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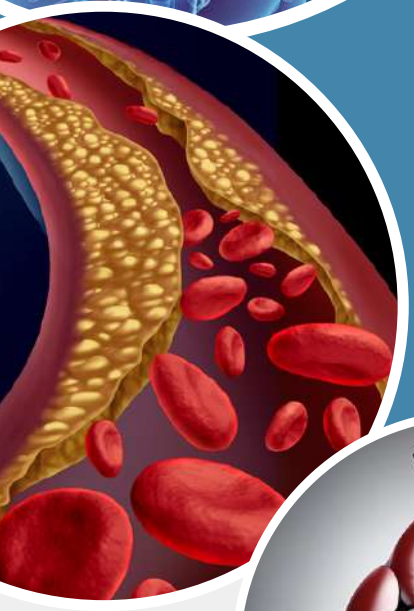

SPECIAL TOPIC

INFECTIVE ENDOCARDITIS

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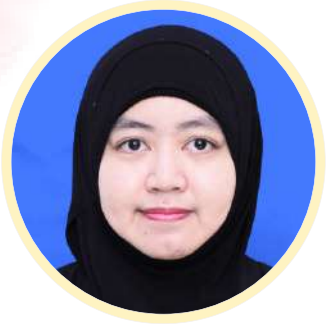

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DISEASE MANAGEMENT

Infective Endocarditis

By Nurul Izzah Amirah binti Abdul Rashid & Wan Anwar bin Wan Nasruddin

1 BACKGROUND [1,2]

Infectious endocarditis (IE) is the inflammation of the endocardium, the inner lining of the heart, as well as the valves that separate each of the four chambers within the heart. It is primarily a disease caused by bacteria and has a wide array of manifestations and sequelae. This disease process has demonstrated a predilection for males, with a male to female ratio of nearly 2 to 1. The annual incidence of IE in the adult population ranges between 3-9 per 100,000 subjects per year.The trend of IE has evolved to affect older patients with co-morbidities and no known structural heart disease.

A local study done in Hospital Kuala Lumpur reported most patients (80.39%) were diagnosed within the first week of admission. Aerococcus viridans (21%) and Enterococcus faecalis (13%) were the most common pathogens and mitral valve was predominantly affected (64%). Embolic complications were common (50%) and in-hospital mortality remains high (42%). Only 21% of those with indications for surgery underwent the procedure.

Another local study in Department of Cardiology in the Sarawak Heart Centre (SHC) shows that the in-hospital mortality due to IE in this department was among the highest in developing countries. Haemodynamic instability and anaemia were found to be strong predictors of IE survival outcome, with an odds ratio of 51.5 and 35.7 respectively.

2 ETIOLOGY [3,4]

- Streptococcus species (spp.)
- Fungal - Candida and Aspergillus
- HACEK organisms (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella)
- Staphylococcus spp.

3 PATHOPHYSIOLOGY [5]

- Infective endocarditis vegetations grow on the valves and produce toxins and enzymes that kill and break down the tissue to cause holes in the valve.
- The resulting complications are: Embolism of material from the vegetation can get in the way of blood flow

3 critical elements:

- Predisposing abnormalities of the cardiac valve, such as congenital heart defects, rheumatic valvular disease, bicuspid or calcific aortic valves, mitral valve prolapse, hypertrophic cardiomyopathy, prior endocarditis, and intracardiac devices
- Bacterial adherence to the valvular surface, which is facilitated by the presence of predisposing abnormalities
- The ability of adherent bacteria to survive on the surface and propagate as vegetation or systemic emboli

4 SYMPTOMS [3]

Aching joints and muscles

Night sweats

Chest pain

Fever

Shortness of breath

5 RISK FACTOR [6]

- **Age > 60 years old**
- **Artificial heart valves**
- **Damaged heart valves**
- **Congenital heart defects**
- **Long-term catheter use**
- **Implanted heart device**

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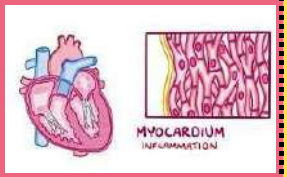
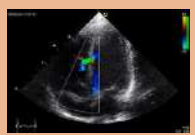


