Clinical Practice Guidelines

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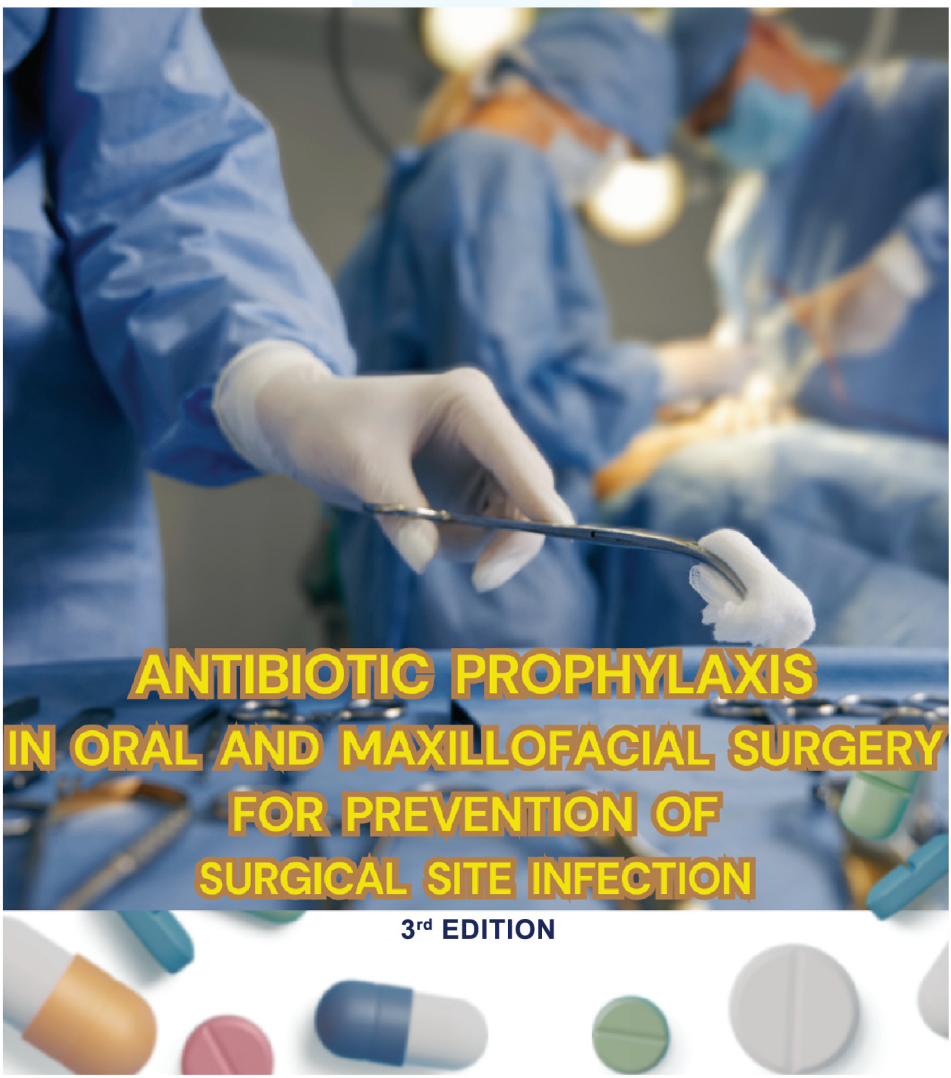
MINISTRY OF HEALTH MALAYSIA
ORAL HEALTH PROGRAMME



ANTIBIOTIC PROPHYLAXIS IN ORAL AND MAXILLOFACIAL SURGERY FOR PREVENTION OF SURGICAL SITE INFECTION

3rd EDITION

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STATEMENT OF INTENT

These guidelines update and supplant the previous guidelines developed in 2015 and are based on the best available contemporary evidence. They are intended as a guide for the best clinical practice on antibiotic prophylaxis in oral and maxillofacial surgery for prevention of surgical site infection. However, it must be noted that adherence to these guidelines do not necessarily lead to the best clinical outcome in individual patient care, as every health care provider is responsible for the management of his/her unique patient based on the clinical presentation and management options available locally.

UPDATING THE CLINICAL PRACTICE GUIDELINES

This guideline was approved in 2024 and will be reviewed in 2029 or earlier if important new evidence becomes available. When it is due for updating, the head of the related specialty will be informed about it. A multidisciplinary team will be formed, and discussion will be done on the need for a revision including the scope of the revised CPG. The Systematic Review (SR) methodology used by the Malaysia Health Technology Assessment Section (MaHTAS) will be employed in reviewing the guidelines.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times.

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LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** was adapted in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG Development Group (DG).
- In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations which includes:
  - overall quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - equity, feasibility and acceptability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Clean Surgery

- Antibiotic prophylaxis should not be given for healthy patients undergoing clean head and neck surgery.

Clean-Contaminated Surgery

- Antibiotic prophylaxis may be administered in impacted tooth surgery when it is indicated.
  - The preferred option is Amoxicillin or Amoxicillin-clavulanate.
- Antibiotic prophylaxis should be given for periodontal surgical procedures involving placement of biomaterials.
- Antibiotic prophylaxis should be administered in dental implant surgery.
  - The preferred option is Amoxicillin.
- Antibiotic prophylaxis may be administered in intraoral bone grafting.
- Antibiotic prophylaxis for cleft lip and palate surgery and orthognathic surgery:
  - should be administered pre-operatively
  - may be considered for post-operatively up to five days

Contaminated Wounds In Oral And Maxillofacial Surgery

- Antibiotic should be administered in contaminated wounds in oral and maxillofacial region.
- Antibiotic should be administered in bite wounds in oral and maxillofacial region.
  - The preferred option Amoxicillin-clavulanate.
  - Should be provided post-operatively up to five days.

Oral And Maxillofacial Trauma

- For oral and maxillofacial trauma surgery, peri-operative antibiotics should be given to prevent surgical site infection but not more than 24 hours post-operatively.

Oncological Head And Neck Surgery

- Antibiotic prophylaxis should be prescribed in oncological head and neck surgery.

Special Population

- Antibiotic prophylaxis should be given to any oral surgical procedures to the following
  - uncontrolled diabetes mellitus patients (BGL >10 mmol/L and HbA1c >7.5%)
  - patients exposed to radiotherapy/chemotherapy
  - patients undergoing chemotherapy with absolute neutrophils count is between 1000-2000mm^3
  - post head and neck irradiated patients, to prevent osteoradionecrosis
  - patients at risk of developing Medication-Related Osteonecrosis of the Jaw (MRONJ)
- Antibiotic prophylaxis should be given to patients at risk of infective endocarditis prior to any invasive oral procedure.
- Clindamycin and Erythromycin should not be given as antibiotic prophylaxis for prevention of infective endocarditis.

Administration Of Antibiotic Prophylaxis

- For patients who are undergoing oral and maxillofacial surgical procedure and allergic to Penicillin:
  - Azithromycin, Cefazolin or Doxycyline may be prescribed
  - Cephalosphorin should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with Penicillin/Ampicillin
  - Clindamycin or Erythromycin may be considered with caution if other antibiotics are not available
- Antibiotic prophylaxis should be given as a single dose and not more than 24 hours, unless specified.
- Redosing should be given if the duration of surgery exceeds the two half-lives of the antibiotics and should follow the initial dose given pre-operatively.
- Antibiotic prophylaxis should be given 30-60 minutes prior to surgical incision or within 120 minutes for Fluoroquinolones and Vancomycin.

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were health care providers from the Ministry of Health (MoH), Ministry of Higher Education and private healthcare. There was active involvement of a multidisciplinary Internal Review (IR) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systematic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published on humans, publication from year "2015 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched, and experts in the field contacted to identify relevant studies. All searches were conducted from October 2022 to July 2024. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 July 2024 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on management of antibiotic prophylaxis in oral and maxillofacial surgery for prevention of surgical site infection which are:

- National Antibiotic Guidelines, 2024
- National Surgical Antibiotic Prophylaxis Guideline (Singapore), 2022

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 7 clinical questions (CQs) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 18 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and IR. Where evidence was insufficient, the recommendations were made by consensus of the two groups. This CPG was developed largely based on the findings of SRs, meta-analyses and clinical trials, with local practices taken into consideration. Although ideally patients'

views and preferences need to be considered in the development of CPGs, in this instance, it was not feasible.

The literature used in these guidelines were graded using the U.S. Preventive Services Task Force Level of Evidence (2015), while the grading of recommendation was done using the principles of GRADE (refer to page i). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

- **General Objective**:
  To provide evidence-based recommendations on the antibiotic prophylaxis in oral and maxillofacial surgery for prevention of surgical site infection.
- **Specific Objectives**:
  - To identify the procedures in oral and maxillofacial surgery that would benefit from surgical antibiotic prophylaxis.
  - To advocate which antibiotics to prescribe and what regime to follow if antibiotic prophylaxis is indicated.

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

These guidelines are applicable to all, who are undergoing oral and maxillofacial surgical procedures.

Inclusion Criteria
Patients undergoing oral and maxillofacial surgical procedures.

TARGET GROUP/USERS

This document is intended to guide those involved in providing antibiotic prophylaxis in oral and maxillofacial surgery for prevention of surgical site infection at any healthcare level including:

i. Dental practitioners
ii. Medical practitioners
iii. Pharmacists
iv. Dental therapists
v. Dental students
vi. Allied health personnel
vii. Patients and their caregivers
viii. Professional societies

HEALTHCARE SETTINGS

Primary and Specialist Oral Healthcare Clinics, Health Clinics and community settings are the common areas of use of these guidelines.

