy; however, the ability to detect a signal for this may have been limited. Metronidazole pharmacokinetics are similar between pregnant and nonpregnant patients. The use of other agents is preferred when treatment is needed for

	Clostridioides difficile during pregnancy. Consult current recommendations for appropriate use in pregnant patients.
Lactation	Metronidazole and its active hydroxyl metabolite are present in breast milk at concentrations similar to maternal plasma concentrations. Breast milk was evaluated following administration of metronidazole 500 mg IV 3 times a day for 2 days to patients following cesarean delivery. Sampling occurred 1 to 2 hours after the dose on the second day of therapy. Metronidazole concentrations were 7.3 to 10.1 mcg/mL (breast milk) and 7.7 to 13.1 mcg/mL (maternal plasma). Metronidazole and its active metabolite can be detected in the serum of breastfeeding infants. A potential for tumorigenicity was observed following chronic oral doses in animal studies; the clinical relevance of this is unclear. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Alternately, the mother can express and discard milk for 48 hours after the last dose and feed the infant stored human milk or formula. Some guidelines note if metronidazole is given, breastfeeding should be withheld for 12 to 24 hours after a single 2 g dose alternatively, the mother may pump and discard breast milk for 24 hours after taking the last metronidazole dose. Use of lower maternal doses may provide lower concentrations of metronidazole in breast milk and use can be considered

	in patients who are breastfeeding. Use of other agents is preferred when treating breastfeeding patients for diseases such as Clostridioides difficile infection, or pouchitis or perianal disease in lactating patients with inflammatory bowel disease
Contraindications	Hypersensitivity to metronidazole, nitroimidazole derivatives, or any component of the formulation; during the first trimester of pregnancy in patients with trichomoniasis (with the exception of Likmez); use of disulfiram within the past 2 weeks; use of alcohol or propylene glycol-containing products during therapy or within 3 days of therapy discontinuation; Cockayne syndrome. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Note: Although the manufacturer's labeling lists use of alcohol-containing products during therapy or within 3 days of therapy discontinuation as a contraindication, the CDC sexually transmitted infection guidelines state refraining from alcohol use while taking metronidazole is not necessary. Clinical data demonstrating an association between concomitant use with alcohol and a disulfiram-like reaction are conflicting. Canadian labeling: Additional contraindications (not in the US labeling): Active neurological disorders; history of blood dyscrasia; hypothyroidism; hypoadrenalism.
Monitoring Requirements	Monitor CBC with differential at baseline, during, and after prolonged or

	repeated courses of therapy. Closely monitor elderly patients and patients with severe hepatic impairment or ESRD for adverse reactions. Neurologic symptoms; observe patients carefully if neurologic symptoms occur and consider discontinuation of therapy.
Precautions	**Concerns related to adverse effects**: • Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. **Disease-related concerns**: • Hepatic impairment: Use with caution in patients with hepatic impairment due to potential accumulation; dosage adjustment recommended in patients with severe hepatic impairment. • Renal impairment: Use with caution in patients with renal impairment due to potential accumulation; dosage adjustments may be required. • Seizure disorder: Use with caution in patients with a history of seizure disorder. **Dosage-form specific issues**: Injection: Use injection with caution in patients with heart failure, edema, or other sodium-retaining states, including corticosteroid treatment due to high sodium content. In patients receiving continuous nasogastric secretion aspiration, sufficient metronidazole may be removed in the aspirate to cause a reduction in serum levels.
Black Box Warning	**Carcinogenic**

REMS*	**N/A**

Conclusion Statement- Metronidazole

For appendectomy, obstructed small intestinal and colorectal surgery, Metronidazole is recommended. It is also added in clean – contaminated head/neck surgeries (cancer or other procedure with exception of tonsillectomy and functional endoscopic sinus procedure) and urology surgeries as a step therapy.

Section 3.0 Key Recommendations Synthesis

Stanford Health Care Surgical Antimicrobial Prophylaxis Guidelines (Revised 2019)

