National surgical antibiotic prophylaxis guideline in Singapore

Wei Teng Gladys Chung 1MClinPharm, Humaira Shafi 2MD, Jonathan Seah 3PharmD, Parthasarathy Purnima 4MBBS, Taweechai Patun 5PharmD, Kai-Qian Kam 6MBBS, Valerie Xue Fen Seah 7PharmD, Rina Yue Ling Ong 7PharmD, Li Lin 8MD, Robin Sing Meng Choo 9MClinPharm, Pushpalatha Lingegowda 10MD, Cheryl Li Ling Lim 11MB (InfectD), Jasmine Shinmin Chung 12FRCP(Edin), Nathalie Grace Chua SY 13PharmD, Tau Hong Lee 14MBBS, Min Yi Yap 15MClinPharm, Tat Ming Ng 15PharmD, Jyoti Somani 16MD

ABSTRACT

Introduction: Institutional surgical antibiotic prophylaxis (SAP) guidelines are in place at all public hospitals in Singapore, but variations exist and adherence to guidelines is not tracked consistently. A national point prevalence survey carried out in 2020 showed that about 60% of surgical prophylactic antibiotics were administered for more than 24 hours. This guideline aims to align best practices nationally and provides a framework for audit and surveillance.

Method: This guideline was developed by the National Antimicrobial Stewardship Expert Panel’s National Surgical Antibiotic Prophylaxis Guideline Development Workgroup Panel, which comprises infectious diseases physicians, pharmacists, surgeons and anaesthesiologists. The Workgroup adopted the ADAPTE methodology framework with modifications for the development of the guideline. The recommended duration of antibiotic prophylaxis was graded according to the strength of consolidated evidence based on the scoring system of the Singapore Ministry of Health Clinical Practice Guidelines.

Results: This National SAP Guideline provides evidence-based recommendations for the rational use of antibiotic prophylaxis. These include recommended agents, dose, timing and duration for patients undergoing common surgeries based on surgical disciplines. The Workgroup also provides antibiotic recommendations for special patient population groups (such as patients with β-lactam allergy and patients colonised with methicillin-resistant Staphylococcus aureus), as well as for monitoring and surveillance of SAP.

Conclusion: This evidence-based National SAP Guideline for hospitals in Singapore aims to align practices and optimise the use of antibiotics for surgical prophylaxis for the prevention of surgical site infections while reducing adverse events from prolonged durations of SAP.

Keywords: Antibiotic prophylaxis duration, antimicrobial resistance, antimicrobial stewardship, hospital-acquired infection, surgical site infections

1 Pharmacy Department, National University Hospital, Singapore
2 Department of Infectious Diseases, Changi General Hospital, Singapore
3 Department of Pharmacy, Changi General Hospital, Singapore
4 Division of Infectious Diseases, Department of General Medicine, Khoo Teck Puat Hospital, Singapore
5 Department of Pharmacy, Khoo Teck Puat Hospital, Singapore
6 Infectious Disease Service, Department of Paediatrics, KK Women’s and Children’s Hospital, Singapore
7 Department of Pharmacy, KK Women’s and Children’s Hospital, Singapore
8 Division of Infectious Diseases, Department of Medicine, Ng Teng Fong General Hospital, Singapore
9 Department of Pharmacy, Ng Teng Fong General Hospital, Singapore
10 Department of General Medicine, Sengkang General Hospital, Singapore
11 Pharmacy Department, Sengkang General Hospital, Singapore
12 Department of Infectious Diseases, Singapore General Hospital, Singapore
13 Department of Pharmacy, Singapore General Hospital, Singapore
14 Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore
15 Division of Pharmacy, Tan Tock Seng Hospital, Singapore
16 Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore

Correspondence: Ms Wei Teng Gladys Chung, Pharmacy Department, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074. Email: wei_teng_chung@nuhs.edu.sg

This article was first published online on 18 November 2022 at annals.edu.sg
CLINICAL IMPACT

What is New

• This is the first surgical antibiotic prophylaxis (SAP) guideline in Singapore that provides evidence-based recommendations for the antibiotic choice, dose, timing and duration for adult patients undergoing elective clean or clean-contaminated surgeries.

• It highlights the evidence that prolonged SAP duration has no benefit, and may be associated with harm.

Clinical Implications

• This guideline aims to align practices and optimise the use of SAP for the prevention of surgical site infections, while also reducing adverse events from prolonged durations of SAP.

INTRODUCTION

Surgical antibiotic prophylaxis (SAP) refers to the administration of antibiotics prior to clean and clean-contaminated surgeries to prevent postoperative surgical site infections (SSIs). An optimal SAP should be highly effective in preventing SSI. An ideal prophylactic antibiotic regimen is: (1) effective against pathogens—generally skin flora—most likely to contaminate the surgical site; (2) appropriately dosed, and timed so that the highest tissue concentration is present upon skin incision; (3) safe; and (4) administered for the shortest effective period to minimise adverse effects, the development of antimicrobial resistance, and costs. Antibiotics should also be re-dosed if surgery is prolonged or there is significant blood loss, to ensure adequate serum and tissue concentrations throughout the entire procedure.

Institutional SAP guidelines are in place at all public hospitals in Singapore but variations exist, and adherence to these guidelines is not reported nationally. Point prevalence surveys on antimicrobial utilisation conducted by Singapore public hospitals in 2020 showed that the prophylactic use of antibiotics for surgeries accounted for 10% of all antimicrobial agents prescribed, and about 60% of these prophylactic antibiotics were administered for more than 24 hours. Current evidence shows that SAP has no benefit when given beyond 24 hours, and may be associated with harm such as an increased risk of acute kidney injury and *Clostridioides difficile* infections. Moreover, unnecessarily long durations of SAP do not prevent wound infections, but in fact, may increase the risk of infections with multidrug-resistant organisms due to antibiotic selection pressure.

Appropriate SAP should be regarded as one of the components of an effective policy for the control of healthcare-associated infection (HAI), and also an important aspect of quality, patient safety, and antibiotic stewardship in the hospital. Based on the first national point prevalence survey conducted in public hospitals in Singapore, SSI was the second most common HAI after pneumonia, accounting for 17.3% of HAI. The establishment of the National SAP Guideline for hospitals in Singapore may reduce the rate of SSI by improving the choice and timing of SAP, while also reducing adverse events from prolonged courses of SAP, thereby promoting patient safety and addressing the problem of antimicrobial resistance.

Thus, the National SAP Guideline provides evidence-based recommendations for the rational use of antibiotic prophylaxis. These include recommended agent(s), dose, timing and duration for patients undergoing more common surgical procedures. This guideline aims to align national best practices and provide a framework for audit and surveillance. The National Antimicrobial Stewardship Expert Panel (NASEP) envisions that this guideline would be an impetus for all institutions to improve the use of SAP for the benefit of patient care and quality.