DEVELOPMENT GROUP

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The draft guidelines were reviewed by a panel of experts. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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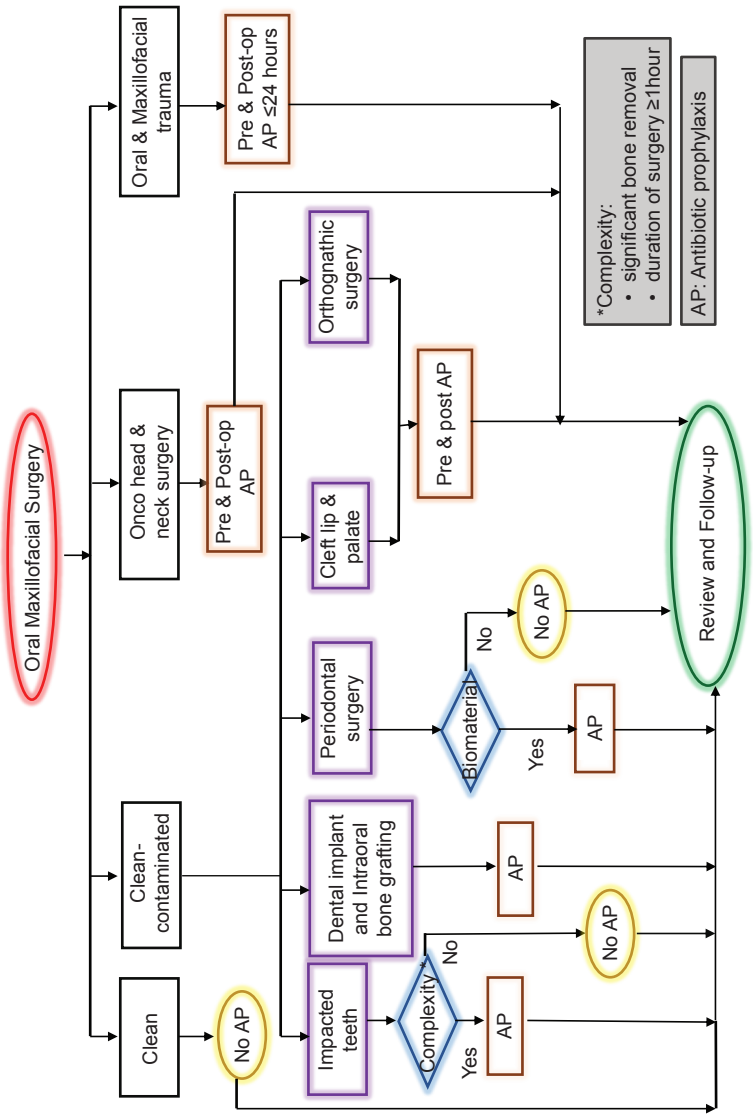
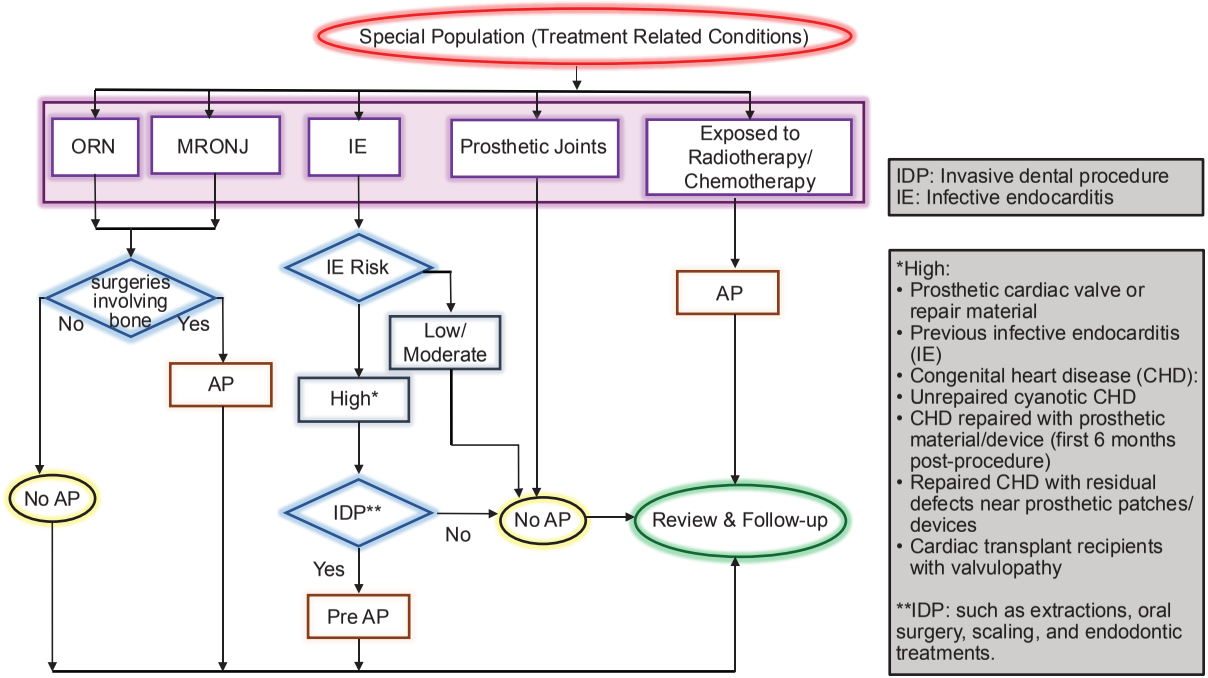
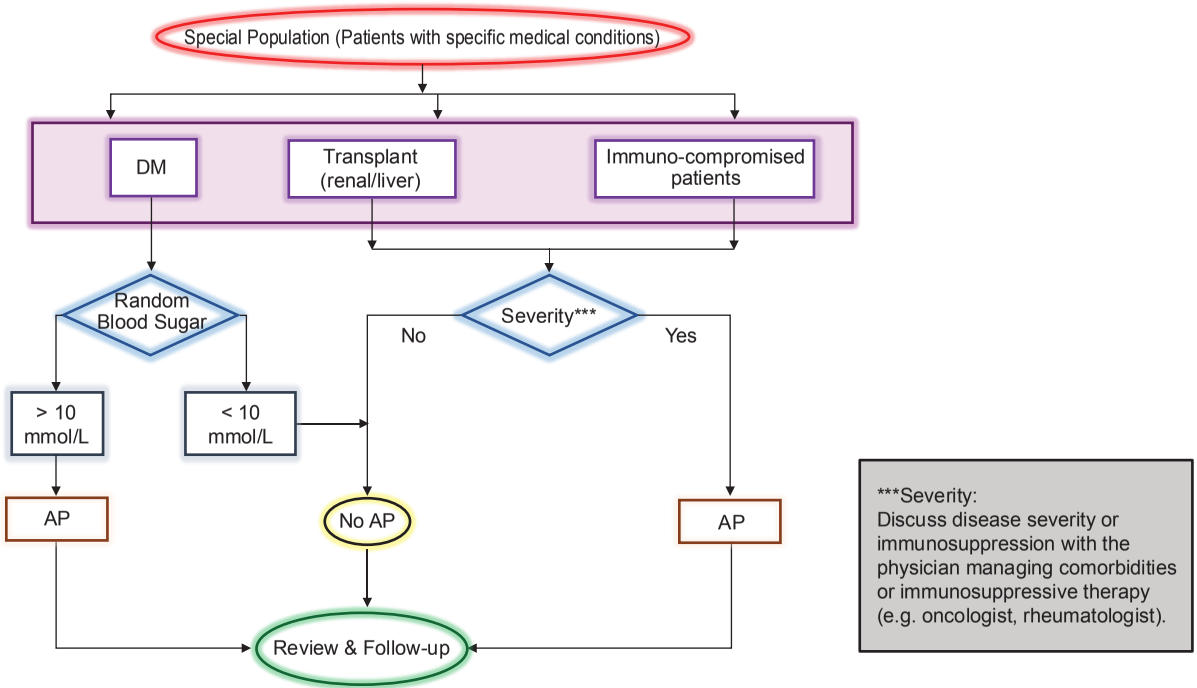
Algorithm 1: Antibiotic Prophylaxis (AP) in Oral and Maxillofacial Surgery for Prevention of Surgical Site Infection



Algorithm 2: Antibiotic Prophylaxis in Special Population (Treatment Related Conditions) for Prevention of Surgical Site Infection in Oral and Maxillofacial Surgery



Algorithm 3: Antibiotic Prophylaxis in Special Population (Patients with specific medical conditions) for Prevention of Surgical Site Infection in Oral and Maxillofacial Surgery



1. INTRODUCTION

Surgical site infections (SSIs) are common complications that surgeons encounter, leading to significant morbidity and mortality. The oral cavity is particularly prone to infections due to its high bacterial load. Even with strict aseptic protocols, infections can occur in oral and maxillofacial surgeries, with a prevalence rate of approximately 10%-15%.[1] Post-operative infections in oral and maxillofacial surgeries are more likely due to the bacterial presence and the accessibility of the incision site during healing.

SSIs may present with obvious clinical signs and symptoms such as inflammation associated with pain, swelling, suppuration with or without pyrexia. However, it may also present as integration failure of oral implants and biomaterials. In this CPG we have also extended SSIs to include distant site infection associated with oral and maxillofacial surgical procedures.

Patients with SSIs are five times more likely to be readmitted within 30 days and twice as likely to succumb compared to those without SSIs. SSIs typically develop within 30 days post-surgery or within 90 days if a prosthesis is implanted. The clinical and financial burden of surgery escalates significantly with an SSI, leading to prolonged hospital stays, additional diagnostic tests and therapies. Some patients may require re-operation with further increasing costs. SSIs also severely impact patients' physical and mental health, with indirect costs including higher morbidity, mortality and lost earnings during recovery.[1]

Antibiotic prophylaxis may play a pivotal role in mitigating the risk of post-operative infections in oral and maxillofacial surgery, safeguarding both the patient's well-being and the success of surgical interventions. Administering antibiotics 30-60 minutes before surgical incision when indicated is crucial to prevent SSIs. This is to ensure effective antibiotic levels in the tissue during surgery. In procedures lasting over 2-4 hours, an additional intra-operative dose may be necessary. The need for antibiotics prophylaxis can also depend on the surgeon's skill and experience, as extended duration of surgery time may increase the risk of infection.

Adjunctive measures such as scaling prior to surgery, maintaining good oral hygiene and using chlorhexidine (CHX mouthwash can significantly reduce the risk of SSIs by lowering the bacterial load. A systematic review and meta-analysis.[2] highlight that using 0.2% CHX rinses or in gel form, significantly improves oral surgical wound healing and reduces the risk of complications such as alveolar osteitis after dental extractions.

As our understanding of antibiotic usage evolves, so does the need for revising clinical practice guidelines (CPGs) to ensure safer and more effective antibiotic prophylaxis. In light of this, the revision of the 2nd edition CPG for antibiotic prophylaxis in oral and maxillofacial surgery emerges as a critical step forward. The revised guidelines are designed not only to optimize patient outcomes but also to address the global concern of antimicrobial resistance (AMR) by promoting judicious antibiotic use.

The World Health Organization (WHO) considers antimicrobial resistance (AMR) a major global health threat. In 2019, AMR directly caused over 1.2 million deaths and contributed to nearly 5 million deaths worldwide.[3] This crisis is largely driven by overuse and misuse of antimicrobials in healthcare, animal husbandry, and farming. AMR's impact goes beyond individual health, affecting entire healthcare systems and economies. It leads to more complicated and expensive treatments, longer hospital stays, and increased healthcare costs. Moreover, it reduces economic productivity as patients and their caregivers spend more time away from work due to prolonged illnesses and treatments.

One of the primary focuses of the updated guidelines is to enhance the safety of antibiotic usage, emphasizing the importance of selecting the right antibiotic at the right dose and duration. The intention is to strike a balance between preventing infections and minimizing the potential for antibiotic resistance. By incorporating the latest research findings and evidence-based practices, the revised CPG aims to provide clinicians with a nuanced understanding of the indications for antibiotic prophylaxis, fostering a more thoughtful and evidence-driven approach.

The layout of the guidelines has been revamped to facilitate easier access for clinicians, recognizing the time constraints and demands of clinical practice. The revised format offers a user-friendly interface that enables quick reference and decision-making in various clinical settings. It integrates practical recommendations, incorporating the diverse scenarios encountered in oral and maxillofacial surgery, ensuring that clinicians can swiftly implement appropriate antibiotic prophylaxis protocols. Recognizing the intricate interplay between systemic health, patient-specific factors, and surgical interventions, the guidelines offer tailored recommendations for different procedures and patient populations. This holistic approach considers not only the surgical site but also the patient's overall health, aiming to optimize outcomes while minimizing the risks associated with antibiotic overuse.

In conclusion, the revised CPG for antibiotic prophylaxis in oral and maxillofacial surgery represents a conscientious effort to align clinical practices with the latest evidence and global initiatives in

antibiotic stewardship. By prioritizing safety, accessibility, and comprehensiveness, these guidelines aspire to usher in a new era of antibiotic prophylaxis that safeguards patient's health, while simultaneously contributing to the global efforts to combat antibiotic resistance.

2.0 CLEAN SURGERY

Surgical wound can be classified according to the degree of bacterial load or contamination (Refer to **Appendix 3**). Clean wound is when an uninfected operative wound in which no inflammation is encountered, and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage.[4] This means that in the head and neck region where the incision and exposure does not breach into the oral cavity. For example, submandibular or parotid gland surgery, temporal (Gillies) zygomatic fracture reduction and temporomandibular surgery are considered clean surgery.

When determining the need for antibiotic prophylaxis (AP) in clean surgeries, it is important to consider the patient's immune status and the use of any implants or grafting materials during the procedure.

A meta-analysis of 4 RCTs found no significant (NS) in reduction of SSIs in clean surgery for head and neck region between groups with and without AP.[5], level I The 4 RCTs included in the review were of moderate quality.

Another small RCT found that in a revision cases of clean head and neck surgery, single-dose 1g Cefazolin compared with placebo showed NS in the incidence of cellulitis up to at least 4 weeks follow-up.[6], level I

This is further supported by a systematic review of 33 guidelines on the risk of SSIs in clean surgery for head and neck surgery, the recommendations were:[7]

- no AP for parotidectomy, submandibular gland resection and other benign pathologies
- AP may be considered for neck dissection

Key Message 1
The CPG DG suggest that AP in clean head and neck surgeries to prevent SSIs can be considered in the following situations:

- patient related factor
  - Immunocompromised conditions
- surgery related factor
  - Neck dissection
  - Use of bone or tissue grafting
  - Use of implants
  - Long duration of surgery

Recommendation 1

- Antibiotic prophylaxis should not be given for healthy patients undergoing clean head and neck surgery.