6 DIAGNOSIS [7,8]

Blood culture test



Echocardiogram

Chest Xray

Electrocardiogram

DEFINITIONS OF THE 2023 EUROPEAN SOCIETY OF CARDIOLOGY MODIFIED DIAGNOSTIC CRITERIA OF INFECTIVE ENDOCARDITIS [8]

Major criteria

(i) Blood cultures positive for IE

(a) Typical microorganisms consistent with IE from two separate blood cultures:
Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, *E. faecalis*

(b) Microorganisms consistent with IE from continuously positive blood cultures:
- ≥2 positive blood cultures of blood samples drawn >12 h apart.
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).

(c) Single positive blood culture for *C. burnetii* or phase I IgG antibody titre >1:800.

(ii) Imaging positive for IE:

Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:
- Echocardiography (TTE and TOE).
- Cardiac CT.
- [18F]-FDG-PET/CT(A).
- WBC SPECT/CT.

Minor criteria

(i) Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs)[a]

(ii) Fever defined as temperature >38°C

(iii) Embolic vascular dissemination (including those asymptomatic detected by imaging only):
- Major systemic and pulmonary emboli/infarcts and abscesses.
- Haematogenous osteoarticular septic complications (i.e. spondylodiscitis).
- Mycotic aneurysms.
- Intracranial ischaemic/haemorrhagic lesions.
- Conjunctival haemorrhages.
- Janeway's lesions.

(IV) Immunological phenomena:
- Glomerulonephritis.
- Osler nodes and Roth spots.
- Rheumatoid factor.

(V) Microbiological evidence:
- Positive blood culture but does not meet a major criterion as noted above.
- Serological evidence of active infection with organism consistent with IE.

IE Classification (at admission and during follow-up)

Definite:
- 2 major criteria.
- 1 major criterion and at least 3 minor criteria.
- 5 minor criteria.

Possible:
- 1 major criterion and 1 or 2 minor criteria.
- 3–4 minor criteria.

Rejected:
- Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

7 MANAGEMENT [1]

ENDOCARDITIS DUE TO PENICILLIN-SUSCEPTIBLE VIRIDANS GROUP STREPTOCOCCI (VGS) AND S. GALLOLYTICUS (BOVIS)

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Penicillin-susceptible VGS and *S. gallolyticus (bovis)* (MIC ≤ 0.125 µg/ml) – native and prosthetic valve				
Benzyl penicillin (Crystalline penicillin)	3MU** every 4 to 6 hourly or 12-18 MU/day as a continuous infusion **MU = mega unit; 600 mg = 1 MU	200,000 -300,000 units/ kg/day IV in 4-6 equally divided doses (up to 12-18 MU daily)	4 (native) 6 (prosthetic)	
Ampicillin	2 g IV 4 hourly	300 mg/kg/day IV in 4-6 equally divided doses		
Ceftriaxone	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)		
Vancomycin[b,c]	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/ day)	4 (native) 6 (prosthetic)	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity.

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Relatively resistant to penicillin VGS and *S. gallolyticus (bovis)* (MIC > 0.125 to 2 µg/ml) – native valve endocarditis				
Benzyl penicillin (Crystalline penicillin) **OR**	4 MU** 4 hourly or 24 MU/day as continuous infusion **MU = megaunit; 600 mg = 1 MU	200,000 - 300,000 units/ kg/day IV in 4-6 equally divided doses (up to 12-18 MU daily)	4 (native) 6 (prosthetic)	Cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type
Ceftriaxone **PLUS**	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	2 (native) 6 (prosthetic)	
(Low dose) Gentamicin[d]	3 mg/kg/day IV once daily	1 mg/kg IV 8 hourly		See notes below on how to monitor for gentamicin toxicity
Vancomycin[b,c] **PLUS**	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 3 equally divided doses (maximum 2g/day)	4 (native) 6 (prosthetic)	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity
(Low dose) Gentamicin[d]	3 mg/kg/day IV once daily	1 mg/kg IV 8 hourly	2 (native) 6 (prosthetic)	See notes below on how to monitor for gentamicin toxicity