METHOD

This guideline was developed by the NASEP’s National Surgical Antibiotic Prophylaxis Guideline Development Workgroup Panel. The workgroup was led by 2 co-chairs and comprised infectious diseases physicians, infectious diseases and/or antimicrobial stewardship-trained pharmacists, surgeons and anaesthesiologists. The workgroup was divided into subgroups of 9 main surgical disciplines, and literature search was performed and presented by the individual subgroups.

The Workgroup Panel adopted the ADAPTE methodology framework with modifications in the development of the guideline. Members of the Workgroup Panel aimed to ensure the validity, reliability and applicability of the guideline for the Singapore setting. The primary literature published...
in the English language through December 2020 was identified by searches of PubMed and the Cochrane Database of Systematic Reviews. Studies from the literature search, together with published international guidelines—such as the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the National Institute for Health and Care Excellence (NICE), and the US Centers for Disease Control and Prevention (CDC)—were reviewed in detail. Particular attention was paid to the study design, with the greatest credence given to systematic reviews, meta-analyses and randomised controlled double-blinded studies.

The recommended duration of antibiotic prophylaxis was graded according to the strength of consolidated evidence-based on the scoring system of the Singapore Ministry of Health (MOH) Clinical Practice Guidelines (Tables 1 and 2). For procedures in which antibiotic prophylaxis is not recommended, the strength of evidence represents the support against prophylaxis. The description of the evidence base can be found in the online Supplementary Appendix 1.

The draft documents for each surgical procedure were collated and edited by the co-chairpersons before being circulated and reviewed by the Workgroup. The completed guideline was formally submitted for review and endorsement by the MOH National Antimicrobial Resistance Control Committee (NARCC) and National Centre for Infectious Diseases (NCID), together with Chapter of Infectious Disease Physicians, College of Anaesthesiologists, and College of Surgeons of the Academy of Medicine, Singapore. Medical practitioners from the private hospitals were also formally engaged for comments. The Workgroup had 6 rounds of

### Table 1. Levels of evidence

| Level | Type of evidence |
|-------|------------------|
| 1++   | High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias |
| 1+    | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1-    | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++   | High-quality systematic reviews of case control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| 2+    | Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| 2-    | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3     | Non-analytic studies, e.g. case reports and case series |
| 4     | Expert opinion |

### Table 2. Grades of recommendation

| Grade      | Recommendation |
|------------|----------------|
| A          | At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results |
| B          | A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ |
| C          | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ |
| D          | Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ |
| GPP (good practice points) | Recommended best practice based on the clinical experience of the guideline development group |
virtual meetings from December 2020 to April 2022 to
discuss the comments and make modifications to the
guideline (Fig. 1).

The recommendations in this guideline apply to
elective clean and clean-contaminated procedures in
the adult population. Clean procedures involve an
incision in which no inflammation is encountered,
without a break in sterile technique, and during which
the respiratory, alimentary or genitourinary tracts are
not entered; clean-contaminated procedures involve
an incision through which the respiratory, alimentary
or genitourinary tract is entered under controlled
conditions but with no contamination encountered.11

This guideline does not cover the following:

• Treatment of infection in patients undergoing
  emergency surgery for contaminated or dirty
  wounds.
• Antibiotic prophylaxis for prevention of infective
  endocarditis.
• Antibiotic prophylaxis in patients with prosthetic
  implants undergoing dental surgery or other surgery
  that may cause bacteraemia.
• Use of antiseptic for prevention of wound infection
  after elective surgery.
• Administration of topical antibiotics in wounds.

Individual healthcare institutions should consider
resistance patterns of organisms and overall SSI rates at
their respective sites when adopting these recommenda-
tions. The Workgroup Panel recognises the importance
of other non-antimicrobial factors to reduce the risk of
SSI, but the discussion of these factors lies outside the
scope of this guideline.

This guideline will be of interest to surgeons, infectious
diseases physicians, anaesthesiologists, pharmacists,
microbiologists, infection control nurses, epidemiologists
and public health professionals.

The full guideline is available at https://www.ncid.sg/
Health-Professionals/Documents/NationalSAPGuideline
Singapore.pdf as a reference to guide practice.

RESULTS

Surgical antibiotic prophylaxis practice points

SAP with the right antibiotic, dose and timing has
been found to be of benefit for most clean-contaminated,

as well as in certain clean procedures where there are
severe consequences of infection (e.g. placement of
prosthesis or implant).1 SAP may not be required in
clean, uncomplicated procedures not involving the
placement of prostheses or implants. For contaminated
or infected wounds, antibiotic treatment is indicated
and not considered as surgical prophylaxis.

Antibiotic choice

Most SSI are caused by skin flora or from flora that
may be found at the site of the organ being operated

In principal approval obtained from the
Director of Medical
Services for the
development of the
guideline.

Oct 2020

Hospital workgroups
formed and drafted the
preliminary guideline
recommendations.

Oct-Nov 2020

First Working
Group review
meeting.

Nov 2020

Second Working
Group review
meeting.

Dec 2020

Evidence
scoring
review
meetings
(2 sessions).

Jan 2021

Third Working
Group review
meeting.

Mar 2021

First draft submitted
to NARCC,
professional bodies
and private hospitals
for feedback.

Jun-Sep 2021

Fourth Working Group
review meeting. The
guideline was revised
based on feedback
obtained. Final draft
reviewed by professional
bodies.

Oct-Dec 2021

Final draft
reviewed by
NASEP and
NARCC.

Jan-Feb 2022

Final draft was sent
out by the subgroups
to the surgical teams
at public hospitals for
feedback.

Jan-Feb 2022

Review and consultation
with MOH in terms of
formatting and clarity.

Mar-Apr 2022

Endorsement obtained
from professional
bodies.

May 2022

Approval obtained
from the Director of
Medical Services.

Aug 2022

MOH: Ministry of Health; NARCC: National Antimicrobial
Resistance Control Committee; NASEP: National Antimicrobial
Stewardship Expert Panel

Fig. 1. Timeline of guideline development process highlighting time points at which feedback was solicited and incorporated into guideline development and revision.

Ann Acad Med Singap Vol 51 No 11 November 2022 | annals.edu.sg
on (e.g. Gram-negative and anaerobic bowel flora for surgeries traversing the colon). The antibiotic selected must cover the expected pathogen for the operative site and concentrate in high levels at the site prior to incision. Narrow-spectrum antibiotic agents are preferred. The association of some antibiotic agents (such as third-generation cephalosporins, fluoroquinolones and clindamycin) with the increased risk of *C. difficile* infections, and the development of multidrug-resistant colonisation or infections, should be taken into consideration. The choice of antibiotics should also take into account the resistance patterns at their respective sites. The recommended antibiotic prophylaxis for specific surgical procedures, along with alternatives for patients with severe penicillin allergy, is provided in Table 3.