3.0 CLEAN-CONTAMINATED SURGERY

Clean-contaminated oral surgery occupies a unique niche in the field of surgical practice, bridging the gap between sterile procedures and those performed in inherently contaminated environments. This type of surgery involves operating on areas that naturally harbor bacteria, such as the oral cavity, which includes the gums, teeth, and surrounding tissues. These procedures often include surgical tooth extractions, periodontal surgery, implant placements, bone grafting and corrective jaw surgeries, which are crucial for treating various conditions such as infections, tumors, trauma, and congenital anomalies. Despite the presence of these microorganisms, meticulous surgical techniques and stringent pre- and post-operative antibiotic protocols are employed to minimize the risk of infection.[8] The oral cavity, being exposed to a constant influx of bacteria from food, air and saliva, presents a complex challenge to surgeons aiming to maintain a balance between cleanliness and the natural microbial flora.

3.1 Impacted Tooth Surgery

Impacted tooth surgery, also known as surgical removal of an impacted tooth, is performed when a tooth fails to emerge through gingiva. This occurs due to factors like inadequate space or abnormal positioning. The most commonly impacted teeth are third molars, but other teeth can also be affected. The surgical procedure may involve significant bone removal as a means to expose the tooth/teeth for the intention of complete removal or to facilitate orthodontic or restorative treatment. The use of AP to prevent infection following impacted tooth surgery needs to be addressed.

In a systematic review, three RCTs compared AP and placebo on healthy patients undergoing third molar removal showed post-operative infection/ complications:[9], level I

- was lower with Amoxicillin-clavulanate (p=0.0001)
- had NS difference with Clindamycin and Metronidazole

However, two RCTs had high risk of bias while one had low risk of bias based on Cochrane RoB.

A meta-analysis published in the same year but used eight RCTs on same study population, intervention and comparator showed the following outcomes:[10], level I

- post-operative infection was lower with:
  - Amoxicillin-clavulanate (RR=0.21, 95% CI 0.12 to 0.40)
  - Amoxicillin (RR=0.37, 95% CI 0.15 to 0.92)
- post-operative infection was lower regardless of timing of antibiotic administration (RR=0.25, 95% CI 0.15 to 0.42):
  - pre-surgery administration (RR=0.32, 95% CI 0.12 to 0.85)

    - post-surgery administration (RR=0.15, 95% CI 0.06 to 0.38)
    - mixed administration (RR=0.32, 95% CI 0.14 to 0.69)
- adverse effects (AE) were:
    - when compared to placebo
        - higher with Amoxicillin-clavulanate (RR 4.12, 95% CI 1.21 to 14.00)
        - NS difference with Amoxicillin
    - higher in pre-surgery administration (RR=3.59, 95% CI 0.47 to 27.40) and post-surgery administration (RR=6.24, 95% CI 1.43 to 27.18) but NS with mixed administration

However, types of adverse effects were not clearly reported and risk of bias was not reported.

A large Cochrane systematic review of 23 RCTs compared the effectiveness and safety of systemic AP with placebo on prevention of infection following third molar removal. The primary outcome of post-surgical infection was varied and not well defined. The systemic AP was effective in preventing post-surgical infection by 66% (RR=0.34 CI 0.19 to 0.64; number needed to treat (NNT)=19, 95% CI 15 to 34). Further analysis showed that:[11], level I

- pre-operative prophylaxis alone
    - reduced post-surgical infection by 68% at day 6 to 7 (RR=0.32, 95% CI 0.16 to 0.62)
    - had NS differences in dry socket, pain, swelling, trismus and adverse events at day 6 to 7.
- post-operative prophylaxis alone
    - reduced post-surgical infection by 79% at day 6 to 7 (RR=0.21,95% CI 0.05 to 0.80)
    - had NS differences in dry socket, pain, swelling, trismus, fever and adverse events at day 6 to 7

However, combined pre-operative and post-operative prophylaxis showed NS difference in post-surgical infection despite having less dry socket on day 6 to 7 (RR=0.50, 95% CI 0.28 to 0.90). Based on risk of bias assessment, 16 trials were at high risk of bias, three at low risk and four as unclear.

In addition, a more recent network meta-analysis of 16 RCTs on healthy patients undergoing lower third molar removal which compared different antibiotics and placebo revealed that the former had:[12], level I

- lower SSIs (OR=0.36, 95% CI 0.22 to 0.57)
- lower incidence of dry socket (OR=0.54, 95% CI 0.33 to 0.90)
- NS in adverse events

The SUCRA ranking on SSIs reduction were as follows:

- Amoxicillin post-operative (77.7%)
- Metronidazole pre-operative (74.2%)
- Amoxicillin-clavulanate pre-operative and post-operative (72.7%)
- Azithromycin pre-operative (67.5%)

- Amoxicillin-clavulanate pre-operative (50.9%) and others.

While SUCRA ranking on dry socket reduction were as follows:

- Clindamycin pre-operative (73.7%)
- Azithromycin pre-operative (71.3%)
- Amoxicillin pre-operative (66.3%)
- Amoxicillin-clavulanate pre- and post-operative (55.1%)
- Clindamycin pre- and post-operative (50.2%) and others.

Based on GRADE, the quality of evidence on SSIs and dry socket were low while it was very low for adverse events.

The use of AP in third molar removal surgery may reduce the risk of infection but should be weighed against the risk of adverse effects. The decision to administer antibiotics should be made based on individual case considerations, taking into account the various local and systemic factors that may predispose to an increased risk of SSIs/complications. In local settings, prophylactic Amoxicillin has been given in lower third molar surgery when there is significant bone removal, and/or prolonged operation time and risk of non-surgical site complications.

Key Message 2

Indications for AP in removal of impacted tooth to prevent SSIs are:

- patient's risk factor and medical history
  - Immunocompromised conditions
  - Smoking status
- complexity of the surgical procedure
  - Significant bone removal
  - Prolonged operation time >1 hour

Recommendation 2

- Antibiotic prophylaxis may be administered in impacted tooth surgery when it is indicated*.
  - The preferred option is Amoxicillin or Amoxicillin-clavulanate.

*Refer to Key Message 2 above

3.2 Periodontal Surgery

Periodontal disease frequently results in soft and hard tissue defects around teeth. Following the removal of the burden of infection through non-surgical periodontal therapy, surgical procedures to rectify these defects are commonly performed under local anaesthesia in a clean-contaminated environment.

In a recent RCT comparing the effect of systemic amoxicillin versus control following regenerative periodontal surgery with Demineralized

Bovine Bone Mineral (DBBM) and Guided Tissue Regeneration (GTR), showed NS difference in terms of gingiva recession (GR), pocket depth (PD) and clinical attachment level (CAL) gain at 1 year follow up.[13], level I

Specifically, there's not enough evidence to decide if antibiotic use is necessary during periodontal surgical procedures employing the use of bone grafts and membranes. This lack of evidence is likely because the patient's safety is prioritized and the financial cost and morbidity is considered too great if the biomaterial is lost through infection. Therefore, the DG members opine that AP should be given for procedures involving placement of biomaterials.

Recommendation 3

- Antibiotic prophylaxis should be given for periodontal surgical procedures involving placement of biomaterials.

3.3 Dental Implant Surgery

Rehabilitation with dental implants is considered the best option to replace missing teeth. The popularity of this treatment modality is increasing exponentially but despite the high success rates published in the literature, implant failures do occur. Bacterial driven infections, both clinical and subclinical, is one of the causes of implant failures and AP has been advocated as a means of prevention.

In a meta-analysis with nine RCTs, assessing the effectiveness of Amoxicillin compared to control group, among patients undergoing dental implant placements showed:[14], level I

- implant failure prevention was
  - significant for single pre-operative dose (RR=0.52, CI 0.30-0.92), (NNT=77, 95% CI of 32 to 250)
  - not significant for post-operative (with or without preoperative) dose
- post-operative infection was
  - not significant for both pre- and post-operative doses

Based on risk of bias assessment, the funnel plot (symmetrical dispersion of points) around a RR of 0.53, 0.54, and 0.74 suggests that there may not be publication bias.

Similarly, in the following year, a network meta-analyses with nine RCTs, assessing the effectiveness of Amoxicillin compared to control group (with and without placebo), among patients undergoing dental implant placements showed:[15], level I

- use of AP was protective in terms of implant loss (OR=0.28, 95% CI 0.14 to 0.55)

- 3g Amoxicillin 1hr pre-op was statistically more effective in preventing implant failures compared to placebo or no prophylaxis (OR=0.41, 95% CI 0.18 to 0.91)

Two trials in this study were assessed to have a low risk of bias, while the remaining seven trials were considered to have a high risk of bias.

Two more recent RCTs assessing the effectiveness of pre-surgical Amoxicillin compared to placebo, among healthy patients undergoing dental implant placements showed:

- implant failure prevention was NS[16], level I
- post-operative infection was NS[16], level III; [17], level I

Based on the evidences above, the use of AP in dental implant surgery may reduce the risk of implant failure. The decision to administer antibiotics should be made based on individual case considerations, taking into account the various local and systemic factors that may predispose to an increased risk of failure/infection.

Key Message 3
Indications for AP in dental implant surgery to prevent SSIs are:

- patient's risk factor and medical history
  - Immunocompromised conditions
  - Smoking status
- complexity of the surgical procedure
  - Prolonged operation time > 1 hour
  - Simultaneous hard/ soft tissue grafting

Recommendation 4

- Antibiotic prophylaxis should be administered in dental implant surgery.
  - The preferred option is Amoxicillin.

3.4 Alveolar ridge augmentation/Intraoral bone graftings

The administration of AP when bone grafts are inserted intraorally has been a controversial decision to make. This statement highlights a common problem in dentistry: the need to balance evidence with practical concerns.

A meta-analysis of four RCTs, among healthy patients undergoing intraoral bone grafting procedures showed NS difference in post-operative infection between pre-op vs pre+post-op antibiotics. A small RCT in this review comparing antibiotic vs placebo within 30 days demonstrated better outcome in terms of:[18], level I

- receptor site infection (0% vs 40%)
- donor site infection (0% vs 30%)
- graft failure (0% vs 30%)

The risk of bias assessment indicated an overall unclear risk of bias.

Specifically, there's not enough evidence to decide if antibiotic use is necessary during intraoral bone graft procedures. This lack of evidence is likely because surgeons prioritize patient safety and consider the financial cost and morbidity too great if a bone graft is lost through infection. In a local setting, the decision to administer antibiotics is based on individual case considerations, taking into account the various local and systemic factors that may predispose to an increased risk of failure/infection.

Key Message 4

Indications for AP in intraoral bone grafting to prevent SSIs are:

- patient related factor
  - Immunocompromised conditions
  - Smoking status
- surgery related factor
  - Prolonged operation time >1 hour

Recommendation 5

- Antibiotic prophylaxis may be administered in intraoral bone grafting.

3.5 Cleft Lip & Palate Surgery

The primary objective of cleft surgery is to restore normal function, appearance, and speech by reconstructing the defect to normal anatomy. Post-operative wound infection is a recognized complication that may lead to breakdown of the wound resulting in palatal fistulas, hemorrhage, poor speech and the need for further surgical intervention.

In a recent narrative review on usage of post-operative AP in cleft lip and palate surgery, there is no consensus on the use of post-operative AP to prevent SSIs.[19], level III However, they did report a RCT published in 2015 evaluated the use of post-operative AP in cleft palate surgery and found that the use of oral Amoxicillin (50 mg/kg body weight/day) for five days reduced the rate of palatal fistulas from 17.1% to 10.7%. [20], level I This trial was also included in a systematic review published in 2021 that concluded that the evidence for reduced risk of SSIs with post-operative antibiotics was lacking.[21], level I

Alveolar bone grafting (ABG) surgery in patients with cleft lip and palate, where soft tissue conditions are inherently more complex due to scarring, increases the risk of surgical complications such as graft failure, fistula formation or even partial or complete loss of the transplanted tissue.

