TRAINING OF CORE TRAINERS CPG

Antibiotic Prophylaxis in Oral And Maxillofacial Surgery for Prevention of Surgical Site Infection

(3rd Edition)

Lecture 3: SELECTION OF ANTIBIOTIC PROPHYLAXIS

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SELECTION OF ANTIBIOTIC PROPHYLAXIS

ASHP Therapeutic Guidelines, 2013

Active against the pathogens present at the surgical site

Appropriate dosage and time

Administered for the shortest effective period to minimize adverse effects, the development of resistance, and costs

Safe

ORGANISMS LIKELY TO PRESENT AT SURGICAL SITE

INTRA ORAL

- ***Streptococci viridans***
  Eg. S.mitis, S.sanguinus, S.salivarius, S.anginosus
- ***Anaerobic organisms***
  Eg. Clostridium, Bacteroides, Prevotella

SKIN

- ***Staphylococci spp***
  eg. S.coagulase negative S.aureus

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ANTIBIOTICS SPECTRUM

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

Adapted from MoH 2024

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

INTRA ORAL

Streptococci viridans

Anaerobic organisms

ORGANISMS LIKELY TO PRESENT AT SURGICAL SITE

SKIN

Staphylococci spp

Surgery confined to intra oral cavity: Amoxicillin, Ampicillin Benzylpenicillin

OPTION OF ANTIBIOTICS

Surgery extend onto skin: Cefazolin, Cloxacillin

Patients allergic to Penicillin

Recommendation 16

For patients who are undergoing oral and maxillofacial surgical procedure and allergic to Penicillin:

- Cefazolin, Azithromycin 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

Why not Clindamycin?....

MA of 4 good quality RCTs showed: NS difference between oral Clindamycin and placebo/no treatment in preventing infectious complication following third molar surgery.

(Arteagoitia et al., 2022), level I

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

(Santamaría Arrieta et al., 2023) level I

Why not Clindamycin?....

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:

· 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)

(Boussaïd et al., 2024), level II-2

A retrospective cohort study comparing post-operative infection among 1,814 patients received 2,961 bone augmentation procedures treated with oral Clindamycin vs oral Amoxicillin showed significant association between post-surgical infection and Clindamycin use in all bone augmentation procedures (OR=5.5, 95% CI 3.1 to 9.6)

(Basma and Misch, 2021), level II-2

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

(ESC, 2023)

Percentage of Resistance of Selected Organisms Isolated in Malaysia in 2022

Organisms \ Antibiotics	Penicillin G	Clindamycin	Erythromycin	Amoxicillin-clavulanate	Metronidazole
	% (n = total number of isolate)				
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
Streptococcus 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)

***Clindamycin** should be used with caution due to its high resistant rates with *S.mutans*, *Fusobacterium sp* & *Peptostreptococcus* (>20%)

Analysis of WHONET surveillance data from Malaysian Hospitals January until December 2022

Dosing of Commonly Prescribed Prophylactic Antibiotics

Recommendation 17

- Antibiotic prophylaxis should be given as a single dose and not more than 24 hours, unless specified.

Dosing of Commonly Prescribed Prophylactic Antibiotics (No Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
Amoxicillin	1-2*g 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
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 Severe hypersensitivity reactions

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Dosing of Commonly Prescribed Prophylactic Antibiotics (No Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
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	Seizures (rapid infusion);Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme. Renal and urinary disorders: Nephropathy, interstitial nephritis. Hypersensitivity reactions
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

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Dosing of Commonly Prescribed Prophylactic Antibiotics (No Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
Benzylpenicillin	2MU IV IV infusion: Infuse over 30 minutes	Not routinely used	Nausea, vomiting, stomatitis, rash, fever	Anaphylaxis, pseudomembranous colitis. Convulsions
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,	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

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Dosing of Commonly Prescribed Prophylactic Antibiotics (with Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
Cefazolin	1-2g IV 3 g if body weight ≥120 kg IV bolus: Administer over 3-5 minutes IV infusion (for doses >1 g): I nfuse 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

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Dosing of Commonly Prescribed Prophylactic Antibiotics (with Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
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.	Severe hypersensitivity (anaphylactic) reactions.
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	Exacerbation of SLE; Serious skin reactions, *Clostridium difficile*-associated diarrhoea (CDAD).

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Dosing of Commonly Prescribed Prophylactic Antibiotics (with Penicillin Allergy)

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 disorders: Diarrhoea, vomiting, abdominal pain, nausea, flatulence, dyspepsia, dysgeusia. Musculoskeletal and connective tissue disorders: Arthralgia. Nervous system disorders : Dizziness, headache Skin and subcutaneous tissue disorders : Pruritus	Myasthenia gravis Rarely, serious hypersensitivity reactions Fulminant hepatitis leading to liver failure, prolonged cardiac repolarisation and QT interval, cardiac arrhythmia, torsades de pointes, Clostridium difficile associated diarrhea (CDAD).

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Dosing of Commonly Prescribed Prophylactic Antibiotics (with Penicillin Allergy)

Antibiotics	Dosage		Possible AE : Common	Possible AE : Caution
	Adult	Pediatric		
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)	Gastrointestinal disorders: Nausea, vomiting, diarrhoea, abdominal pain, dysgeusia. Nervous system disorders: Headache, dizziness.	Clostridioides difficile-associated diarrhoea (CDAD) Severe cutaneous adverse reactions
*Erythromycin base	500mg PO	Not routinely used	Hepatic dysfunction including increased liver enzymes and/or cholestatic hepatitis, with or without jaundice; Gastrointestinal disorders: Nausea, vomiting, diarrhoea, pancreatitis, upper abdominal pain	Pseudomembranous colitis, Clostridium difficile-associated diarrhoea, QT interval prolongation, torsades de pointes, severe skin reactions
*Erythromycin ethylsuccinate	800mg PO			

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Redosing of Antibiotic Prophylaxis

Redosing should be given if the duration of surgery exceeds two half-lives of the antibiotics 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.

The redosing dosage will follow the initial dose given pre-operatively.

MoH, 2023, NAG, 2024

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 2 half-lives of the antibiotics and should follow the initial dose given pre-operatively.

Recommended Redosing Interval in Adults with Normal Renal Function (From Initiation of Preoperative Dose), (hr)

ASHP 2013, NAG, 2024

Ampicillin	2
Amoxicillin-clavulanate	3
Ampicillin-sulbactam	2
Benzylpenicillin	2
Cefazolin	4
Cefuroxime	4
Clindamycin	6
Metronidazole	* NA
Azithromycin	* NA
Doxycycline	NA

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

Timing of Administration of Antibiotic Prophylaxis

- 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. (WHO, 2018)

Evidence for Timing of Antibiotic Prophylaxis dosing

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)

(Weber et al., 2017), level I

MA of 9 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:

- 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

(de Jonge et al., 2017), level II-2

Evidence for Timing of Antibiotic Prophylaxis dosing

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.

(WHO, 2018)

Other international guidelines (ASHP and APSIC) recommends the administration of AP prior to surgical incision within 60 minutes.

(ASHP, 2013, Ling et al., 2019)

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

(MoH, 2023)

Recommendation 18

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

Antibiotic Prophylaxis in Pregnancy and Breast-Feeding Category

Antibiotics	Pregnancy Category*	Breastfeeding Category
Amoxicillin	B	Acceptable
Amoxicillin-clavulanate	B (increased risk of necrotizing enterocolitis in newborns)	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
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.

Alternative :
Cephalosporin + Metronidazole
Ampicillin-sulbactam

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).
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).

THANK YOU

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