**Administration timing**

The ideal antibiotic dose should be given in time to reach and maintain optimal levels in both blood and tissue from the time of incision until the closure of surgical wounds. Therefore, the dose and timing of antibiotic administration are important. The optimal time for administration of most preoperative doses is 30 to 60 minutes before surgical incision. The antibiotic should be infused completely prior to the incision. Specific agents (fluoroquinolones and vancomycin) that require longer infusion time should be administered at least 1 hour before the incision. Prospective cohort studies specifically in cardiac surgeries have demonstrated that incomplete infusion of preoperative vancomycin was associated with a higher risk for SSI. For emergency procedures when vancomycin cannot be infused due to limited time, teicoplanin is an effective option. Teicoplanin may be administered over 3 to 5 minutes or as a 30-minute infusion.

**Methicillin-resistant Staphylococcus aureus (MRSA) risk and antimicrobial coverage**

Screening and selective decolonisation of patients positive for MRSA have been shown to prevent SSI. The Workgroup Panel recommends screening and decolonisation for patients who will be undergoing high-risk surgeries (cardiac, orthopaedic and neurosurgery with implant). Decolonisation without screening is not recommended as the widespread use of mupirocin has been shown to promote resistance.

Vancomycin prophylaxis should be considered for patients with known MRSA colonisation or recent MRSA infection. This is recommended for (but not limited to) patients undergoing high-risk surgeries.

As vancomycin is less effective than cefazolin in preventing SSI caused by methicillin-susceptible *Staphylococcus aureus*, the addition of cefazolin to vancomycin should be considered for prophylaxis in MRSA colonised patients. This combination was shown to have lower SSI rates, although some studies showed a slightly higher risk of acute kidney injury. The Workgroup Panel recommends the use of this combination in MRSA-colonised patients, who undergo cardiac or orthopaedic (involving implants) procedures.

**Antibiotic dosing and re-dosing intervals**

The recommended re-dosing intervals for commonly used antibiotics are provided in Table 4.

For aminoglycosides, once-daily dosing is recommended. Gentamicin dosing regimens have been compared for prophylaxis in colorectal surgery. A single gentamicin dose of 5mg/kg was found to be more effective in SSI prevention than multiple doses of 1.5mg/kg given 8-hourly. A large retrospective cohort study of surgical patients (*n*=1,590) showed that the use of once-daily gentamicin was safe, with similar nephrotoxicity risk between gentamicin versus control (2.5% vs 1.8%, *P*=0.17).

Intraoperative re-dosing is required when:

- the duration of the procedure exceeds 2 half-lives of the drug, or
- there is excessive intra-operative blood loss (i.e. >1,500mL), or
- there are extensive burns.

Therapeutic drug monitoring for vancomycin and aminoglycosides is not required due to the short duration of prophylaxis. If these antibiotics are continued beyond the recommended duration for surgical prophylaxis, therapeutic drug monitoring should be initiated according to institutional guidelines.

**Dosing in obese patients**

Obesity has been linked to an increased risk of SSI. These patients may require higher doses to ensure adequate tissue concentrations.

These are the recommended dosing for obese patients:

- For cefazolin, the recommended dose if weight is >120kg is 3g instead of the usual 2g.
- For aminoglycoside use in obese patients (actual body weight is 20% above the ideal body weight), the dose is calculated based on the patient’s adjusted body weight.
| Types of surgery | First line | Alternative for severe penicillin allergy | Duration | Remarks | Level of evidence (Grade) |
|------------------|------------|------------------------------------------|----------|---------|--------------------------|
| **Breast surgery** | | | | | |
| Breast cancer surgery without oncoplastic/reconstruction surgery | Not recommended | Not recommended | Single dose | Risk factors: - Post-neoadjuvant chemotherapy - Immunocompromised individuals | Level 1- (Grade B) |
| | For patients with risk factors IV cefazolin 2g | For patients with risk factors IV clindamycin 600–900mg or IV vancomycin 15–20mg/kg | | | |
| Breast cancer surgery with oncoplastic/reconstruction surgery | IV cefazolin 2g Followed by: 1–2g q8h | IV clindamycin 600–900mg Followed by: 600mg q8h or IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | Up to 24 hours | | Level 1+ (Grade A) |
| Breast lump excision biopsy | Not recommended | Not recommended | NA | If prophylactic antibiotic is used, it should not exceed a single dose. Refer to the above choices if prophylactic antibiotic is used | Level 1- (Grade B) |
| Wire localisation excision biopsy | | | | | |
| **Cardiothoracic and vascular surgery** | | | | | |
| Cardiac (aortic dissection, CABG, TEVAR, valve repair or replacement, LVAD placement, permanent pacemaker/defibrillator insertion) | IV cefazolin 2g Followed by: 1–2g q8h | IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | 24–48 hours | IV vancomycin dose of 20mg/kg preoperatively may be preferred to achieve sufficient tissue concentrations at the time of surgery At the onset of bypass: May consider an additional 1–2g of IV cefazolin via cardiopulmonary bypass circuit | Level 1+ (Grade A) |
| | **MRSA colonised** IV cefazolin 2g + IV vancomycin 15–20mg/kg Followed by: IV cefazolin 1–2g q8h + IV vancomycin 15mg/kg q12h | | | | |
| Thoracic (decortication, lobectomy, thymectomy, VATS) | IV cefazolin 2g | IV clindamycin 600–900mg or IV vancomycin 15–20mg/kg | Single dose | | Level 1- (Grade B) |
| | **MRSA colonised** IV vancomycin 15–20mg/kg | | | | |
| Vascular (artery or vein repair, AVF or AVG creation, excision, jump graft, aortic stent graft) | IV cefazolin 2g Followed by: 1–2g q8h | IV clindamycin 600–900mg Followed by: 600mg q8h or IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | Up to 24 hours | | Level 1- (Grade B) |
| | **MRSA colonised** IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | | | | |
| Cardiac or vascular (angioplasty, stent insertion) | Not recommended | Not recommended | NA | | Level 3 (Grade D) |
Table 3. Recommendations for surgical antibiotic prophylaxis (Cont’d)