A retrospective cohort study on cleft patients who underwent ABG showed NS in post-operative infection between pre-op (30 mins prior with Cefuroxime or Clindamycin) and pre+post-op (30 mins prior and continued post-operatively with a median of 5 days with Penicillin G or Cefuroxime). This study showed that the reduction in AP to a single pre-operative dose did not lead to an increased rate of post-operative infection. However, the study's retrospective approach and small sample size may limit the significance of the results presented.[22], level II-2

In the local setting, the administration of pre-operative AP is the current practice for all cleft lip and palate related surgeries.

Recommendation 6
- Antibiotic prophylaxis for cleft lip and palate surgery:
  - should be administered pre-operatively
  - may be considered for post-operatively up to five days

3.6 Orthognathic Surgery

Orthognathic surgery procedures often involve extensive utilisation of fixation implants in a microbial-rich environment of the oral cavity, nasal cavity and maxillary sinuses. Post-operative infection is one of the complications of this procedure and it occurs at the prevalence of 7.4%.[23]

A Cochrane systematic review of 11 RCTs looked on the use of antibiotics to prevent infections in orthognathic surgery. Administering antibiotics over a long-term period (before or during surgery and continuing >1 day after surgery) showed 58% SSIS reduction (RR=0.42, 95% CI 0.24 to 0.74) compared with short-term period (given only before or during surgery or on the same day). However, NS difference in SSIs between administration of antibiotics pre-operatively (one dose before surgery) vs short-term. There was no report on adverse effects associated with the antibiotics. Most of the primary papers had an unclear risk of bias and the quality downgraded based on GRADE assessment.[24], level I

A double-blinded RCT determined the effectiveness of a 3-day vs 1-day regimen of post-operative antibiotics following orthognathic surgery

and showed reduction of SSIs in the 3-day regimen (7% vs 17.6%, p=0.04). The NNT for one additional patient to benefit from the regimen was 10.[25], level I

An overview of SRs on various antibiotic regimens in orthognathic surgery reveals that long-term antibiotic therapy (three days or more post-surgery) is associated with lower infection rates (less than 3.5%) compared to shorter regimens or placebo. However, extended antibiotic use raises safety concerns, with potential side effects including nausea, pain, swelling, headache, vomiting and skin rash particularly with Cefazolin, Clindamycin and Penicillin therapies.[26], level I

In local practice, post-operative orthognathic surgery patients in general typically receive AP for a duration of 5 days.

In the previous edition of local CPG on AP in oral surgery for prevention of SSIs, AP is indicated for major clean-contaminated maxillofacial surgery which includes orthognathic surgery.[27]

Recommendation 7

- Antibiotic prophylaxis for orthognathic surgery:
  - should be administered pre-operatively
  - may be considered for post-operatively up to five days

4.0 CONTAMINATED WOUNDS IN ORAL AND MAXILLOFACIAL SURGERY

Contaminated wounds in oral and maxillofacial surgery are surgical sites that have been exposed to pathogens, significantly increasing the risk of infection. These wounds may result from various sources, including breaches in sterile technique, accidental trauma, surgical procedures in areas with a high bacterial load (such as the oral cavity) and bite wounds.

In a recent meta-analysis with 11 trials, evaluating the necessity for AP for animal bite injuries in the maxillofacial area found that the risk of wound infection was slightly higher in control group compared to AP group, however it was statistically NS difference between the two groups.This study also showed deeper wounds (class II and III) based on Lackmann's classification had the highest infection rate (20.0%).[28], level I The included trials were of high risk of bias.

Lackmann's classification of facial bite injuries, detailing various types ranging from superficial injuries without muscle involvement (Type I) to deep injuries with concomitant bony fractures (Type IVB) (refer **Appendix 4**).

Oral maxillofacial soft tissue injuries with significant tissue destruction, extensive contamination or large dead space will increase the risk of infection. The CPG DG opines that the use of AP is crucial to minimize the risk of infections.

National Antimicrobial Guideline (NAG) recommends Amoxicillin-clavulanate 625mg for five days for bite wounds.[29]

Key Message 5
Indications for AP in contaminated wounds to prevent SSIs are:
- wound characteristics
  - bites
  - extensive through and through lacerations
  - crush injuries
  - gross contamination
  - penetrating injuries (ballistics, stab wounds)
- patient related factors
  - diabetes
  - immunosuppression
  - steroids
  - extremes of age
  - obesity

Recommendation 8

- Antibiotic should be administered in contaminated wounds in oral and maxillofacial region.
- Antibiotic should be administered in bite wounds in oral and maxillofacial region.
  - The preferred option is Amoxicillin-clavulanate.-clavulanate.
  - Should be provided post-operatively up to five days.

5.0 ORAL AND MAXILLOFACIAL TRAUMA

Oral and maxillofacial trauma surgery encompasses both clean (fractures not involving oral cavity), and clean-contaminated surgeries (fractures involving oral cavity). The use of AP in oral and maxillofacial trauma surgery aims to prevent SSIs and reduce the risk of post-operative complications however its use differs widely.

In a meta-analysis of 16 studies on AP in traumatic mandibular fractures management showed NS difference in SSIs between:[30], level I

- short <1 day vs extended > 1 day
- pre-operative vs pre-operative + post-operative
- pre-operative + post-operative IV (≤ 3 doses) then oral 5 days vs pre-operative IV + post-operative oral 5 days

Most of the primary papers were high risk of bias and the pooled result was of high heterogeneity.

Another meta-analysis of 26 studies on option is Amoxicillin-clavulanate. reduction and internal fixation (ORIF) (mandible, mid-face and orbit) fractures prescribed AP showed NS in developing SSIs between:[31], level I

- peri-operatively (post operatively <24 hours) vs post-operatively 24–72 hours
- peri-operatively (post operatively <24 hours) vs extended post-operatively >72hours
- post-operatively 24–72 hours vs extended post-operatively

This study showed varied lengths of AP, leading to the division into three groups. There is also inconsistency in reporting which antibiotics were used.

A meta-analysis of 14 clinical trials on patients undergoing mostly oral and maxillofacial trauma surgery showed:[32], level I

- NS difference in SSIs between short course (<24 hours) vs extended course AP (>72 hours)
- more AEs (unrelated to surgical site) in the extended course group (RR=2.40, 95% CI 1.20 to 3.54)

A limitation in this study was that the trials used different regimens and types of AP, potentially impacting the study results.

In a systematic review of four studies on patients undergoing ORIF of facial fractures receiving AP showed NS difference in preventing SSIs between peri-operative (2 hours prior until 24 hours after surgery) with peri-operative + post-operative (>24hours after surgery) group.[33), level I

The included primary papers in this systematic review were of moderate quality.

Another systematic review of five studies assessing SSIs in mandibular fracture showed NS difference in the use of post-operative (>24hours) AP in the presence of peri-operative (within 24hours) and/or pre-operative AP.[34), level I] However, the quality assessment of the included studies in the SR was not done.

A large retrospective cohort study on patients with open mandibular fractures undergoing ORIF prescribed AP intra-operative (1 hour before the incision with possible intra-operative redosing) showed:[35), level II-2]

- NS difference in SSIs with:
  - Pre-operative (at the time of initial consultation of injury prior to op) + intra-operative
  - Post-operative (within 24 hours after surgery) + Intra-operative
  - Pre-operative + Intra-operative + post-operative

In the same study, 83% of SSIs was associated with smoking ($p<0.001$).

A scoping review and critical appraisal to provide an overview of the current evidence that support the use of AP in the treatment of maxillofacial fractures found that shortening the duration of AP to one day or less for operatively treated fractures should be sufficient, there is no evidence for the use of systemic AP in conservatively treated fractures. Overprescribing may contribute to increased long term infectious complications and AMR. High quality studies are needed to clarify the optimal duration of AP.[36), level I]

The Surgical Infection Society's 2020 guidelines specifically advise against using post-operative antibiotics for more than 24 hours in cases of both operative non-mandibular and mandibular facial fractures. Studies show that extended post-operative antibiotic use does not reduce infection rates, hospital stays, or mortality. Moreover, administering antibiotics beyond 24 hours post-surgery is more expensive and increases the risk of antibiotic-related complications.[37)]

A recent narrative review on AP for patients with traumatic facial fractures suggested:[38), level III]

- to avoid prolonged post-operative AP based on moderate-quality evidence
- a narrow-spectrum antibiotic ie Cefazolin to be administered within 1 hr of surgery and no longer than 24 hours after surgery.

The CPG DG members opine that prolonged AP in oral and maxillofacial trauma surgery may be considered in cases involving complex or contaminated surgery, however the benefits must be weighed against the risks of developing antibiotic-resistant infections and other adverse effects. The CPG DG members also point out that current research on AP use shows bias and inconsistency, highlighting the need for

more studies and better guidelines to determine the antibiotic type and optimal duration of AP.

Key Message 6

Indications for post-operative AP >24 hours in oral and maxillofacial trauma surgery to prevent SSIs are:

- **Patient related factor**
  - Immunocompromised conditions
  - Smoking status
  - Polytrauma
- **Surgery related factor**
  - Complex fracture and bone loss
  - Soft tissue loss at the surgical site/ insufficient soft tissue closure
  - Wound breakdown
  - Presence of contaminants
  - Presence of foreign bodies

Recommendation 9

- For oral and maxillofacial trauma surgery, peri-operative antibiotics should be given to prevent surgical site infection but not more than 24 hours post-operatively.

6.0 ONCOLOGICAL HEAD AND NECK SURGERY

Oncological head and neck surgical procedure involves operation which requires the removal of benign as well as malignant lesions or tumours. In local setting, surgical procedures performed can range from simple removal of small lesion with or without local flap closure to complex major tumour resections, neck dissection and reconstruction with loco-regional or free flap.

In a meta-analysis of five RCTs on oncological head and neck surgical cases, it was noted that AP was more effective than placebo in the prevention of SSIs (RR 0.36, 95% CI 0.21 to 0.60).[39], level I Based on GRADE assessment, the included primary papers were moderate to good quality.

Also, in a systematic review of 6 studies assessing the effectiveness of peri-operative AP, showed that the AP reduced SSIs in clean-contaminated oncological head & neck surgical cases.[40], level I Nonetheless, the types of the antibiotics used were varied and the results were mentioned descriptively.

The above findings were supported by another systematic review of 22 moderate studies, which were mostly retrospective cohort studies, whereby AP was strongly recommended (using Oxford Center EBM) for intra-operative and post-operative antibiotic use (24-48 hours) in head & neck surgery with neck dissection procedure.[41], level I

In addition, a meta-analysis of four moderate quality RCTs showed there was NS difference in the risk of wound infection within 1 day compared to 5 days of systemic AP among head and neck cancer surgery patients.[42], level I

Lastly, in a small prospective study comparing AP regimen among patients undergoing major oncological head and neck surgery showed fewer patients having SSIs in the combined peri-operative and post-operative AP group as compared to:[43], level II-2

- peri-operative AP only (p=0.011)
- combined peri-operative and local antiseptic group (n=9) (p=0.011)

According to various guidelines, there are many AP regimens used. According to American Society of Health-System Pharmacists (ASHP) guidelines, Cefazolin or Cefuroxime with Metronidazole, or Ampicillin-sulbactam are recommended for oncological clean-contaminated head and neck surgery.[44]

Existing guidelines for clean-contaminated oncological head and neck surgery are summarised below:[29, 45-47]

Guidelines	Main Antibiotic	Alternative Antibiotic (Penicillin Allergic)
4th Edition of National Antimicrobial Guideline (NAG), 2024	IV Cefazolin 2g + IV Metronidazole 500mg **Or** IV Cefuroxime 1.5g + IV Metronidazole 500mg **Or** IV Ampicillin/ Sulbactam 3g	IV Clindamycin 600-900mg; may add IV Gentamicin 5mg/kg
National Surgical Antibiotic Prophylaxis Guideline (Singapore), 2022	IV Amoxicillin/ Clavulanate 1.2g x TDS **Or**, IV Cefazolin 2g x tds + IV Metronidazole 500mg x tds	IV Clindamycin x 600-900mg x tds +/- IV Gentamicin x 5mg/kg once
The National Health Service Tayside, 2020	IV Amoxicillin x 1g tds + IV Metronidazole x 500mg x tds for three days then review	IV Clindamycin 600mg qid
South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR), 2022*	IV Cefazolin 30mg/kg (maximum 2g) as a single dose. If surgery > 3 hours, then repeat dose intra-operatively at 3 hours. + Metronidazole 12.5mg/kg (maximum 500mg) as a single dose. If surgery > 12 hours, then repeat dose intra-operatively at 12 hours.	Clindamycin and Gentamicin (for extensive neck dissection, debulking or reconstruction surgery)

* For this guideline, even though it is for the paediatric population, the DG members opine the dosage calculation can be of use for cases such as in underweight and overweight cancer patients.