DISEASE MANAGEMENT

ABIOTROPHIA DEFECTIVE AND GRANULICATELLA SPECIES (BOTH FORMERLY KNOWN AS NUTRITIONALLY VARIANT STREPTOCOCCI; NVS)

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Ampicillin **OR** **Benzyl penicillin (Crystalline penicillin)** **PLUS** **(Low dose) Gentamicin[d]**	2 g IV 4 hourly 4 MU** IV 4 hourly or 24 MU/day as a continuous infusion). **MU = megaunit; 600 mg = 1 MU 1 mg/kg IV 8 hourly	300 mg/kg/day IV in 4-6 equally divided doses 300,000 units/kg/day IV in 4-6 equally divided doses 1 mg/kg IV 8 hourly	6 2	Follow susceptibility test results, if available See notes below on how to monitor for gentamicin toxicity
Ceftriaxone **PLUS** **(Low dose) Gentamicin[d]**	2 g IV once daily 1 mg/kg IV 8 hourly	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day) 1 mg/kg IV 8 hourly	6 2	Ceftriaxone is preferred if clinically not responding with penicillin
Vancomycin[b,c]	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	40 mg/kg/day IV in 2-3 equally divided doses (maximum 2g/day)	6	Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity

STAPHYLOCOCCAL ENDOCARDITIS IN THE PRESENCE OF A PROSTHETIC VALVE OR OTHER PROSTHETIC MATERIAL

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Methicillin-susceptible staphylococci (MSSA)				
Cloxacillin **PLUS** **Rifampicin** **PLUS** **(Low dose) Gentamicin[d]**	2 g IV 4 hourly 300-450 mg PO 12 hourly** 1 mg/kg IV 8 hourly	200-300 mg/kg/day IV in 4-6 equally divided doses 20 mg/kg/day PO in 3 divided doses 1 mg/kg IV 8 hourly	≥ 6 ≥ 6 2	Allergy to penicillin but not immediate- type hypersensitivity use cefazolin or vancomycin Immediate-type hypersensitivity to penicillin use vancomycin **Rifampicin has better penetration. However to avoid the development of resistance, it should be started after 3-5 days of effective initial cloxacillin therapy and/or once the bacteraemia has been cleared.
Methicillin-Resistant Staphylococci (MRSA)				
Vancomycin[b,c] **PLUS** **Rifampicin** **PLUS** **(Low dose) Gentamicin[d]**	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose 300-450 mg PO 12 hourly** 1 mg/kg IV 8 hourly	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range) 20 mg/kg/day PO in 3 divided doses 1 mg/kg IV 8 hourly	≥ 6 ≥ 6 2	For adults, loading dose of 25-30 mg/kg (actual body weight) may be considered for seriously ill patients. **Rifampicin has better penetration. However to avoid the development of resistance, it should be started after 3-5 days of effective initial vancomycin therapy and/or once the bacteraemia has been cleared.

NATIVE VALVE ENDOCARDITIS DUE TO S. AUREUS (RIGHT SIDED)

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Methicillin-susceptible staphylococci (MSSA) – left-sided				
Cloxacillin	12 g/day IV in 4-6 equally divided doses	200-300 mg/kg/day IV in 4-6 equally divided doses	4- 6	
Methicillin-susceptible staphylococci (MSSA) – right-sided; tricuspid valve				
Cloxacillin	12 g/day IV in 4-6 equally divided doses	200-300 mg/kg/day IV in 4-6 equally divided doses	2-4; see comments	2 weeks regime is sufficient provided the patient fulfils all the following criteria: • MSSA • Good response to treatment • Absence of metastatic sites of infection or empyema • Absence of cardiac and extracardiac complications • Absence of associated prosthetic valve or left-sided valve infection • < 20 mm vegetation • Absence of severe immuno-suppression (< 200 CD4 cells/ml) with or without acquired immune deficiency syndrome (AIDS)