| Types of surgery               | First line                        | Alternative for severe penicillin allergy | Duration | Remarks                                                                 | Level of evidence (Grade) |
|--------------------------------|-----------------------------------|------------------------------------------|----------|--------------------------------------------------------------------------|---------------------------|
| **Gastrointestinal surgery**   |                                   |                                          |          |                                                                          |                           |
| Appendectomy                   | IV cefazolin 2g + IV metronidazole 500mg or IV ceftriazone 2g + IV metronidazole 500mg or IV amoxicillin-clavulanic acid 1.2g | IV gentamicin 5mg/kg + IV metronidazole 500mg or IV gentamicin 5mg/kg + IV clindamycin 600–900mg | Single dose |                                                                          | Level 1+ (Grade A)         |
| Gastroduodenal and oesophageal | IV cefazolin 2g or IV ceftriazone 2g or IV amoxicillin-clavulanic acid 1.2g | IV gentamicin 5mg/kg +/- IV clindamycin 600–900mg | Single dose |                                                                          | Level 1+ (Grade A)         |
| Small bowel                    | IV cefazolin 2g + IV metronidazole 500mg or IV ceftriazone 2g + IV metronidazole 500mg or IV amoxicillin-clavulanic acid 1.2g | IV gentamicin 5mg/kg + IV metronidazole 500mg or IV gentamicin 5mg/kg + IV clindamycin 600–900mg | Single dose |                                                                          | Level 1+ (Grade B)         |
| Colorectal                     | IV cefazolin 2g + IV metronidazole 500mg or IV ceftriazone 2g + IV metronidazole 500mg or IV amoxicillin-clavulanic acid 1.2g | IV gentamicin 5mg/kg + IV metronidazole 500mg or IV gentamicin 5mg/kg + IV clindamycin 600–900mg | Single dose |                                                                          | Level 1++ (Grade A)        |
| Hernia repair                  | To be used in conjunction with mechanical bowel preparation (MBP) (if given): PO neomycin sulfate 1g + PO erythromycin base 1g or PO amoxicillin sulfate 1g + PO metronidazole 1g | Three doses in conjunction with MBP |          | To be administered over approximately 10 hours the day before operation (e.g. 1 pm to 11 pm) Need for MBP + PO prophylaxis to be decided by individual institutions | Level 1++ (Grade B)        |
| Hernioplasty (i.e. with mesh placement) | IV cefazolin 2g | IV vancomycin 15mg/kg | Single dose | Recommendations for prophylaxis are mainly derived from studies on inguinal/femoral hernia repairs. Mixed outcomes for other types of hernias and studies were often of poor quality. | Level 1++ (Grade B)        |
| Herniorrhaphy (i.e. no mesh placement) | Not recommended | Not recommended | NA | | Level 1++ (Grade A) |
| Types of surgery                                      | First line                                      | Alternative for severe penicillin allergy | Duration | Remarks                                                                 | Level of evidence |
|------------------------------------------------------|-------------------------------------------------|------------------------------------------|----------|-------------------------------------------------------------------------|-------------------|
| **Hepatobiliary surgery**                            | IV cefazolin 2g or IV ceftriaxone 2g or IV amoxicillin-clavulanic acid 1.2g | IV clindamycin 600–900mg or IV vancomycin 15–20mg/kg + IV gentamicin 5mg/kg or IV aztreonam 2g | Single dose | It is reasonable to give a single dose of prophylaxis to patient undergoing laparoscopic cholecystectomy although evidence showed that antibiotic is not required for low-risk patients. This is because some of these risk factors cannot be determined prior to surgery. | Level 1+ (Grade A) |
| **Hepatectomy**                                      | IV cefazolin 2g Followed by: 1–2g 8h or IV ceftriaxone 2g once | IV clindamycin 600–900mg or IV vancomycin 15–20mg/kg + IV gentamicin 5mg/kg or IV aztreonam 2g | Up to 24 hours | If the procedure is expected to involve the lower gastrointestinal tract, consider adding anaerobic coverage | Level 1+ (Grade A) |
| **Splenectomy or left-sided pancreatic surgery**     | IV cefazolin 2g | IV vancomycin 15–20mg/kg | Single dose | There is no need to extend the antibiotic duration for patients who are not immunised. Administer the appropriate immunisations | GPP |
| **Whipple’s operation (no recent biliary intervention/stenting)** | IV cefazolin 2g Followed by: 1.2g 8h or IV ceftriaxone 2g once or IV amoxicillin-clavulanic acid 1.2g Followed by: 1.2g 8h | IV clindamycin 600–900mg or IV vancomycin 1520mg/kg +/– IV gentamicin 5mg/kg or IV aztreonam 2g | Up to 24 hours | For patients with recent biliary intervention/stenting, there is a higher incidence of bacterobilia with ESBL-producing organisms. Antibiotic should be tailored according to in-house antibiogram or recent bile/blood cultures from the patient. | Level 2+ (Grade C) |
| **Endoscopic retrograde cholangiopancreatography (ERCP)** | Not recommended except in cases of incomplete biliary drainage or obstructive biliary tract disease | Not recommended except in cases of incomplete biliary drainage or obstructive biliary tract disease | Single dose | Antibiotic prophylaxis for ERCP was shown to increase the proportion of resistant bacteria\(^{58-59}\) | Level 1+ (Grade A) |
| **Obstetrics and gynaecology**                       | IV cefazolin 2g | IV clindamycin 900mg | Single dose | Continuation of antimicrobial prophylaxis (up to 2 days) may be considered for patients with major risk factors for surgical infections, e.g. obesity (body mass index ≥30). | Level 1- (Grade B) |
| Types of surgery                        | First line                          | Alternative for severe penicillin allergy | Duration | Remarks                                                                 | Level of evidence (Grade) |
|----------------------------------------|-------------------------------------|------------------------------------------|----------|-------------------------------------------------------------------------|---------------------------|
| Normal vaginal delivery (non-operative/instrumental) | Not recommended                     | Not recommended                           | NA       | Antibiotic prophylaxis may be considered in the setting of a third- or fourth-degree perineal laceration Group B Streptococcus and preterm premature rupture of membranes prophylaxis are excluded in this guideline. | Level 1- (Grade B)        |
| Normal vaginal delivery (operative/instrumental) | IV amoxicillin-clavulanic acid 1.2g | IV clindamycin 900mg                      | Single dose after delivery | Antibiotic prophylaxis may be considered in the setting of a third- or fourth-degree perineal laceration Group B Streptococcus and preterm premature rupture of membranes prophylaxis are excluded in this guideline. | Level 1- (Grade B)        |
| Hysterectomy Abdominal/vaginal/ laparoscopic | IV cefazolin 2g + IV metronidazole 500mg | IV clindamycin 900mg + IV gentamicin 5mg/kg | Single dose | The risk of infection is very low, antibiotic prophylaxis generally not necessary unless high risk e.g. dilated fallopian tubes, history of pelvic inflammatory disease, tubal damage or abnormal tubal architecture (associated with risk of postoperative pelvic inflammatory disease/endometritis). If evidence of endometritis/infection found at point of procedure, treat accordingly. | Level 2- (Grade C)        |
| Hysteroscopy                           | Not recommended                     | Not recommended                           | NA       | As above.                                                               | Level 1- (Grade B)        |
| Hysterosalpingography                  | Not recommended                     | Not recommended                           | NA       | As above.                                                               | Level 2- (Grade C)        |
| Endometrial biopsy, cervical tissue excision, cervical cone procedures | Not recommended                     | Not recommended                           | NA       | Consider sexually transmitted infections screens in high-risk populations and advise to complete treatment prior procedure. | Level 1+ (Grade A)        |
| Intrauterine device insertion          | Not recommended                     | Not recommended                           | NA       | Consider sexually transmitted infections screens in high-risk populations and advise to complete treatment prior procedure. | Level 1+ (Grade A)        |
| Types of surgery                                                                 | First line                                                                 | Alternative for severe penicillin allergy | Duration  | Remarks                                                                                                                                  | Level of evidence (Grade) |
|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Orthopaedic/spine surgery                                                                                                                   |                                                                            |                                      |           |                                                                                                                                         |                            |
| Clean orthopaedic, non-spinal procedure with no implantation (arthroscopy, tendon repair surgery) | Not recommended                                                           | Not recommended                           | Single dose | Risk factors include dermatological conditions, predicted prolonged operative time, malnutrition, immunosuppressant use and poorly controlled diabetes mellitus | Level 1- (Grade B)          |
|                                                                                      | For patients with risk factors                                             | IV cefazolin 2g                           |           |                                                                                                                                         |                            |
|                                                                                      | MRSA colonised                                                             | IV cefazolin 2g +/- IV vancomycin 15–20mg/kg |           |                                                                                                                                         |                            |
| Clean orthopaedic surgery with implants                                              | IV cefazolin 2g Followed by: 1–2g q8h                                      | IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | Up to 24 hours |                                                                                                                                         | Level 1++ (Grade A)        |
| Wrist arthroplasty                                                                  | IV cefazolin 2g Followed by: IV cefazolin 1–2g q8h + IV vancomycin 15mg/kg q12h | IV cefazolin 1–2g q8h + IV vancomycin 15mg/kg q12h | Up to 24 hours |                                                                                                                                         | Level 1++ (Grade A)        |
| Spine surgery (with and without implants)                                            | IV cefazolin 2g Followed by: 1–2g q8h                                      | IV vancomycin 15–20mg/kg Followed by: 15mg/kg q12h | Up to 24 hours |                                                                                                                                         | Level 1++ (Grade A)        |
| Bedford hospital                                                                     | IV cefazolin 2g Followed by: IV cefazolin 1–2g q8h + IV vancomycin 15mg/kg q12h | IV cefazolin 1–2g q8h + IV vancomycin 15mg/kg q12h | Up to 24 hours |                                                                                                                                         | Level 1++ (Grade A)        |
| Otorhinolaryngology                                                                  |                                                                            |                                      |           |                                                                                                                                         |                            |
| Clean head and neck (thyroidectomy, parotidectomy, salivary gland excisions)       | Not recommended                                                           | Not recommended                           | NA        |                                                                                                                                         | Level 1+ (Grade A)         |
| Clean-contaminated head and neck procedures                                          | IV amoxicillin-clavulanic acid 1.2g q8h or IV cefazolin 2g q8h + IV metronidazole 500mg q8h | IV clindamycin 600-900mg q8h +/- IV gentamicin 5mg/kg once | Up to 24 hours | Prolonged course of oral antibiotics has not been shown to reduce postoperative infections and may increase the risk of complications. | Level 1+ (Grade A)         |
| Neck dissection procedures                                                           |                                                                            |                                      |           | For neck dissection: Level 2+ (Grade C)                                                                                               |                            |
| Clean otologic procedures                                                            | Not recommended                                                           | Not recommended                           | NA        |                                                                                                                                         | Level 1+ (Grade A)         |
| Types of surgery | First line | Alternative for severe penicillin allergy | Duration | Remarks | Level of evidence (Grade) |
|-----------------|------------|------------------------------------------|----------|---------|--------------------------|
| Clean-contaminated otologic procedures | IV amoxicillin-clavulanic acid 1.2g q8h or IV cefazolin 2g q8h + IV metronidazole 500mg q8h | IV clindamycin 600–900mg q8h +/- IV gentamicin 5mg/kg once
t | Up to 24 hours | | Level 1- (Grade B) |
| Tonsillectomy | Not recommended | Not recommended | NA | | Level 1+ (Grade A) |
| Simple septorhinoplasty | Not recommended | Not recommended | NA | Infection rates are very low, especially when nasal packing/splint use ≤48 hours | Level 1- (Grade B) |
| Complex Septorhinoplasty | IV amoxicillin-clavulanic acid 1.2g q8h or IV cefazolin 2g q8h + IV metronidazole 500mg q8h | IV clindamycin 600–900mg q8h +/- IV gentamicin 5mg/kg once | Up to 24 hours | | Level 1- (Grade B) |
| Endoscopic sinus surgery | IV amoxicillin-clavulanic acid 1.2g or IV cefazolin 2g + IV metronidazole 500mg | IV clindamycin 600–900mg +/- IV gentamicin 5mg/kg | Single dose | Post-operative antibiotics should not be given if there is no mucous seen intra-operatively. | Level 1- (Grade B) |
| Neurosurgery | | | | | |
| Clean wounds | | | | | |
| Elective craniotomy, external ventricular drain (EVD), intracranial pressure (ICP) monitors | IV cefazolin 2g | IV vancomycin 15–20mg/kg or IV clindamycin 600–900mg | Single dose
t | | Level 1+ (Grade A) |
| Clean wounds with foreign bodies or instrumentation | | | | | For EVD and ICP: Level 2++ (Grade B) |
| Cerebrospinal fluid shunting procedures | | | | | |
| Urological procedures | | | | | |
| Lower urinary tract instrumentation | | | | | |
| Cystourethroscopy | | | | | |
| -With or without minor manipulation, and without a significant break in mucosal barriers | Not recommended, except in those with risk factors, to manage as transurethral cases (refer to the section on transurethral procedure) | Not recommended, except in those with risk factors, to manage as transurethral cases (refer to the section on transurethral procedure) | NA | If urine culture shows no growth prior to the procedure, antimicrobial prophylaxis is not necessary | Level 1+ (Grade A) |
| -With a significant break in mucosal barriers/significant manipulation | To manage as transurethral cases (refer to transurethral section) | | | Risk factors: poor functional status/frailty, anatomic anomalies of the urinary tract, chronic steroid use, immunocompromising condition or recent systemic chemotherapy, poorly controlled diabetes mellitus, prior severe urosepsis |
| Types of surgery                                                                 | First line                        | Alternative for severe penicillin allergy | Duration | Remarks                                                                 | Level of evidence |
|---------------------------------------------------------------------------------|-----------------------------------|------------------------------------------|----------|-------------------------------------------------------------------------|-------------------|
| Transurethral cases and minimally invasive surgical therapy to the prostate     | IV/IM gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g | IV/IM gentamicin 3–5mg/kg or PO ciprofloxacin 500mg/IV 400mg<sup>d</sup> | Single dose |                                                                 | Level 1+ (Grade B) |
| Transrectal prostate biopsy                                                     | PO ciprofloxacin 500 mg + IV/IM gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g/ PO 625mg + IV/IM gentamicin 3–5mg/kg or IV ceftriaxone 2g | PO ciprofloxacin 500 mg + IV/IM gentamicin 3–5mg/kg | Up to 48 hours | For PO ciprofloxacin, dose 1–2 hours before the procedure For PO amoxicillin-clavulanic acid, dose 24 hours before the procedure | Level 1+ (Grade A) |
| Transperineal procedures e.g. prostate brachytherapy, transperineal prostate biopsy | Not recommended                    | Not recommended                          | NA       | Prophylaxis may be recommended in patients with risk factors (chronic steroid use, immunocompromising condition or recent systemic chemotherapy, poorly controlled diabetes mellitus), prior severe urosepsis or post-biopsy infection. Antibiotic choice: PO cephalosporins or amoxicillin-clavulanic acid 2 hours before the procedure | Level 2+ (Grade C) |
| Upper urinary tract instrumentation                                              |                                   |                                          |          |                                                                         |                   |
| Percutaneous renal surgery, e.g. percutaneous nephrolithotomy                   | IV cefazolin 2g + IV gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g | IV gentamicin 3–5mg/kg + IV clindamycin 600–900mg or IV gentamicin 3–5mg/kg + IV vancomycin 15–20mg/kg | Single dose |                                                                         | Level 1+ (Grade A) |
| Ureteroscopy (including laser lithotripsy)                                       | IV gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g | IV gentamicin 3–5mg/kg or PO ciprofloxacin 500mg/IV 400mg<sup>d</sup> | Single dose |                                                                         | Level 1+ (Grade A) |
Table 3. Recommendations for surgical antibiotic prophylaxis (Cont’d)