In local practice for oncological head and neck surgery, we routinely administer AP peri-operatively and prolonged post-operatively. However, the post-operative recovery of the patient determined the duration of post-operative antibiotic. In patients allergic to Penicillins, Clindamycin may be considered with caution if other antibiotics are not available.

Recommendation 10

- Antibiotic prophylaxis should be prescribed in oncological head and neck surgery.

7.0 SPECIAL POPULATION

Special population includes pregnant, breastfeeding patients, those with specific medical conditions and treatment related conditions in oral and maxillofacial surgery. The rationale for prophylaxis was that patients with these conditions have an increased risk for SSIs and serious distant site infections.

7.1 Pregnant and Breastfeeding Patients

Antibiotics are essential for treating bacterial infections, but their use during pregnancy and breastfeeding requires careful considerations due to potential impacts on both mother and child. The safety of antibiotic therapy is paramount to ensure effective treatment while minimizing risks to fetal and infant health.

A population-based retrospective cohort study showed NS association between first trimester exposure to Amoxicillin or Amoxicillin-clavulanate to malformation of the fetus (adjusted RR 1.09, 95% CI 0.98 to 1.20).[48], level II-2

A SR reported all antibiotic studied had been detected in breast milk in subtherapeutic concentration compared to Therapeutic Infant Dose ranging from 0.05% to 10.61%. Nevertheless, low dose exposure may induce antibiotic resistance.[49], level II 2

Both studies suggested that administering certain antibiotics to pregnant and breastfeeding women had minimal or negligible effects when needed. Hence, the clinical development group has suggested a list of commonly used antibiotics for oral surgery when deemed suitable. This is summarised in **Table 1**.

Key message 7
The CPG DG members opine that for pregnant women scheduled for oral and maxillofacial surgery:
- the oral healthcare provider should consult an obstetrician if necessary.
- elective procedures should be postponed until after childbirth.

Table 1: Commonly use drugs for Antibiotics Prophylaxis Used in Oral and Maxillofacial Surgery (Pregnancy and Breast-Feeding Category).

Antibiotics	Pregnancy Category*	Breastfeeding Category
Amoxicillin	B	Acceptable
Amoxicillin-clavulanate	B (increase risk of necrotising enterocolitis in newborn)	Acceptable
Ampicillin	B	Acceptable
Ampicillin-Sulbactam	B	Acceptable
Azithromycin	B	Monitor the infant for possible Gastrointestinal (GI) effect.
Benzylpenicillin	B	Acceptable
Cefazolin	B	Acceptable
Cephalexin	B	Acceptable
Cefuroxime	B	Acceptable
Clindamycin	B	Monitor the infant for possible GI effect. Alternative may be considered for the breastfeeding women.
Doxycyline	D	Concern of possible staining of infant dental enamel.
Erythromycin	B	Monitor the infant for possible GI effect.
Metronidazole	B	Effect to infant is unknown. Concern of possible mutagenicity.

***Source**: Drugs and Lactation Database (LactMed®) https://www.ncbi.nlm.nih.gov/books/NBK501922/ Safety of Drugs in Pregnancy https://www.mims.com/pregdef https://online1.mimsgateway.com.my/*

*Pregnancy category was based on Monthly Index of Medical Specialities (MIMS). Refer to **Appendix 5**

7.2 Patients with specific medical conditions

a. Diabetes Mellitus Patients

In a systematic review, two cohort studies reported there was NS association between diabetes mellitus and delayed healing among post dental extraction patients, regardless of the administration of AP. In the first cohort study, the odds of having delayed healing were higher in the control group (30.9%), while in the second cohort study, the higher odds of having delayed healing were among patients with diabetes mellitus (35.0%). Delayed healing was defined as presence of dry socket, necrotic bone, excessive granulation tissues or infection. For patients with Type 2 Diabetes Mellitus (T2DM) on hypoglycemic tablets with pre-operative controlled blood glucose level (BGL <10 mmol/L and HbA1c <7.5%) AP is not necessary for simple oral procedures such as simple tooth extraction.[50], level II-2 The studies however, did not include sufficient number of patients and lacked homogeneity.

Although the preceding systematic review did not suggest AP for DM patients, the CPG DG opines AP is generally unnecessary for well-managed diabetic patients undergoing simple procedures. Clinicians should consider other factors, such as age, smoking habits, presence of local infection and presence of co-morbidities that weaken the patient's defensive ability.

Key Message 8
- Antibiotic prophylaxis administration for routine dental extractions should not be prescribed for patients with well controlled diabetes mellitus.
- Clinicians should consider patients blood glucose level, Hemoglobin A1c or glycated hemoglobin (HbA1c) and extent of surgery prior to AP prescription.

Recommendation 11
- Among uncontrolled diabetes mellitus patients (BGL >10 mmol/L and HbA1c >7.5%), antibiotic prophylaxis should be provided prior to any oral surgical procedure.

b. Immunocompromised Patients

Immunocompromised patients are more vulnerable to oral infections and delayed healing, even after routine dental procedures. In conditions like diabetes, HIV/AIDS, and renal failure, the immune system is weakened, increasing susceptibility to orofacial infections. Appropriate

use of prophylactic and post-operative antibiotics can help prevent complications and support recovery.[51]

A narrative review based on five existing guidelines, the indications for AP of patients with various immunocompromised state undergoing dental procedure is presented in the table below (refer **Table 2**):[52], level III

Table 2: Antibiotic prophylaxis recommendations for patients in immunocompromised state

No	Immunocompromised condition	Recommendations
1.	Patients receiving immunosuppressive therapy	• AP prior to dental procedure indicated when absolute neutrophils count 1000-2000/mm^3 • dental procedure should be deferred when absolute neutrophils count <1000/mm^3
2.	Patients with Human Immunodeficiency Virus (HIV)	• AP prior to dental procedure indicated based on CD4 level and when neutrophil <500/mm^3
3.	Patients with neutrophils disorders	• AP indicated in all patients
4.	Patients with complement deficiency	• AP is only added if patients are not stable on their standard AP
5.	Patients with antibody deficiency	• AP is not required prior to dental procedures

AP is not necessary for HIV patients who are under antiretroviral therapy with controlled viral load.[53]

Key Message 9

- For immunocompromised patients who undergo surgical procedure, there are factors to consider prior to AP such as glucose level, HbA1c, neutrophil count and CD4 level.

7.3 Treatment Related Conditions in Oral and Maxillofacial Surgery

a. Patients with Prosthetic Joints

Two systematic reviews examining the relationship between dental procedures and prosthetic joint infections (PJI) in patients with prosthetic joint implants found that all the studies reported no association between dental procedures and the risk of PJI. Additionally, the reviews concluded that antibiotic prophylaxis does not provide meaningful protection against infections in patients with total joint arthroplasty (TJA). As a result, the DG members opine there is no evidence to support the use of antibiotics prior to dental procedures in these patients.[54] level II-2;[55] level II-2

American Dental Association (ADA) suggested that for patients with a history of complications associated with joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, AP should only be considered after consultation with the patient's orthopaedic surgeon.[56]

Key Message 10
- Antibiotics prophylaxis is not indicated for patients with prosthetic joints.
- Consultation with orthopaedic surgeon is suggested for patients with history of complications associated with prosthetic joint replacement.

b. Patients with the Risk of Infective Endorcarditis

Infective Endocarditis (IE) following dental procedure is a known complications for patients with certain heart conditions. Due to the high mortality of the disease, several guidelines recommended the use of antimicrobial agents prior to invasive medical or dental procedure.

A large cohort study was conducted among high-risk cardiac patients [IE-risk based on American Heart Association (AHA) (refer to **Table 3**)] showed:[57], level II-2

- significantly higher IE incident following Invasive Dental Procedures (IDP) (refer to **Appendix 6**) compared to non-IDP (OR=6.58, 95% CI 2.76 to 20.33)
- significant reduction in IE incident among patients receiving AP compared to non-AP (OR=0.20, 95% CI 0.06 to 0.53)

There was no significant effect of AP on the odds of developing IE following any type of dental procedure in individuals at moderate or low/unknown IE-risk.

Findings from this study is consistent with AHA guidelines, which are also the main references for the Malaysian Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Infective Endocarditis.

Table 3: List of Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for which prophylaxis with Dental Procedures is Reasonable

- Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts
- Prosthetic material used for cardiac valve repair, such as annuloplasty rings, chords or clips
- Previous IE
- Unrepaired cyanotic congenital heart defect (CHD) or repaired CHD, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device*
- Cardiac transplant with valve regurgitation due to a structurally abnormal valve

* Except for the conditions listed above, antibiotic prophylaxis before dental procedures is not recommended for any other types of CHD.

Based on AHA 2020, antibiotic prophylaxis for prevention of IE prior to the invasive dental procedures is summarized in **Table 4**.

Table 4: Antibiotic Prophylactic Regimens for Dental Procedures Regimen – Single dose 30 to 60 minutes before procedure

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral regimen	Cephalexin* OR	2 g	50 mg/kg
	Azithromycin or clarithromycin	500 mg	15 mg/kg
	Doxycycline	100 mg	<45 kg: 2.2 mg/kg >45 kg: 100 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV

Clindamycin is no longer recommended for antibiotic prophylaxis for a dental procedure.
IM indicates intramuscular; and IV, intravenous.
Other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosing.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

According to NAG 2024, Clindamycin and Erythromycin are no longer recommended as AP for prevention of IE.[29]

Recommendation 12
- Antibiotic prophylaxis should be given to patients with high risk of developing infective endocarditis undergoing invasive oral procedure.
- Clindamycin and Erythromycin should not be given as antibiotic prophylaxis for prevention of infective endocarditis.

c. Patients Exposed to Radiotherapy/Chemotherapy

The evidence of AP for patients exposed to radiotherapy prior to oral surgery is scarce. AP is commonly used in head and neck oncology surgery, due to the clean-contaminated nature of these procedures.

A retrospective cohort was conducted on 418 patients' records comparing short-term (≤ 7 days) and long-term AP on the development of head and neck SSIs on oncology patients showed NS difference in SSIs between the groups. There was also NS difference in SSIs rates between patients with and without pre-operative radiotherapy.[58], level II-2 However, it was not mentioned clearly whether those exposed to radiotherapy received AP prior to the head and neck surgical procedure.

According to a narrative review based on five guidelines, for patients receiving immunosuppressive therapy and/ or radiation:[52], level III
- AP prior to dental procedure indicated when absolute neutrophils count 1000-2000mm^3
- dental procedure should be deferred when absolute neutrophils count <1000mm^3

Recommendation 13
- Antibiotic prophylaxis should be given for patients exposed to radiotherapy/chemotherapy prior to oral and maxillofacial surgery.
- In patients undergone chemotherapy antibiotic prophylaxis should be given when absolute neutrophils count is between 1000-2000mm^3.

d. Osteoradionecrosis

Osteoradionecrosis (ORN) of the jaw is a severe complication of radiation therapy (RT) for head and neck cancer (HNC). It is characterized by exposed, non-healing bone in the irradiated area for more than three months without local tumor recurrence.

A retrospective study involving 49 irradiated HNC patients found that administering 300 mg of Clindamycin three times daily, starting three days before dental extraction and continuing for ten days, resulted in only 3.7% (2 patients) developing ORN post-extraction.[59], level II-2

A prospective study involving 89 irradiated HNC patients found that none developed ORN post-extraction. These patients received 500 mg of Amoxicillin three times daily along with 10 ml of Chlorhexidine Gluconate 0.2% solution every 12 hours, starting ten days before extraction and continuing for seven days post-extraction.[60], level II-2

Both studies suggest that antibiotic prophylaxis before dental extraction may reduce the incidence of ORN in irradiated patients. However, the absence of control groups and lack of systematic reviews (SRs) or randomized controlled trials (RCTs) limit the strength of these findings.