- Cefazolin is the preferred regimen for cardiac, vascular, thoracic surgeries, cardiac device insertion (e.g., pacemaker implantation), gastroduodenal surgeries, biliary tract surgeries, gynecological surgeries, head and neck surgeries (clean incision through the skin and ear/sinonasal procedure (clean-contaminated), urological surgeries, neurosurgeries, orthopedics surgeries, other general surgeries, plastic surgeries and cesarean delivery.
- The combination of cefazolin and vancomycin is considered as the preferred regimen for cardiac surgeries with prosthetic material and heart transplant surgeries. In cases of beta-lactam allergy, the use of vancomycin monotherapy is recommended in cardiac surgeries with prosthetic material, however, in heart transplant surgeries, the combination of vancomycin and levofloxacin is recommended.
- The combination of cefazolin and metronidazole is recommended as the preferred regimen in colorectal surgeries and appendectomy.
- The combination of vancomycin and cefepime is recommended as the preferred regimen in lung or heart-lung transplant surgeries. In cases of beta-lactam allergy, the use of vancomycin and aztreonam is recommended.
- Metronidazole is added to cefazolin in clean-contaminated (head and neck surgeries) such as procedures with oral mucosa breach and contaminated incisions.
- In liver transplant surgeries, piperacillin/tazobactam is the preferred agent. In cases of beta-lactam allergy, the recommended regimens constitute of either vancomycin or clindamycin plus ciprofloxacin.
- The combination of metronidazole and levofloxacin is recommended in biliary tract surgeries, colorectal surgeries and appendectomy.

- The combination of clindamycin and gentamicin is recommended as an alternative regimen for cesarean delivery and gynecological surgeries.
- Clindamycin is recommended as an alternative agent in head and neck surgeries in cases of beta-lactam allergy.
- Vancomycin is recommended as an alternative to cefazolin for neurosurgeries, orthopedic surgeries, and pediatric surgeries in cases of beta-lactam allergies.
- Cefoxitin is preferred in cases of open/laparoscopic involving intestine surgeries (clean-contaminated, e.g., radical cystectomy with ileal conduit). If prosthetic material is involved in urologic procedures, a one-time dose of gentamicin should be added.
- In case of beta-lactam allergy, the combination of gentamicin and clindamycin is used as an alternative to cefazolin in urologic surgeries in cases of beta-lactam allergies. For open/laparoscopic surgeries (clean skin incision, does not involve GU tract), clindamycin can be used as monotherapy. For open/laparoscopic involving intestine surgeries (clean-contaminated, e.g., radical cystectomy with ileal conduit), the combination of metronidazole and levofloxacin is recommended. If prosthetic material is involved in urologic procedures, a one-time dose of gentamicin should be added if not already given.
- In cases of beta-lactam allergy, the use of vancomycin is recommended for cardiac, vascular, thoracic surgeries, cardiac device insertion (e.g., pacemaker implantation), cardiac surgery with prosthetic material, other general surgeries (e.g. hernia repair, breast), neurosurgeries and orthopedics surgeries.
- The combination of gentamicin and vancomycin is recommended in gastroduodenal surgeries as an alternative to cefazolin in cases of beta-lactam allergy.

American Dental Association (ADA) Antibiotic Prophylaxis Prior to Dental Procedures (2022)

- In general, prophylactic antibiotics are not recommended for patients with prosthetic joint implants before dental procedures to prevent prosthetic joint infection.
- Prophylaxis is reasonable for specific patient categories, including those with prosthetic cardiac valves, a history of infective endocarditis, or certain congenital heart diseases.

- Prophylactic antibiotics may be appropriate for children with cyanotic congenital heart disease, unrepaired defects, or repaired defects within the first six months post-repair.
- Clindamycin is no longer recommended due to potential severe reactions; alternative antibiotics include cephalexin, azithromycin, clarithromycin, doxycycline, cefazolin, and ceftriaxone.
- Cephalosporins should be avoided in individuals with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in surgical antibiotic prophylaxis.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed

- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for guideline search:

Query	Filters	Search Details	Results
((((((Antibiotic Prophylaxis[MeSH Terms]) OR (Prophylaxis, Antibiotic[Title/Abstract])) OR (Premedication, Antibiotic[Title/Abstract])) OR (Antibiotic Premedication[Title/Abstract])) OR (Antibiotic Premedications[Title/Abstract])) OR (Premedications, Antibiotic[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))) AND (((General Surgery[MeSH Terms]) OR (Surgery, General[Title/Abstract])) OR (Surgery[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])))	Guideline, in the last 5 years	("antibiotic prophylaxis"[MeSH Terms] OR "prophylaxis antibiotic"[Title/Abstract] OR (("premedicate"[All Fields] OR "premedicated"[All Fields] OR "premedicating"[All Fields] OR "Premedication"[MeSH Terms] OR "Premedication"[All Fields] OR "Premedications"[All Fields]) AND "Antibiotic"[Title/Abstract]) OR "antibiotic premedication"[Title/Abstract] OR (("anti bacterial agents"[Pharmacological Action] OR "anti bacterial agents"[MeSH Terms] OR ("anti bacterial"[All Fields] AND "agents"[All Fields]) OR "anti bacterial agents"[All Fields] OR "Antibiotic"[All Fields] OR "antibiotics"[All Fields] OR "antibiotic s"[All Fields] OR "antibiotical"[All Fields]) AND "Premedications"[Title/Abstract]) OR (("premedicate"[All Fields] OR "premedicated"[All Fields] OR "premedicating"[All Fields] OR "Premedication"[MeSH Terms] OR "Premedication"[All Fields] OR "Premedications"[All Fields]) AND "Antibiotic"[Title/Abstract])) AND ("2018/12/12 00:00":"3000/01/01 05:00"[Date - Publication] AND "guideline"[Publication Type]) AND (("general surgery"[MeSH Terms] OR "surgery general"[Title/Abstract] OR "Surgery"[Title/Abstract]) AND ("2018/12/12 00:00":"3000/01/01 05:00"[Date - Publication] AND "guideline"[Publication Type]))	6