| Types of surgery | First line | Alternative for severe penicillin allergy | Duration | Remarks | Level of evidence |
|-----------------|------------|------------------------------------------|----------|---------|-------------------|
| Urethroplasty; reconstruction of anterior urethra, stricture repair, including urethrectomy; controlled entry into the urinary tract e.g. renal surgery, nephrectomy, ureterectomy, pyeloplasty, radical prostatectomy; partial cystectomy | IV cefazolin 2g + IV gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g | IV gentamicin 3–5mg/kg + IV clindamycin 600–900mg or IV gentamicin 3–5mg/kg + IV vancomycin 15–20mg/kg | Single dose | Consider preoperative urine cultures and treat accordingly | Level 2+ (Grade B) |
| Urinary diversion involving small or large bowel | IV cefazolin 2g + IV gentamicin 3–5mg/kg + IV metronidazole 500mg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g + IV metronidazole 500mg | IV gentamicin 3–5mg/kg + IV metronidazole 500mg or IV gentamicin 3–5mg/kg + IV clindamycin 600–900mg | Single dose | Metronidazole may be optional for small bowel surgery | Level 2- (Grade C) |
| Implanted prosthetic devices: AUS, IPP, sacral neuromodulators | IV cefazolin 2g + IV gentamicin 3–5mg/kg or IV amoxicillin-clavulanic acid 1.2g or IV ceftriaxone 2g | IV vancomycin 15–20mg/kg + IV aztreonam 2g or IV clindamycin 600–900mg + IV gentamicin 3–5mg/kg | Single dose | | Level 4 (GPP) |