Recommendation 14

- Antibiotic prophylaxis should be given in post head and neck irradiated patients prior to oral and maxillofacial surgical procedures to prevent osteoradionecrosis.

e. Patient at Risk of Medication-Related Osteonecrosis of the Jaw

Patients on medications such as antiresorptive, antiangiogenic and chemotherapeutic agents are at risk of developing medication-related osteonecrosis of the jaw (MRONJ). Tooth extraction, dental implants and other invasive dental procedures that potentially initiate MRONJ.

The incidence of MRONJ in osteoporosis patients is 0.06%, with an incidence rate of 22.9 per 100,000 person-years. In contrast, among cancer patients, the incidence is significantly higher at 1.47%, with an incidence rate of 1,232 per 100,000 person-years.[61] The risk increases for those who undergo dental extraction: 2.7% for osteoporosis patients (95% CI 1.6 to 4.6%) and 26.4% for cancer metastasis patients (95% CI 20.4 to 34.2%).[62], level II-2 (refer to **Appendix 7** for the potential of antiresorptive and non-antiresorptive drugs to cause MRONJ).

A meta-analysis including various study designs reported that a single cohort study among patients undergoing invasive dental procedures showed a significant reduction of 57 incidences of MRONJ per 100 individuals in the group receiving AP compared to the control group (RD = -0.57%, 95% CI -0.85 to -0.29). The majority of AP used in this review were Amoxicillin and Penicillin-based.[63], level II-2 However, most studies had a high risk of bias due to the inclusion of non-randomized studies.

Two SRs identified protocols of AP used in managing patients with antiresorptive agents, which can reduce the risk of MRONJ in patients undergoing dental extraction. Most AP protocols suggested:

- the most commonly used antibiotic is Amoxicillin or Amoxicillin-clavulanate.[64], level II-2; [65], level II-2
- Clindamycin is the alternative for Penicillin-allergic patients.[64], level II-2
- the total duration of antibiotic administration varied from 3 to 20 days, including:[64], level II-2
  - 3 to 7 days pre-procedure
  - 7 to 17 days post-procedure

The evaluation of quality indicated a moderate to high risk of bias.

Royal Australian College of General Practitioners (RACGP) guideline recommends AP prescription for cases at high risk of MRONJ which is patients on the medication for cancer related treatment, treatment for > 4 years and patients with risk factors (eg poor oral hygiene, smoking, on corticosteroids or angiogenesis inhibitors or medical comorbids such as anemia and diabetes mellitus).[66]

In local setting, AP is prescribed for all patients at risk of developing MRONJ prior to invasive dental procedures.

Key Message 11

- Most AP used in preventing MRONJ is Penicillin-based.
- The duration of the AP should be given pre and post-operatively based on:
  - the medication for cancer related treatment
  - treatment for > 4 years
  - other risks factors (eg poor oral hygiene, smoking, on corticosteroids or angiogenesis inhibitors or medical comorbids such as anemia and diabetes mellitus)
- Patients at risk of MRONJ should be referred to OMFS prior to any invasive dental procedures.

Recommendation 15

- Antibiotic prophylaxis should be given to patients at risk of developing Medication- Related Osteonecrosis of the Jaw (MRONJ) prior to invasive dental procedures.

8.0 ADMINISTRATION OF ANTIBIOTIC PROPHYLAXIS

8.1 Choice

The selection of appropriate AP is guided by their effectiveness against common pathogens present at the site of surgery and the local resistance patterns. For surgical procedure confined to oral cavity, the source of pathogens is the endogenous flora of the patient's oral cavity. The oral flora are dominated by bacteria, consisting of anaerobes *(i.e Clostridium spp, Prevotella, Fusobacterium)* and *Streptococcus spp* including *S. mitis,S. sanguinus, S. salivarius, and S. anginosus.* For surgery extending onto the skin, *Staphylococci species such as Staphyloccus aureus* may also be involved in addition to the oral organisms. (67)

Table 5 shows the general spectrum of different antibiotics against selected organisms. The spectrum of activity for Amoxicillin, Ampicillin and Benzylpenicillin includes coverage against intraoral organisms such as Streptococcus species and anaerobic organisms. Thus, these antibiotics are appropriate choice for surgery confined to intraoral cavity. For surgery extending onto the skin, Cefazolin is preferred due to additional coverage towards *Methicillin-Sensitive Staphylococci species* which are the predominant organisms present on the skin.

Broader spectrum antibiotics such as Amoxicillin-clavulanate and Ampicillin-sulbactam have activities against *Methicillin-Sensitive Staphylococci species, Streptococcus species,* anaerobic organisms and some gram-negative organisms. They are, however best avoided when other more narrow-spectrum antibiotics could be used, to reduce the risk of antimicrobial resistance.

According to American Society of Health-System Pharmacists (ASHP), the selection of appropriate AP agent should be:(44)

- active against the pathogens most likely to contaminate the surgical site
- given in an appropriate dosage and time
- safe
- administered for the shortest effective period to minimize adverse effects, the development of resistance, and costs

In addition to antibacterial agents' activity spectra, local antibiotic resistance pattern is also important when choosing an appropriate AP. The antibiotic resistance profiles of selected oral organisms isolated in Malaysia in 2022 are detailed in **Table 6**. The antibiogram reveals that resistance rates for the *Streptococcus anginosus and Streptococcus intermedius* were below 5% for Penicillin G, Clindamycin and Erythromycin. In contrast, for *Streptococcus mutans*, no resistance to

Penicillin was observed, but nearly 30% of isolates showed resistance to Clindamycin and Erythromycin. A significant limitation of this antibiogramis a limited number of certain organisms that may reduced its statistical validity. (Analysis of WHONET surveillance data from Malaysian Hospitals January until December 2022)

Table 5: Antibiotics Spectrum

ANTIBIOTIC CLASS	GRAM POSITIVE COCCI			ANAEROBES		GRAM NEGATIVE	
	Methicillin Sensitive Staphylococcus aureus (MSSA)	Methicillin Sensitive Staphylococci spp	Streptococcus	Clostridium	Bacteroides	E.coli	Klebsiella spp
PENICILLINS	Cloxacillin		Penicillin				
			Amoxicillin				
			Ampicillin				
	Amoxicillin-clavulanate						
	Ampicillin-sulbactam						
LINCOSAMIDE	Clindamycin						
IMIDAZOLE				Metronidazole			
CEPHALOSPHORIN	Cefazolin					Cefazolin	
	Cefuroxime					Cefuroxime	
MACROLIDES	Azithromycin						
TETRACYCLINE	Doxycyline						

Table 6: Percentage of Resistance of Selected Organisms Isolated in Malaysia in 2022

Antibiotics / Organisms	Penicillin G	Clindamycin	Erythromycin	Amoxicillin-clavulanate	Metronidazole
	% (n = total number of isolate tested)				
Streptococcus anginosus	1.1 (94)	3.1 (318)	4.6 (459)	NA	NA
Streptococcus constellatus	3.2 (53)	7.8 (206)	7.5 (321)	NA	NA
Streptoccocus intermedius	0 (13)	0 (44)	0 (82)	NA	NA
Streptococcus mutans	0 (2)	28.6 (14)	28.6 (14)	NA	NA
Prevotella sp	25 (4)	0 (1)	NA	0 (3)	0 (2)
Fusobacterium sp	0 (1)	100 (1)	NA	0 (1)	0 (1)
Peptostreptococcus	66.7 (3)	100 (1)	NA	25 (4)	0 (1)

8.2 Allergic to Penicillins

Allergies to Penicillins require alternative options to ensure patient safety and treatment efficacy.

A meta-analysis of four good quality RCTs showed NS difference between oral Clindamycin and placebo/no treatment in preventing infectious complication following third molar surgery.[68], level I

A good quality RCT assessing the effectiveness of AP in patients who underwent single oral implant comparing oral Clindamycin (600 mg) versus placebo showed NS difference in terms of post-operative infection between the groups.[69] level I

A retrospective cohort study comparing post-operative infection among 1,814 patients received 2,961 bone augmentation procedures treated with oral Clindamycin versus oral Amoxicillin showed significant association between post-surgical infection and Clindamycin use in:[70], level II-2

- All bone augmentation procedures (OR=5.5, 95% CI 3.1 to 9.6)
- Socket grafting procedures (OR=4.5, 95% CI 2.3 to 8.7)
- Ridge augmentation procedures (OR=6.9, 95% CI 3.2 to 14.8)

A retrospective cohort study comparing post-operative infection among 111 patients underwent a pre implant surgery and given oral

Clindamycin versus oral Amoxicillin shows significant association between post-surgical infection and Clindamycin use in:[71], level II-2

- Sinus lift procedure (OR=7.8, 95 % CI 1.1 to 54.8)
- onlay graft procedures (OR=4.8, 95 % CI 1.9 to 12.3)

Another meta-analysis of 12 trials evaluating the effectiveness of AP on the incidence of bacteremia post dental procedure compared with placebo/no antibiotic showed decreased rates of bacteremia (RR=0.50, 95% CI 0.38 to 0.67) with:[72], level I

- Amoxicillin (RR=0.41, 95% CI 0.27 to 0.62)
- Clindamycin (RR= 0.89, 95% CI 0.81 to 0.97)
- Azithromycin (RR= 0.51, 95% CI 0.39 to 0.67)
- IV Amoxicillin-clavulanate (RR=0.01; 95% CI 0.0 to 0.16)
- Moxifloxacin (RR=0.59, 95% CI 0.47 to 0.74)
- Cephalosporin NS

However, there was significant heterogeneity among studies and risk of bias were unclear.

An RCT comparing the anti-inflammatory effects among 13 patients prior to surgical placement of one-stage dental implants given Azithromycin versus Amoxycillin showed:[73], level I

- at day 6, Azithromycin concentrations in gingival crevicular fluid (GCF) and peri-implant crevicular fluid (PICF) were 3.39±0.73μg/ml and 2.77±0.90μg/ml, respectively, while Amoxicillin was below the limit of detection
- at days 6, 13 and 20, patents in the Azithromycin group exhibited a significantly greater decrease in GCF volume ($p=0.03$, ANOVA) than Amoxicillin group
- The Azithromycin group exhibited significantly lower levels of IL-6 and IL-8 in GCF than the Amoxicillin group and exhibited significantly lower levels of G-CSF, IL-8, MIP-1β and IP-10 in PICF ($P<0.05$).

This study showed that Azithromycin was available at the surgical site for a longer period of time than Amoxicillin, and patients taking Azithromycin exhibited lower levels of specific pro-inflammatory cytokines and chemokines in GCF and PICF. Thus, pre-operative Azithromycin may enhance resolution of post-operative inflammation to a greater extent than Amoxicillin.