Appendix D. Treatment Algorithm

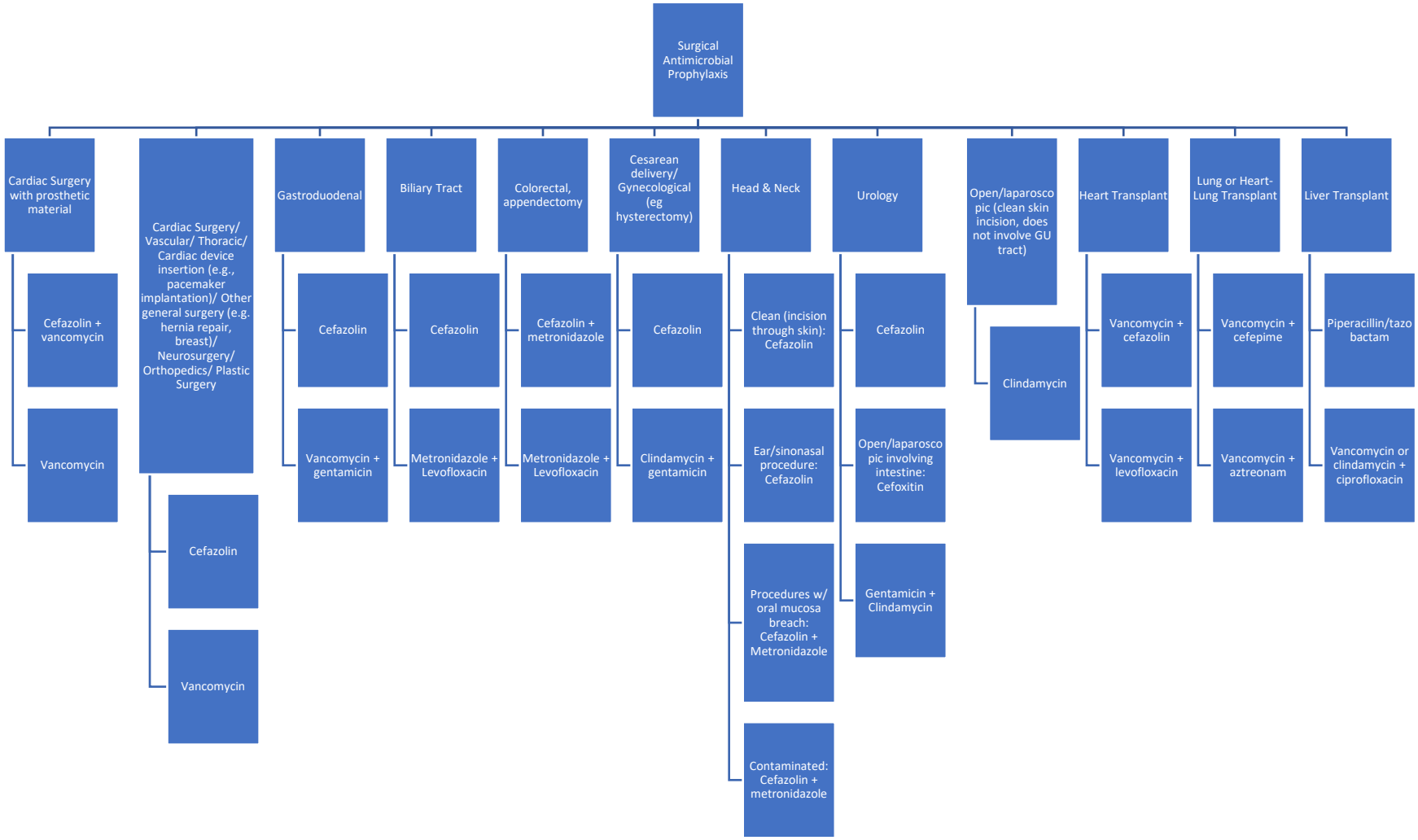

***Figure 3**. Treatment algorithm for surgical antimicrobial prophylaxis (based on the Stanford Health Care surgical antimicrobial prophylaxis guidelines)*