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Regimens for β-lactam allergic patients – both left-sided and right-sided				
Cefazolin	2 g IV 8 hourly	100 mg/kg/day IV in 3 equally divided doses	4-6	Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin. Cefazolin has inadequate blood-brain barrier penetrability. In cases of brain abscesses complicating MSSA IE, watch out for treatment failure.
Vancomycin[b,c]	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range)	4-6	Loading dose of 25-30 mg/kg (actual body weight) may be considered for seriously ill patients. Vancomycin is inferior to cloxacillin for treatment of MSSA. Vancomycin therapy is recommended **only** for patients with immediate-type penicillin hypersensitivity
Methicillin-Resistant Staphylococci (MRSA) – left-sided and right-sided				
Vancomycin[b,c]	15-20 mg/kg/dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose	60 mg/kg/day IV in 2-3 equally divided doses (maximum 2 g/day unless unable to achieve therapeutic range)	4-6	Loading dose of 25-30 mg/kg (actual body weight) may be considered for seriously ill patients
Daptomycin	10 mg/kg IV daily	10 mg/kg IV daily	4-6	Daptomycin is superior to vancomycin for MRSA bacteraemia with vancomycin MIC > 1 mg/l

ENDOCARDITIS DUE TO ENTEROCOCCUS-NATIVE AND PROSTHETIC VALVE

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Fully penicillin-susceptible strains (penicillin MIC ≤ 8 mg/l)				
Ampicillin **PLUS** **(Low dose) Gentamicin[d]**	2 g IV 4 hourly 1 mg/kg IV 8 hourly	200-300 mg/ kg/day IV in 4-6 equally divided doses 1 mg/kg IV 8 hourly	4 or 6 depending on duration of symptoms and type of valve; see comments 2 or 6 depending on duration of symptoms and type of valve; see comments	Duration of symptoms < 3 months and native valve: Ampicillin duration - 4 weeks Gentamicin duration - 2 weeks Duration of symptoms > 3 months or prosthetic valves: Ampicillin duration - 6 weeks Gentamicin duration - 6 weeks See notes below on how to monitor for gentamicin toxicity For patients who develop renal impairment or ototoxicity secondary to gentamicin switch to ampicillin/ceftriaxone regime
Ampicillin **PLUS** **Ceftriaxone**	2 g IV 4 hourly 2 g IV 12 hourly	200-300 mg/ kg/day IV in 4-6 equally divided doses 100 mg/ kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	6	Preferred in patients with renal impairment (≤ 50 ml/min) or elderly Ceftriaxone should not be used alone for *enterococcus* infection, as they are intrinsically resistant This combination is not active against *E. faecium*

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric[a]	Duration of therapy (weeks)	Comments
Sensitive to penicillin and vancomycin but high level resistance to gentamicin (MIC > 500 mg/l)				
Ampicillin **PLUS** **Ceftriaxone**	2 g IV 4 hourly 2 g IV 12 hourly	300 mg/kg/ day IV in 4-6 equally divided doses 100 mg/ kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	6	Ceftriaxone should not be used alone for *enterococcus* infection, as they are intrinsically resistant This combination is not active against *E. faecium*
Resistant to penicillin and susceptible to aminoglycosides and vancomycin				
Vancomycin[b,c] **PLUS** **(Low dose) Gentamicin[d]**	15-20 mg/kg/ dose (actual body weight) IV every 8-12 hourly; not to exceed 2 g/dose 1 mg/kg IV 8 hourly	40 mg/kg/ day IV in 3 divided doses (maximum 2 g/day unless unable to achieve therapeutic range) 1 mg/kg IV 8 hourly	6 6	

ANTIMICROBIAL CHOICES FOR PSEUDOMONAS ENDOCARDITIS (6 WEEKS DURATION) IN ADULTS

Column A	Column B
Anti Pseudomonal β-lactams	**Aminoglycosides**
Ceftazidime 2 g IV 8 hourly	Gentamicin 5-7 mg/kg IV daily
Cefepime 2 g IV 8 hourly	Amikacin 15 mg/kg IV daily
Piperacillin-tazobactam 4.5 g IV 6 hourly	OR
	Flouroquinolones**
	Ciprofloxacin 400 mg IV 8 hourly
	Levofloxacin 750 mg IV daily