Others

| Procedure | First line | Duration | Remarks | Level of evidence |
|-----------|------------|----------|---------|-------------------|
| Urodynamic study | Not recommended except in those with risk factors (see cystourethroscopy section) | NA | NA | Level 1+ (Grade A) |
| Penile surgery | | | For shockwave lithotripsy, consider antibiotic prophylaxis (single-dose IV gentamicin or IV ceftriaxone) only if high risk of infection e.g. infected stones, recent instrumentation, nephrostomy tubes, positive urine culture, or history of recent urinary tract infection/sepsis | |
| Shockwave lithotripsy | | | | |

* The addition of gentamicin may be appropriate when there is an increased likelihood of Gram-negative contamination of the surgical site.
* While single-dose prophylaxis is usually sufficient, the duration of prophylaxis for all procedures should be less than 24 hours.
* Clindamycin resistance has been increasing in *Bacteroides* species. Metronidazole may be preferred if the procedure transverses the lower gastrointestinal tract.
* Due to the high local resistance of Gram-negative organisms to quinolones, this is only recommended if the organism is shown to be sensitive in the preoperative urine culture.
* An additional single dose of IV azithromycin 500mg to routine prophylaxis may be considered for a non-elective Caesarean section. However, the extrapolation of benefit to local centres where rates of post-C-section infections are low still remains to be determined.

AUS: Artificial urinary sphincter; AVF: arteriovenous fistula; AVG: arteriovenous graft; CABG: coronary artery bypass grafting; ERCP: endoscopic retrograde cholangio-pancreatography; GPP: good practice points; IPP: intravesical prostatic protrusion; IM: intramuscular; IV: intravenous; LVAD: left ventricular assist device; MRSA: methicillin-resistant *Staphylococcus aureus*; NA: not applicable; PO: per oral (oral administration); TEVAR: thoracic endovascular aortic repair; VATS: video-assisted thoracoscopic surgery

Superscript numbers: Refer to REFERENCES
Adjusted body weight = Ideal body weight + 0.4 x (Total body weight - Ideal body weight)

where

Ideal body weight (male) is 50 + 2.3 × (height in inches - 60)
Ideal body weight (female) is 45.5 + 2.3 × (height in inches - 60)

(1 inch = 2.54cm)

- For vancomycin, it should be dosed at 15–20mg/kg of actual body weight, with the first dose capped at 3g per dose.1,3,40-43

Patients with β-lactam allergy

β-lactams, including cephalosporins, are the mainstay of SAP and have the highest efficacy. Studies have shown that patients with reported β-lactam allergy have increased odds of SSI, attributed to the receipt of second-line antibiotics.44,45 Thus, patients with a history of β-lactam allergy should have a detailed antibiotic and allergy assessment to determine if a true allergy exists, and to exclude any non-immunological adverse reaction (for example diarrhoea, vomiting and non-specific rash). This can be done in advance for elective surgeries, so patients with no true allergy or a mild allergy to penicillin can be given the first-line SAP.

Patients with severe penicillin allergy should not receive β-lactam for surgical prophylaxis. These include patients with severe immunoglobulin E (IgE)-mediated reactions (anaphylaxis, urticaria, bronchospasm and angioedema), or non-IgE-mediated reactions (Steven-Johnson syndrome, toxic epidermal necrolysis and drug-induced hypersensitivity syndrome). Alternatives to β-lactam antibiotics are provided in Table 3.

In patients with an uncomplicated non-IgE-mediated allergic reaction to penicillin (i.e. maculopapular rash), cephalosporins (i.e. cefazolin or 3rd generation cephalosporins) can be considered after discussion with the patient and the allergy team (if available). Cefazolin, in particular, has a unique R1 side chain that is distinct from other cephalosporins and β-lactams, and side chain cross-reactivity with penicillin and other beta-lactams is not expected.46,47

Patients receiving therapeutic antibiotics for an active infection before surgery

If the antibiotic used to treat the current infection is deemed appropriate for surgical prophylaxis, an extra dose should be administered within 60 minutes before the surgical incision. If the current antibiotic is insufficient for surgical prophylaxis, the recommended antibiotic prophylaxis for the procedure should be used. The need for re-dosing should be individualised and evaluated on a case-by-case basis.