The European Society of Cardiology (ESC) Guideline 2023 does not recommend the use of Clindamycin for AP for a dental procedure due to adverse effects (mainly related to *Clostridioides difficile* infections). Cefazolin, Azithromycin or Doxycycline are recommended for patients who are allergic to Penicillin/ Ampicillin.[74]

Key Message 12
The choice of AP for patients who are undergoing oral and maxillofacial surgical procedures will be determined by
- surgical site involved/ microorganism presence
- local antibiotic resistance pattern
- patient's medical condition

Recommendation 16
For patients who are undergoing oral and maxillofacial surgical procedure and allergic to Penicillin:
- Azithromycin, Doxycyline or Cefazolin may be prescribed
- Cephalosphorin should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with Penicillin/Ampicillin
- Clindamycin or Erythromycin may be considered with caution if other antibiotics are not available

8.3 Dosing

Single dose of AP is usually sufficient and the duration is not more than 24 hours.[1, 29, 44]

Table 7: Antibiotic Prophylaxis Dosage Commonly Used in Oral Maxillofacial Surgery(1, 29, 44)

NO ALLERGY TO PENICILLIN-BASED ANTIBIOTIC				
Antibiotics	**Dosage**		**Possible AE : Common**	**Possible AE : Caution**
	Adult	**Pediatric**		
Amoxicillin	1-2g PO (2g is the recommended dosage in high risk patient developing IE)	50 mg/kg PO	*Gastrointestinal effects*: Diarrhoea, nausea, vomiting	Hypersensitivity reactions including anaphylaxis, anaphylactoid and severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms);

				C. difficile-associated diarrhoea or pseudomembranous colitis.
Amoxicillin-clavulanate	1.2g IV (IV bolus: Administer over 3 – 4 minutes) OR 1.25 g PO	30 mg/kg IV (maximum 1.2g)	*Gastrointestinal disorders:* Diarrhoea, Nausea, vomiting, indigestion *Immune system disorders:* urticaria *Nervous system disorders:* Headache, dizziness, reversible hyperactivity	Convulsions (at high doses or in patients with renal impairment) *Skin and subcutaneous tissue disorders:* Rash, pruritus, Stevens-Johnson syndrome. Rarely, erythema multiforme Severe hypersensitivity reactions, including anaphylactoid and severe cutaneous reactions (e.g. acute generalised exanthematous pustulosis); Clostridium difficile-associated diarrhoea or pseudomembranous colitis.
Ampicillin	2g IV (IV bolus (<1g): Administer over 3 – 4 minutes IV infusion (≥1 g): Infuse over 10 – 15 minutes)	50 mg/kg IV	*Gastrointestinal disorders:* Diarrhoea, nausea, vomiting, indigestion, epigastric discomfort, sore mouth *General disorders and administration site conditions:* Fever; injection site pain or phlebitis.	Seizures (rapid infusion);Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme. *Renal and urinary disorders:* Nephropathy, interstitial nephritis. Hypersensitivity reactions (e.g. anaphylaxis, angioedema,

			Skin and subcutaneous tissue disorders: Pruritus, purpura.	erythematous or urticarial rash), Clostridium difficile-associated diarrhoea, pseudomembranous colitis.
Ampicillin-sulbactam	3g IV (IV bolus: Administer over 3 minutes IV infusion: Infuse over 15 – 30 minutes)	50 mg/kg IV	GI discomfort	Severe hypersensitivity reactions
Benzylpenicillin	2MU IV (IV infusion: Infuse over 30 minutes)	Not routinely used	Nausea, vomiting, stomatitis, rash, fever	Anaphylaxis, pseudomembranous colitis. Convulsions
ALLERGY TO PENICILLIN-BASED ANTIBIOTIC				
Antibiotics	**Dosage**		**Possible AE : Common**	**Possible AE : Caution**
	Adult	**Pediatric**		
Azithromycin	500mg PO/IV (IV infusion: Infuse over 1 hour)	15 mg/kg PO Not routinely used, dosage based on ESC 2023	*Gastrointestinal effects*: Diarrhoea, vomiting, abdominal pain, nausea, flatulence, dyspepsia, dysgeusia. *General disorders and admin site conditions:* Injection site pain, fatigue Musculoskeletal and connective tissue disorders: Arthralgia *Nervous system disorders:* Headache,	Myasthenia gravis Rarely, serious hypersensitivity reactions (e.g. anaphylaxis, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis drug reaction with eosinophilia and systemic symptoms), fulminant hepatitis leading to liver failure, prolonged cardiac repolarisation and QT interval, cardiac arrhythmia, torsades de pointes,

			dizziness, paraesthesia *Skin and subcutaneous tissue disorders:* Pruritus, rash	Clostridium difficile associated diarrhea (CDAD)
Cefazolin* **	1-2g IV 3 g if body weight ≥120 kg (IV bolus: Administer over 3 – 5 minutes IV infusion (for doses >1 g): Infuse over 30 – 60 minutes)	30 mg/kg IV (maximum 2g/dose)	Diarrhoea, oral candidiasis, vomiting, nausea, stomach cramps	Anaphylaxis, pseudomembranous colitis,Stevens-Johnson syndrome;
Cephalexin* **	2 g orally	50 mg/kg orally up to maximum of 2 g Dosage based on ESC 2023	GI disturbances	Hypersensitivity reaction, anaphylaxis
Cefuroxime* **	1.5g IV (IV bolus: Administer over 3 – 5 minutes IV infusion: Infuse over 30 minutes)	50 mg/kg IV (maximum 1.5g/dose)	Clostridium difficile-associated diarrhoea and pseudomembranous colitis; *Gastrointestinal disorders*: Diarrhoea, nausea, vomiting, abdominal pain *General disorders and administration site conditions:*	Severe hypersensitivity (anaphylactic) reactions

			Inj site reaction (e.g. pain, thrombophlebitis) *Nervous system disorders:* Headache, dizziness *Skin and subcutaneous tissue disorders:* Skin rash, urticaria, pruritus	
Clindamycin	600mg-900mg PO/IV (IV infusion: Infuse over 10 – 60 minutes (not exceeding 30 mg/min)	10 mg/kg PO/IV (maximum dose : 900mg IV)	Superinfection (particularly yeasts), acute kidney injury (including acute renal failure) *Gastrointestinal disorders:* Nausea, vomiting, diarrhoea, abdominal pain, dysgeusia *General disorders and administration site conditions:* Pain and/or abscess at the injection site *Nervous system disorders:* Headache, dizziness *Skin and subcutaneous tissue disorders:* Rash, urticaria, pruritus *Vascular disorders:* Thrombophleb-itis (IV)	Clostridioides difficile-associated diarrhoea (CDAD), pseudomembranous colitis; severe cutaneous adverse reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Doxycycline	100mg PO	<45 kg, 2.2 mg/kg PO >45 kg, 100 mg PO Not routinely used, dosage based on ESC 2023	Permanent discolouration (yellow-grey-brown) of the teeth (when given during tooth development [last half of pregnancy; infancy and childhood to the age of 8 years]), enamel hypoplasia, photosensitivity *Gastrointestinal disorders*: Nausea, vomiting, diarrhoea, upper abdominal pain, dry mouth, dysphagia, glossitis *Immune system disorders:* Hypersensitivity reactions (e.g. urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis). *Nervous system disorders*: Headache, dizziness *Skin and subcutaneous tissue disorders*: Rash (e.g. maculopapular, erythematous or morbilliform rash), nail discolouration.	Exacerbation of SLE; Serious skin reactions (e.g. exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms [DRESS]), *pseudomembranous colitis,* Clostridium difficile-associated diarrhoea (CDAD).

			Vascular disorders: Hypertension	
***Erythromycin base**	500mg PO	Not routinely used	Hepatic dysfunction including increased liver enzymes and/or cholestatic hepatitis, with or without jaundice; *Cardiac disorders:* Chest pain. *Gastrointestinal disorders:* Nausea, vomiting, diarrhoea, pancreatitis, upper abdominal pain. *General disorders and administration site conditions:* Fever, malaise. *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Vascular disorders:* Hypotension	Pseudomembranous colitis, Clostridium difficile-associated diarrhoea, QT interval prolongation, torsades de pointes, severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), angioneurotic oedema, anaphylaxis.
***Erythromycin ethylsuccinate**	800mg PO			

OTHERS				
Antibiotics	**Dosage**		**Possible AE : Common**	**Possible AE : Caution**
	Adult	**Pediatric**		
Metronidazole	500mg IV (Infuse over 30 minutes) Or 400mg PO	15 mg/kg IV (maximum dose : 1.5g/day)	Bacterial or fungal superinfection (e.g. Clostridium difficile-associated diarrhoea and pseudomembranous colitis) *Gastrointestinal disorders:* Nausea, vomiting, diarrhoea, taste disorders, furred tongue, glossitis, stomatitis, eructation with bitter taste, metallic taste, epigastric pain, dysphagia. *General disorders and administration site conditions:* Fever; vein irritations including thrombophlebitis (IV). *Nervous system disorders:* Headache. *Skin and subcutaneous tissue disorders:* urticaria. Pruritus, dry skin, burning or stinging of the skin, skin irritation, worsening of rosacea (topical).	Severe hepatotoxicity/ acute hepatic failure (patients with Cockayne syndrome). Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis *Immune system disorders:* Angioedema *Skin and subcutaneous tissue disorders:* Erythema multiforme

**Dosage based on different formulation from MIMS Gateways, accessed online https://online1.mimsgateway.com.my/,* Dilution Guide For Fluid Restricted Critically Ill Adults 1st Edition 2024

*** Dosage adjustments needed in renal impairment if treatment extends beyond 24 hours.*
**** Cephalosphorin should not be used in an individual with a history of anaphylaxis, angioedema, or urticarial with Penicillin/Ampicillin*

In patients with kidney disease, if the antibiotic is continued for more than 24 hours, the dosage should be adjusted according to the patients' creatinine clearance.

All antibiotics listed above may cause gastrointestinal effects such as diarrhoea, nausea and vomiting.[75] A scientific statement consisting of experts in prevention and treatment of infective endocarditis concluded that overall risks of a serious adverse reaction such as hives, angioedema, and anaphylaxis are low for an antibiotic when used for prophylaxis for a dental procedure, except for Clindamycin which may cause more frequent and severe reactions than other antibiotics used for AP.[76], level III Notably, clindamycin prophylaxis has been linked to an increased incidence of severe complications, particularly Clostridioides difficile infection.[77]

8.3.1 Redosing

If the length of the procedure is longer than the antibiotic's two half-lives and/or there are other conditions that could shorten the drug's half-life (such as burns or excessive blood loss greater than 1.5L), redosing the AP intraoperatively is necessary.[1] The redosing dosage will follow the initial dose given pre-operatively (refer **Table 8**).

Table 8: Antibiotic Prophylaxis Redosing Interval[29, 44, 74]

Antibiotics	**Recommended Redosing Interval in Adults with Normal Renal Function (From Initiation of Preoperative Dose), (hr)**
Ampicillin/Amoxicillin	2
Amoxicillin-clavulanate	3
Ampicillin-Sulbactam	2
Benzylpenicillin	2
Cefazolin	4
Cefuroxime	4
Clindamycin	6
Metronidazole	NA*
Azithromycin	NA*

*Recommended redosing intervals marked as "not applicable" (NA) are based on typical case length; for unusually long procedures, redosing may be needed

According to the National Antimicrobial Guideline, when a patient has a known or suspected pre-existing infection, an appropriate antibiotic treatment regimen should be administered instead of a prophylactic regimen. The chosen antibiotic must be effective against the organisms most likely to cause postoperative infections. Dosage adjustments are necessary to ensure adequate plasma and tissue concentrations at the time of surgical incision and throughout the surgical procedure. Consultation with Infectious Disease specialists/pharmacist is recommended.[29]

Recommendation 17
- Antibiotic prophylaxis should be given as a single dose and not more than 24 hours, unless specified.
- Redosing should be given if the duration of surgery exceeds the two half-lives of the antibiotics and should follow the initial dose given pre-operatively.

8.4 Timing

Timing for AP is important to ensure the serum and tissue concentrations of the AP exceed the minimum inhibitory concentration for organisms likely to be present at the surgical site throughout the operation. For any AP medication, the half-life and protein binding are the most important pharmacokinetic factors in order to ensure appropriate blood and tissue concentration at the time of incision and during the entire surgical operation.[78]

A meta-analysis of nine cohort studies involving variety of surgical procedures (gastrointestinal, orthopedic, vascular, traumatology, gynecology and cardiac surgery) with various types of antibiotics on the effect of timing of pre-operative AP on SSIs showed:[79], level II-2
- higher SSIs when AP was administered after incision vs before incision (OR=1.89, 96% CI 1.05 to 3.40)
- higher SSIs when AP given more than 120 minutes prior to incision vs administration within 120 minutes (OR=5.26, 95% CI: 3.29 to 8.39)
- NS between AP given 120–60 minutes vs 60–0 minutes
- NS between AP given 60–30 minutes vs 30–0 minutes

Overall, the quality of included primary papers in this MA was very low to moderate.