THERAPY FOR ENDOCARDITIS DUE TO HACEK MICROORGANISMS BOTH NATIVE AND PROSTHETIC VALVE

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric	Duration of therapy (weeks)	Comments
Ceftriaxone **OR**	2 g IV once daily	100 mg/kg/day IV in 1-2 equally divided doses (maximum 4 g/day)	4 (native) 6 (prosthetic)	HACEK-group bacilli produce beta-lactamases; definitive treatment should be adjusted based on the cultures
Ampicillin + Sulbactam **OR** **Ciprofloxacin**	3 g IV 6 hourly 400 mg IV 12 hourly or 500 mg PO 12 hourly	200-300 mg/ kg/day IV in 4-6 equally divided doses (ampicillin component)	4 (native) 6 (prosthetic) 4 (native) 6 (prosthetic)	May be an option if isolate is susceptible If unable to tolerate cephalosporin and ampicillin therapy fluoroquinolones generally not recommended for patients < 18 years old

THERAPY FOR CANDIDA ENDOCARDITIS (NATIVE AND PROSTHETIC VALVE)

Antimicrobial	Dosage and route: Adult	Dosage and route: Paediatric	Duration of therapy (weeks)	Comments
Amphotericin B deoxycholate **OR** **Lipid formulation Amphotericin B** **with or without Flucytosine**	0.6-1.0 mg/ kg IV once daily 3-5 mg/kg IV once daily 25 mg/kg PO 6 hourly	1.0 mg/kg IV once daily 3-5 mg/kg IV once daily 100-150 mg/ kg PO in 4 equally divided doses	At least 6 weeks after surgery At least 6 weeks after surgery	Step down therapy: fluconazole 400-800 mg (6-12 mg/kg) orally daily for susceptible microorganism in stable patients with negative blood cultures (clearance of *Candida* from blood stream) For synergistic effect Causes dose related marrow toxicity Avoid using in patients with renal failure
Micafungin **Caspofungin** **Anidulafungin**	150 mg IV daily 150 mg IV daily 200 mg IV daily		At least 6 weeks after surgery	Step down therapy: fluconazole 400 -800 mg (6-12 mg/kg) orally daily for susceptible microorganism in stable patients with negative blood cultures (clearance of *Candida* from blood stream)

THERAPY FOR OTHER MICROORGANISMS (ADULTS)

Pathogen	Antimicrobial	Dosage and route	Duration of therapy
***Brucella* spp.[109]**	Doxycycline **PLUS** Rifampicin **ADD** Streptomycin (For first 2-3 weeks only) **OR** Gentamicin	100 mg PO 12 hourly 300-600 mg PO daily 1 g IM daily 5 mg/kg IV daily	3-6 months
***C. burnetii* (agent of Q fever)[110]**	Doxycycline **PLUS** Hydroxychloroquine	100 mg PO 12 hourly 600 mg PO daily or 200 mg PO 8 hourly	18-24 months based on clinical and serological response
***Bartonella* spp.[111,112]**	Doxycycline **PLUS** Gentamicin	100 mg PO 12 hourly 3 mg/kg IV daily	2 weeks

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ORAL CONTRACEPTION PILLS AND ITS RISK

By: Syakirah binti Mohamed Saat

Background

Family planning allows people to attain their desired number of children, if any, and to determine the spacing of their pregnancies. It is achieved through use of contraceptive methods. Among the methods include hormonal contraceptive methods, intrauterine devices (IUDs), emergency contraception, using condoms and lactational amenorrhea method. As for hormonal contraceptive method , it is available as oral pills or implants, patches or vaginal rings. They release small amounts of one or more hormones which prevent ovulation. [1]

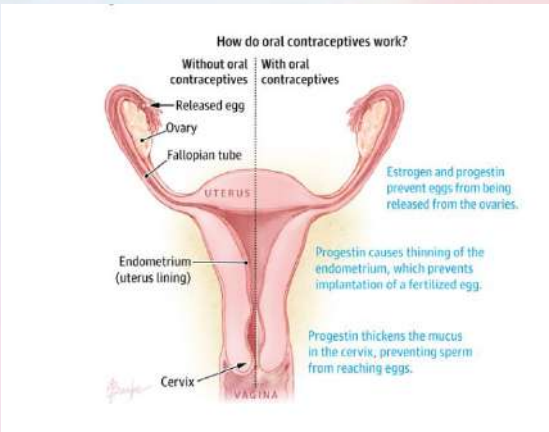

Figure 1: How do OCP works? [2]