Patients with prior colonisation or infection with multidrug-resistant pathogens

The causative link between the carriage of multidrug-resistant organisms and the resultant SSI caused by these pathogens has not been established. Whether prophylaxis should be expanded to cover these pathogens depends on many factors, including the host, the pathogen and its antimicrobial susceptibility profile, the procedure, and the proximity of the reservoir of the pathogen to the operative site.1 These patients should be evaluated on a case-by-case basis.
Consideration for formal infectious diseases consultation

Formal infectious diseases consultation should be considered for the following patients:

- Patients who have contraindications to both the first- and second-line antibiotic prophylaxis regimen (including complex allergy history and impaired renal function).
- Patients with a recent history of colonisation and/or infection with multidrug-resistant organisms and who are undergoing high-risk procedures.

Duration of surgical antibiotic prophylaxis

In clean and clean-contaminated procedures, additional prophylactic antibiotic agents should not be administered after the surgical incision is closed, even in the presence of a drain. This recommendation also applies to patients on systemic corticosteroids or other immunosuppressive therapy. At most, the duration of antibiotic prophylaxis should not exceed 24 hours for most procedures. A recent systematic review of 83 randomised controlled trials across various surgical subspecialties found no additional benefit from extending the duration of prophylaxis as compared to immediate discontinuation. A prespecified subgroup analysis in this study also showed that when best practice standards (defined as the first dose within an hour of incision and appropriate re-dosing) were applied, prolonged antibiotic prophylaxis had no effect on the risk of SSI. Prolonged SAP beyond 24 hours has been shown to be associated with acute kidney injury and *C. difficile* infections. This practice may also increase selective pressure favouring the emergence of multidrug-resistant organisms. The recommended duration of antibiotic prophylaxis for various surgical procedures is provided in Table 3.

Recommendations for monitoring and surveillance

The Workgroup Panel recommends the following indicators for monitoring and audit:

- The choice, dosage, and route of administration of antimicrobial agents are consistent with the national guideline.
- The first dose of prophylaxis is given at the right time in relation to the incision time.
- Re-dosing of antimicrobial agents is consistent with the national guideline.
- The duration of prophylaxis is consistent with the national guideline.

Data on the choice and duration of SAP in public hospitals in Singapore are collected annually through the Antimicrobial Utilisation-Point Prevalence Survey (AMU-PPS). The above additional process measures may be incorporated into the AMU-PPS to provide useful information to improve antimicrobial stewardship initiatives.

Limitations

Immunocompromised patients and patients colonised with multidrug-resistant organisms may be under-represented in a majority of the studies. Some of these patients who are undergoing high-risk surgeries are recommended for a formal infectious disease consultation prior to surgery. Additional limitations pertaining to the studies in certain surgical specialties were stated in the respective sections under the online Appendix 1. The cost-effectiveness of the recommended antibiotic regimen was also not discussed in this guideline. The majority of the antimicrobial agents recommended are generic formulations and of relatively low price.

CONCLUSION

This is the first national surgical antibiotic prophylaxis guideline in Singapore. It provides evidence-based recommendations for the rational use of antibiotic prophylaxis—including the recommended agent(s), dose, timing and duration for adult patients undergoing elective clean or clean-contaminated surgeries. This guide aims to align best practices nationally and provide a framework for audit and surveillance. Current evidence indicates that SAP has no benefit when given beyond 24 hours, and may be associated with harm. The establishment of the national SAP guideline for hospitals in Singapore may lower the rate of SSI, while also reducing adverse events from the prolonged duration of SAP.

Acknowledgements

The full list of contributors to the guideline is stated in the online version of the guideline. We would like to thank the Antimicrobial Resistance Coordinating Office, National Centre for Infectious Diseases for providing administrative support.

REFERENCES

1. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195-283.
2. National Antimicrobial Resistance Control Committee (2020). National Antimicrobial Resistance Control Committee (NARCC) Report on 2020 Data. [Unpublished]
3. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017 JAMA Surg 2017;152:784-91. Erratum in JAMA Surg 2017;152:803.
4. World Health Organization. Global Guidelines for the Prevention of Surgical Site Infection, 2018. https://www.who.int/publications/i/item/global-guidelines-for-the-prevention-of-surgical-site-infection-2nd-ed. Accessed 1 June 2022.

5. Phillips BT, Sheldon ES, Ohrhuru V, et al. Preoperative Versus Extended Postoperative Antimicrobial Prophylaxis of Surgical Site Infection During Spinal Surgery: A Comprehensive Systematic Review and Meta-Analysis. Adv Ther 2020;37:2710-33.

6. McDonald M, Grabsch E, Marshall C, et al. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. ANZ J Surg 1998;68:388-95.

7. Branch-Elliman W, O’Brien W, Smyth J, et al. Association of Duration and Type of Surgical Prophylaxis With Antimicrobial-Associated Adverse Events. JAMA Surg 2019;154:590-8.

8. Harbarth S, Samore MH, Lichtenberg D, et al. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. Circulation 2000;101:2916-21.

9. Cai Y, Venkatachaliam I, Tee NW, et al. Prevalence of Healthcare-Associated Infections and Antimicrobial Use Among Adult Inpatients in Singapore Acute-Care Hospitals: Results From the First National Point Prevalence Survey. Clin Infect Dis 2017;64(suppl 2):S61-7.

10. The ADAPTE Collaboration (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0. https://g-i-n.net/wp-content/uploads/2021/03/ADAPTE-Resource-toolkit-March-2010.pdf. Accessed 19 December 2020.

11. National Institute for Health and Care Excellence. Surgical site infections: Prevention and treatment, updated 19 August 2020. www.nice.org.uk/guidance/ng125. Accessed 9 December 2020.

12. Paterson DL. “Collateral damage” from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis 2004;38(Suppl 4):S341-5.

13. Cho SM, Lee JJ, Yoon HJ. Clinical risk factors for Clostridium difficile-associated diseases. Braz J Infect Dis 2012;16:256-61.

14. van Kasteren MEE, Manniën J, Ott A, et al. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007;44:921-7.

15. Steinberg JP, Braun BI, Hellinger WC, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. Ann Surg 2009;250:10-6.

16. Garey KW, Dao T, Chen H, et al. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. J Antimicrob Chemother 2006;58:645-50.

17. Cotogni P, Barbiero C, Passera R, et al. Violation of prophylactic vancomycin administration timing is a potential risk factor for rate of surgical site infections in cardiac surgery patients: a prospective cohort study. BMC Cardiovasc Disord 2017;17:73.

18. Vardakas KZ, Soteriades ES, Chrysanthopoulou SA, et al. Perioperative anti-infective prophylaxis with teicoplanin compared to cephalosporins in orthopaedic and vascular surgery involving prosthetic material. Clin Microbiol Infect 2005;11:775-7.