An RCT including various surgical procedures administered with 1.5 gram of IV Cefuroxime demonstrated NS difference in preventing SSIs between early AP (30-75 min before incision) vs late AP (0-30 min before incision).[80], level I

WHO recommends the administration of AP <60 minutes closer to the incision time for antibiotics with a short half-life, such as Cefazolin and Penicillins.[78] Other international guidelines (ASHP and APSIC) recommend the administration of AP prior to surgical incision within 60 minutes.[44, 81]

Current local guidelines recommend the optimal time for administration of AP prior to surgical incision is within 60 minutes[27] and within 30 - 60 minutes.[1] For Fluoroquinolones and Vancomycin, on the other hand, within 120 minutes, because of the prolonged infusion times required.[1]

Recommendation 18

- Antibiotic prophylaxis should be given 30-60 minutes prior to surgical incision or within 120 minutes for Fluoroquinolones and Vancomycin.

9.0 IMPLEMENTING THE GUIDELINES

The use of antibiotic prophylaxis should be guided by an evidence-based CPG in order to manage it appropriately. Clinicians are required to keep abreast with knowledge through continuing professional education as well as understanding of patients' expectations.

Therefore, it is important for these guidelines to be disseminated to all healthcare professionals in primary and secondary healthcare facilities. This can be facilitated through the development of appropriate training modules and quick references. Several factors may affect the implementation of the recommendations of the CPG.

9.1 Facilitating and Limiting Factors

Existing facilitators for the application of the recommendations in the CPG include:

a. wide dissemination of the CPG to healthcare professionals and teaching institutions via printed and electronic copies
b. continuing professional education on the rationale use of antibiotic prophylaxis in oral and maxillofacial surgery for healthcare professionals
c. adequate facility and supply of the antibiotics

Existing barriers for the application of the recommendations of the CPG include:

a. lack of understanding or limited knowledge on the implementation of antibiotic prophylaxis
b. variation in skills and treatment practices
c. constraints in facilities and availability of antibiotics

9.2 Potential Resource Implication

To implement the CPG, there must be a strong commitment to:

a. ensure widespread distribution of the CPG in hard and soft copy to healthcare professionals in primary and secondary healthcare facilities
b. strengthen training of healthcare professionals to ensure knowledge and information are up to date
c. empower the funding of consumables purchasing of antibiotics

9.3 Proposed Clinical Audit Indicators

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management of oral and maxillofacial trauma:

Percentage of patients undergoing open reduction and internal fixation (ORIF) of oral & maxillofacial fractures given post op antibiotics ≤24hrs (Target ≥ 80%)	No. of patients given antibiotic prophylaxis post-ORIF ≤ 24 hours in 6 months ——————— Total number of patients undergoing ORIF in 6 months	X	100%

b. Trauma Indicator: Percentage of patients undergoing open reduction and internal fixation (ORIF) of oral & maxillofacial fractures given post op antibiotics ≤ 24%.

No. of patients given antibiotic prescriptions post-ORIF ≤ 24 hours in 6 months x 100%

No. of patients undergoing ORIF in 6 month

Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective antibiotic prophylaxis indicated for the prevention of surgical site infections in clean oral and maxillofacial surgery?

Database: Ovid MEDLINE(R) ALL <1946 to July 22, 2024>
Search Strategy:

1. SURGERY, ORAL/ (8296)
2. Exodonti*.tw. (529)
3. ((maxillofacial or oral) adj1 surg*).tw. (18210)
4. TEMPOROMANDIBULAR JOINT/ (12769)
5. Tmj.tw. (10687)
6. (temporomandibular adj1 joint*).tw. (18832)
7. SALIVARY GLANDS/ (17794)
8. (salivary adj1 gland*).tw. (41511)
9. ORBITAL FRACTURES/ (3838)
10. ((blow out or blow-out) adj2 fracture*).tw. (553)
11. (orbital adj1 fracture*).tw. (1615)
12. SURGERY, PLASTIC/ (28701)
13. cosmetic surg*.tw. (2989)
14. esthetic surg*.tw. (301)
15. plastic surg*.tw. (26345)
16. HEAD.mp. and NECK NEOPLASMS/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (68020)
17. ((head or neck) adj1 cancer*).tw. (35402)
18. ((head or neck) adj1 neoplasm*).tw. (633)
19. (cancer of adj1 (head or neck)).tw. (31170)
20. (neoplasm adj1 (upper aerodigestive tract or uadt)).tw. (2)
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (223254)
22. ANTIBIOTIC PROPHYLAXIS/ (15907)
23. (antibiotic adj1 (premedication* or prophylaxis)).tw. (11595)
24. SURGICAL WOUND INFECTION/ (41588)
25. (postoperative wound adj2 infection*).tw. (1952)
26. (surgical adj2 (site infection* or wound infection*)).tw. (18805)
27. 22 or 23 or 24 or 25 or 26 (67859)
28. 21 and 27 (1646)
29. limit 28 to (english language and humans and yr=”2015 - 2024”) (480)

Appendix 2

CLINICAL QUESTIONS

1. What are the safe and effective antibiotic prophylaxis indicated for the prevention of surgical site infections in clean oral and maxillofacial surgery?

2. What are the safe and effective antibiotic prophylaxis indicated for the prevention of surgical site infections in clean-contaminated oral and maxillofacial surgery?
   - Dental extraction & impacted third molar
   - Dental implant
   - Periodontal surgery
   - Surgery associated with the use of bone grafts
   - Orthognathic and cleft surgery
   - Head and neck oncology surgery

3. What are the safe and effective antibiotic prophylaxis indicated for the prevention of surgical site infections in contaminated oral and maxillofacial surgery?

4. What are the safe and effective antibiotic prophylaxis indicated for the prevention of surgical site infections in oral and maxillofacial trauma surgery?

5. What are the safe and effective antibiotic prophylaxis indicated for the oral and maxillofacial surgery in patients with:
   - pregnant and breastfeeding
   - undergoing bone antiresorptive medication
   - undergoing radiation therapy/chemotherapy
   - prosthetic implanted devices
   - immune deficiency condition

6. What is the appropriate timing and dosing protocol for antibiotic prophylaxis?

7. What are the safe and effective antibiotic prophylaxis indicated for oral and maxillofacial surgery in patients with allergies?

Appendix 3

Surgical Wound Classification

Surgical Wound Classification Grades (I-IV) as Defined by the CDC

CDC Surgical Wound Classification Definitions
Class I/Clean: An uninfected operative wound in which no inflammation is encountered, and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow no penetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in a sterile technique is encountered.
Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in a sterile technique (eg, open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute or no purulent inflammation is encountered are included in this category.
Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

CDC = Centers for Disease Control and Prevention.

Source: Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999 Apr;27(2):97-132; quiz 133-4; discussion 96. PMID:

Appendix 4

Lackmann's Classification of Facial Bite Injuries

Type	Clinical Findings
I	Superficial injury without muscle involvement
IIA	Deep injury with muscle involvement
IIB	Full thickness injury of the cheek or lip with oral mucosal involvement (through and through wound)
IIIA	Deep injury with tissue defect (complete avulsion)
IIIB	Deep avulsive injury exposing nasal and auricular cartilages
IVA	Deep injury with severed facial nerve and/or parotid duct
IVB	Deep injury with concomitant bony fracture

Appendix 5

Pregnancy category based on Monthly Index of Medical Specialities (MIMS)

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of foetal harm remains remote.
B	Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that is not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or others) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.
D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
E	Studies in animals or human beings have demonstrated foetal abnormalities or there is evidence of foetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Appendix 6

Classification of dental procedure based on The American Dental Association (ADA)

Classification	Dental procedure involved
Invasive Dental Procedure	Procedures involving manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa, for example, dental extractions, oral surgical procedures, scaling, and endodontic procedures
Intermediate Dental Procedures	Procedures that may require AP when gingival manipulation is required to complete the procedure, for example, most restorative dental procedures, but not otherwise
Non-invasive Dental Procedure	Procedures where AP is not recommended, for example, routine dental examination or radiographs, placement of removable prosthodontic or orthodontic appliances

Common Dental Terminology (CDT) codes (American Dental Association (ADA), 2019) and ICD-9 procedural codes (Centers for Disease Control and Prevention (S), 2019)

Appendix 7

List of Potential Drug that can cause MRONJ

Generic Name	Primary Indication	Common Dose	Route
Antiresorptive Drugs			
Biphosphonate (First Generation, Non Nitrogen Containing)			
Clodronate	Treatment of hypercalcaemia due to maglinancy	300mg per day 400mg per day	Intravenous Oral
Etidronate	Malignant Tumour	300 - 750mg per day	Oral
Tiludronate	Paget's disease	400mg per day	Oral
Biphosphonate (Second Generation, Nitrogen Containing, with an amino terminal group)			
Alendronate	Osteoporosis	70mg per week	Oral
Pamidronate	Treatment of hypercalcaemia due to maglinancy	90mg every 3 weeks	Intravenous
Biphosphonate (Third Generation, Nitrogen Containing, with a cyclic side-chain or a tertiary amino group)			
Ibandronate	Osteoporosis	150mg per month	Oral
Risedronate	Osteoporosis	5mg per day 35mg per week	Oral Oral
Zoledronate	Osteoporosis	5mg per year	Intravenous
	Treatment of hypercalcaemia due to maglinancy	4mg every 3 week	Intravenous
Non-Antiresorptive Drugs			
Humanized Monoclonal Antibody			
Denosumab	Osteoporosis	60mg every 6 months	Subcutaneous
	Bone Metastases	120mg every 4 months	Subcutaneous
Tyrosine kinase inhibitor (TKI)			
Erlotinib	Second line for local advanced or metastatic Non Small Cell Lung Cancer	150mg per day	Oral
Imatinib	Chronic Myeloid Leukemia	40mg per day	Oral
Sunitinib	Advanced Renal Cell Carcinoma	50mg per day	
B-Raf inhibitor			
Dabrafenib	Melanoma	150mg bd	Oral
Mammalian target of Rapamycin inhibitor			
Sirolimus	Immunosuppression agent	According to indicaton	Oral
Everolimus	Malignant Tumour	According to indicaton	Oral
Vascular Endothelial Growth Factor (VEGF) inhibitor			
Bevacizumab	Malignant Tumour	According to indicaton	Intravenous
Monoclonal antibodies used in immunotherapy			
Rituximab	Hematology Cancer & Severe RA	According to indicaton	Intravenous

LIST OF ABBREVIATIONS

ABG	Alveolar bone grafting
ADA	American Dental Association
AE	adverse effect
AGREE	Appraisal of Guidelines for Research and Evaluation
AHA	American Heart Association
AMR	antimicrobial resistance
AP	antibiotic prophylaxis
ASHP	American Society of Health-System Pharmacists
BGL	blood glucose level
CAL	clinical attachment level
CDAD	Clostridium difficile associated diarrhea
CDC	Centers for Disease Control and Prevention
CDT	Common Dental Terminology
CHD	Congenital heart disease
CI	Confidence Interval
CPG	Clinical Practice Guidelines
CQs	clinical questions
DBBM	Demineralized Bovine Bone Mineral
DG	Development Group
DM	Diabetes Mellitus
EBM	Evidence-Based Medicine
ESC	European Society of Cardiology
GCF	gingival crevicular fluid
GI	Gastrointestinal
GR	gingiva recession
GRADE	Grading Recommendations, Assessment, Development and Evaluation
GTR	Guided Tissue Regeneration
HbA1c	Hemoglobin A1c
HIV	Human Immunodeficiency Virus
HNC	head and neck cancer
IDP	Invasive Dental Procedures
IE	Infective Endocarditis
IR	Internal Review
MaHTAS	Malaysia Health Technology Assessment Section
MIMS	Monthly Index of Medical Specialities
MOH	Ministry of Health
MRONJ	Medication-Related Osteonecrosis of the Jaw
MS	Methicillin-Sensitive
NAG	National Antimicrobial Guideline
NNT	number needed to treat
NS	no significant
ORIF	open reduction and internal fixation
ORN	Osteoradionecrosis
PD	pocket depth
PICF	peri-implant crevicular fluid
PJI	prosthetic joint infections
RACGP	Royal Australian College of General Practitioners
RCTs	Randomised Controlled Trials
RD	Risk Difference
RoB	Risk of Bias

RR	relative risk
RT	radiation therapy
SMD	Standard Mean Difference
SR	Systematic Review
SSIS	Surgical site infections
SUCRA	Surface Under the Cumulative Ranking Curve
T2DM	Type 2 Diabetes Mellitus
TEN	Toxic Epidermal Necrolysis
WHO	World Health Organization

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