Oral Contraception Pill (OCP)[1]

OCP are commonly known as birth control pills. There are two types of OCP available in the market:

- Progestogen-only pills (POP), or “the mini-pill”, that works by thickens the cervical mucous to block sperm and egg from meeting and prevents ovulation. Eg; Levonorgestrel, Norethisterone
- Combined Oral Contraceptives (COC), or “the pills” contains an estrogen combined with a progestogen, works by preventing the release of eggs from the ovaries (ovulation). Eg; Desogestrel & Ethinylestradiol

Adverse effect of oral contraceptive pills[3]

Most side effects of OCP's are mild and disappear with continued use or switching to another pill formulation. The most common adverse effect of combined oral contraceptive pills is breakthrough bleeding, venous thromboembolism & hypertension. Women will also complain of nausea & vomiting, fatigue, increase weight, mood alteration, headaches, abdominal cramping, acne, breast pain, irregular menstruation and contact lens intolerance. Nausea can be avoided by taking the medication at night before sleep. Most of the other consequences will resolve with time or switching OCP to a different preparation

OCP & Disease Interaction

Risk of Venous Thromboembolism (VTE)

The absolute rate of venous thromboembolism in young women is low, however, with the use of OCP, the risk increase by three- to five-fold. The reported incidence of venous thromboembolism in users of oral contraceptives is about 0.06 per 100 pill-years,[4] significantly lower than the rate of 0.2 per 100 years at risk during pregnancy and the postpartum period.[5] The high contraceptive efficacy of oral contraceptives, despite their thrombotic risk, should be weighed against the risks associated with less effective contraception methods, including the potential thrombotic consequences of an unwanted pregnancy.

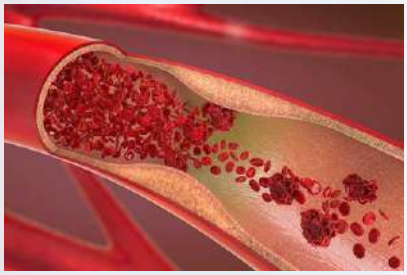

Figure 2: Incidence of VTE.[6]

OCP in Cardiovascular Disease Patients.[7]

Most studies indicate that current use of combined hormonal contraception (CHC) is associated with **increased risk of ischemic stroke and myocardial infarction (MI)** compared to non-use of CHC; risk appears to increase with **increasing dose of estrogen in COC**. The absolute risk of arterial thromboembolism remains extremely small for CHC users; a large Danish cohort study reported 2.1 thrombotic strokes and 1.0 myocardial infarction per 10 000 woman-years of use of hormonal contraception (the majority of the cohort used COC).

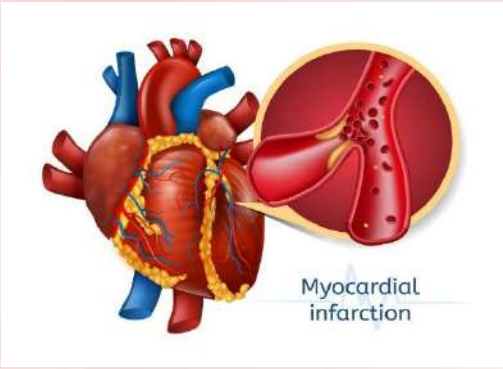

Figure 3: Myocardial infarction (MI), colloquially known as "heart attack," is caused by decreased or complete cessation of blood flow to a portion of the myocardium.

Risk of Cancer [7]

Women should be advised that current use of CHC is associated with a small **increased risk of breast cancer** which reduces with time after stopping CHC. A recent large Danish cohort study reported a relative risk of breast cancer of 1.19 (95% CI 1.13–1.26) for current or recent users of COC compared to never-users of hormonal contraception. Risk appeared to increase with duration of use. Besides that, **use of CHC for more than 5 years is associated with a small increased risk of cervical cancer**; risk reduces over time after stopping CHC and is no longer increased by about 10 years after stopping.