19. Periti P, Stringa G, Minì E. Comparative multicenter trial of teicoplanin versus cefazolin for antimicrobial prophylaxis in prosthetic joint implant surgery. Italian Study Group for Antimicrobial Prophylaxis in Orthopedic Surgery. Eur J Clin Microbiol Infect Dis 1999;18:113-9.

20. Humphreys H, Becker K, Dohmen PM, et al. Staphylococcus aureus and surgical site infections: benefits of screening and decolonization before surgery. J Hosp Infect 2016;94:295-304.

21. Kim DH, Spencer M, Davidson SM, et al. Institutional prescreening for detection and eradication of methicillin-resistant Staphylococcus aureus in patients undergoing elective orthopaedic surgery. J Bone Joint Surg Am 2010;92:1820-6.

22. Lee AS, Cooper BS, Malhotra-Kumar S, et al. Comparison of strategies to reduce methicillin-resistant Staphylococcus aureus rates in surgical patients: a controlled multicentre intervention trial. BMJ Open 2013;3:e003126.

23. Schweizer ML, Chiang HY, Septimus E, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. JAMA 2015;313:2162-71.

24. Edmiston CE Jr, Ledeboer NA, Buchan BW, et al. Is Staphylococcal Screening and Suppression an Effective Interventional Strategy for Reduction of Surgical Site Infection? Surg Infect (Larchmt) 2016;17:158-66.

25. Schelenz S, Tucker D, Georgeu C, et al. Significant reduction of endemic MRSA acquisition and infection in cardiothoracic patients by means of an enhanced targeted infection control programme. J Hosp Infect 2005;60:104-10.

26. Lopez WY, Rider SM, Nwosu K, et al. The Impact of Vancomycin and Cefazolin as Standard Preoperative Antibiotic Prophylaxis on Surgical Site Infections Following Instrumented Spinal Fusion. Spine (Phila Pa 1976) 2019;44:E366-71.

27. Ponce B, Raines BT, Reed RD, et al. Surgical Site Infection After Arthroplasty: Comparative Effectiveness of Prophylactic Antibiotics: Do Surgical Care Improvement Project Guidelines Need to Be Updated? J Bone Joint Surg Am 2014;96:970-7.

28. Burger JR, Hansen BJ, Leary EV, et al. Dual-Agent Antibiotic Prophylaxis Using a Single Preoperative Vancomycin Dose Effectively Reduces Prosthetic Joint Infection Rates With Minimal Renal Toxicity Risk. J Arthroplasty 2018;33(7S):S213-18.

29. Branch-Elliman W, Ripollone JE, O’Brien WJ, et al. Risk of surgical site infection, acute kidney injury, and Clostridium difficile infection following antibiotic prophylaxis with vancomycin plus a beta-lactam versus either drug alone: A national propensity-score-adjusted retrospective cohort study. PLoS Med 2017;14:e1002340.

30. Courtney PM, Melnic CM, Zimmer Z, et al. Addition of Vancomycin to Cefazolin Prophylaxis Is Associated With Acute Kidney Injury After Primary Joint Arthroplasty. Clin Orthol Relat Res 2015;473:2197-203.

31. Zelenitsky SA, Silverman RE, Duckworth H, et al. A prospective, randomized, double-blind study of single high dose versus multiple standard dose gentamicin both in combination with metronidazole for colorectal surgical prophylaxis. J Hosp Infect 2000;46:135-40.

32. Dubrovskaya Y, Tejada R, Bosco J 3rd, et al. Single high dose gentamicin for perioperative prophylaxis in orthopedic surgery: Evaluation of nephrotoxicity. SAGE Open Med 2015;3:2050312115612803.

33. Zelenitsky SA, Ariano RE, Harding GK, et al. Antibiotic pharmacodynamics in surgical prophylaxis: an association between intraoperative antibiotic concentrations and efficacy. Antimicrob Agents Chemother 2002;46:3026-30.

34. Zanetti G, Giardina R, Platt R. Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery. Emerg Infect Dis 2001;7:828-31.
35. Markantonis SL, Kostopanagiotou G, Panidis D, et al. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. Clin Ther 2004;26:271-81.

36. Swoboda SM, Merz C, Kostuik J, et al. Does intraoperative blood loss affect antibiotic serum and tissue concentrations? Arch Surg 1996;131:1165-72.

37. Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. Surg Infect (Larchmt). 2006;7:473-80.

38. Winfield RD, Reese S, Bochicchio K, et al. Obesity and the Risk for Surgical Site Infection in Abdominal Surgery. Am Surg 2016;82:331-6.

39. Bauer LA, Edwards WA, Dellinger EP, et al. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol 1983;24:643-7.

40. Crawford T, Rodvold KA, Solomkin JS. Vancomycin for surgical prophylaxis? Clin Infect Dis 2012;54:1474-9.

41. Hafermann MJ, Kiser TH, Lyda C, et al. Weight-based versus set dosing of vancomycin for coronary artery bypass grafting or aortic valve surgery. J Thorac Cardiovasc Surg 2014;147:1925-30.

42. Crass RL, Dunn R, Hong J, et al. Dosing vancomycin in the super obese: less is more. J Antimicrob Chemother 2018;73:3081-6.

43. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020;77:835-64.

44. Lam PW, Tarighi P, Elligsen M, et al. Self-reported beta-lactam allergy and the risk of surgical site infection: A retrospective cohort study. Infect Control Hosp Epidemiol 2020;41:438-43.

45. Blumenthal KG, Ryan EE, Li Y, et al. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. Clin Infect Dis 2018;66:329-36.

46. Zagursky RJ, Pichichero ME. Cross-reactivity in β-Lactam Allergy. J Allergy Clin Immunol Pract 2012;6:72-81.e1. Erratum in: J Allergy Clin Immunol Pract 2022;10:651.

47. Romano A, Valluzzi RL, Caruso C, et al. Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins. J Allergy Clin Immunol Pract 2018;6:1662672.

48. de Jonge SW, Bolding QJJ, Solomkin JS, et al. Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. Lancet Infect Dis 2020;20:1182-92.

49. Minami T, Sasaki T, Serikawa M, et al. Antibiotic prophylaxis for endoscopic retrograde cholangiopancreatography increases the detection rate of drug-resistant bacteria in bile. J Hepatobiliary Pancreat Sci 2014;21:712-8.

50. Masadeh M, Chandra S, Livorsi D, et al. Evaluation of Biliary Bacterial Resistance in Patients with Frequent Biliary Instrumentation, One Size Does Not Fit All. Dig Dis Sci 2018;63:3474-9.

51. Du M, Suo J, Liu B, Xing Y, et al. Post-ERCP infection and its epidemiological and clinical characteristics in a large Chinese tertiary hospital: a 4-year surveillance study. Antimicrob Resist Infect Control 2017;6:131.