OCP & Drugs interaction[8]

Antiepileptic Drugs.

Antiepileptic drugs like carbamazepine and phenytoin may induce the hepatic metabolism of progestogens leading to reduced progestogen levels, with subsequent risk of menstrual irregularities/breakthrough bleeding and pregnancy.

These combination of drugs must be used with extreme caution or consider alternative and/or additional contraception

Antifungal Drugs

Fluconazole, Itraconazole and Ketoconazole are antifungal (azoles group) drugs that may increase the serum levels of progestogens by inhibiting their CYP3A4-mediated metabolism. Several studies found that azole antifungals increased the systemic exposure of progestogens (e.g. norethisterone, dienogest, drospirenone, levonorgestrel) as part of a combined contraceptive.

Antituberculosis Drugs.

Rifampicin is antituberculosis drugs that may induce the hepatic metabolism of progestogens, which could lead to reduced progestogen levels. Reduction in ovulation suppression effect and cases of contraception failure has been described in women on oral combined hormonal contraceptives or progestogen implants concurrently with rifampicin.

REFERENCES

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3. Mimsgateway. Desogestrel. https://online1.mimsgateway.com.my/#
4. Lidegaard O, Lokkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.
5. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143:697–706
6. https://www.radiometer.com/en/products/immunoassay-testing/venous-thromboembolism
7. The Faculty of Sexual and Reproductive Healthcare (FSRH) Guideline, Combined Hormonal Contraception. 2019
8. Mimsgateway. Drug Interaction- Desogestrel. https://online1.mimsgateway.com.my/

DRUG UPDATES

LENALIDOMIDE 15MG CAPSULE

DESCRIPTION

Lenalidomide is an immunomodulatory drug with potent antineoplastic, anti-angiogenic, and anti-inflammatory properties. It is a thalidomide derivative used to treat multiple myeloma and anaemia in low to intermediate risk myelodysplastic syndrome.

REGISTRATION NUMBER

MAL20046073AZ (Lenangio).

PRICE

RM 1,775.00/pack of 21 capsules.

DEPARTMENT

Medical (Haematology).

PRESCRIBER CATEGORY

A* - (Consultant/ Specialist for specific indications only).

PREGNANCY CATEGORY

Category X (MIMS Gateway).

INDICATION IN FUKKM

In combination with dexamethesone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

DOSE AND ADMINISTRATION

Recommended starting dose: 25 mg once daily on days 1 to 21 of repeated 28 day cycle with dexamethasone 40 mg once daily on days 1 to 4, 9 to 12 and 17 to 20 of each 28 day cycle for the first 4 cycles of therapy, thereafter dexamethasone 40 mg once daily on day 1 to 4 every 28 day cycle.

MECHANISM OF ACTION

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties.

It inhibits proliferation of certain haematopoietic tumour cells, enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-a and IL-6) by monocytes.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Women who are pregnant.
- Women of childbearing potential.

ADVERSE EFFECTS

Common:

- Cardiovascular: Peripheral edema (13% to 26.3%).
- Dermatologic: Pruritus (4% to 41.9%).
- Gastrointestinal: Constipation (5.4% to 40.5%).
- Hematologic: Thrombocytopenia, All Grades (15% to 72.3%).
- Neurologic: Insomnia (1% to 27.6%).
- Other: Fatigue (10.6% to 43.9%).

Serious:

- Cardiovascular: Atrial fibrillation
- Dermatologic: Stevens-Johnson syndrome
- Hepatic: Hepatotoxicity (15%)
- Musculoskeletal: Rhabdomyolysis
- Other: Tumor lysis syndrome

USE IN SPECIFIC POPULATION

Paediatric:

- Should not be used in children and adolescents from birth to less than 18 years because of safety concerns.

Geriatric:

- Has been used in multiple myeloma patients up to 91 years of age.

Patients with renal & hepatic impairment:

- Excreted by the kidney, therefore it is important to adjust patients with renal impairement in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity.

Pregnancy:

- Contraindicated during pregnancy as it is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Breastfeeding:

- It is not known whether lenalidomide is excreted in human milk. Therefore, breast-feeding should be discontinued during therapy with lenalidomide.

PRECAUTIONS

Myocardial infarction:

- Reported in patients receiving lenalidomide when used in combination with dexamethasone.

Venous and arterial thromboembolic events:

- In patients with multiple myeloma, the combination of lenalidomide with dexamethasone are associated with an increased risk of venous thromboembolism and arterial thromboembolism.

Neutropenia and thrombocytopenia:

- The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia.
- A complete blood cell count should be performed at baseline every week for the first 8 weeks and monthly thereafter to monitor for cytopenias.

Severe skin reactions:

- Severe cutaneous reactions including SJS, and TEN and DRESS have been reported.

STORAGE

- Keep this medicine out of the sight and reach of children.
- Do not store this medicine above 30°C.

PHARMACIST ROLE

- Counsel patient/caregiver on common side effects after starts taking the medication.
- Educate patients about the drug regimens and the importance of implications.
- Provide medication therapy management services that includes:
  - drug administration education, missed dose instructions.
  - drug-drug and drug-food interactions.

REFERENCE

Product information leaflet, FUKKM, QUEST3+, MIMS, UpToDate

BY: SHANTINI KANASAN

DRUG UPDATES

Macitentan 10mg Film-Coated Tablet

A. DESCRIPTION

Macitentan 10mg Film-Coated Tablet is orally active potent endothelin (ET) receptor antagonists, active on both ET_A and ET_B receptors used for treatment the symptoms of pulmonary arterial hypertension (PAH). It displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

B. REGISTRATION NUMBER

MAL20016146ACRZ

C. PRICE

RM 3,525.00 / pack of 30's

D. DEPARTMENT

Paediatric Department.

E. PRESCRIBER CATEGORY

A*
(Consultant / Specialist for specific indications only).

F. INDICATION IN FUKKM

As monotherapy or combination for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

G. DOSE AND ADMINISTRATION

Recommended daily dose of Macitentan is 10mg (1 tablet), with or without food. The film-coated tablets are not breakable and must be swallowed whole with water.

H. MECHANISM OF ACTION

Endothelin (ET)-1 and its receptors (ET_A and ET_B) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Macitentan is an orally active potent endothelin receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B in vitro.

I. ADVERSE REACTIONS

Common

- **Hematologic**: Anemia (13%)
- **Immunologic**: Influenza (6%)
- **Neurologic**: Headache (14%)
- **Renal**: Urinary tract infectious disease (9%)
- **Respiratory**: Bronchitis (12%), Nasopharyngitis, Pharyngitis

Uncommon/Serious:

- **Hepatic:** Hepatitis, Increased liver aminotransferase level (2.1% to 3.4%)

J. STORAGE

Store below 30 °C and keep out of the sight and reach of children.

K. PRECAUTION

- **Cardiovascular**: Peripheral oedema, fluid retention, and worsening heart failure have been reported, increased risk in patients with underlying left ventricular dysfunction; monitoring recommended and discontinuation may be warranted.
- **Concomitant use**: Avoid strong CYP3A4 inducers, such as rifampicin.
- **Concomitant use**: Avoid strong CYP3A4 inhibitors, such as ketoconazole or ritonavir.
- **Hematologic**: Decreases in haemoglobin concentration and haematocrit and monitoring recommended. Not recommended in patients with severe anaemia.
- **Hepatic**: Hepatotoxicity, elevated aminotransferases, and liver failure have occurred with other endothelin receptor antagonists; monitoring recommended and discontinuation may be necessary.
- **Reproductive**: Like with other endothelin receptor antagonists, this drug may have an adverse effect on spermatogenesis.
- **Respiratory**: Pulmonary oedema with pulmonary venoocclusive disease may occur; discontinue if confirmed.

L. CONTRAINDICATION

- Hypersensitivity to the active substance, soya or to any of the excipients listed.
- Pregnancy.
- Women of childbearing potential who are not using reliable contraception.
- Breastfeeding.
- Patients with severe hepatic impairment (with or without cirrhosis.
- Baseline values of hepatic aminotransferases aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) greater than 3 times the upper limit of normal.

M. USE IN SPECIFIC POPULATION

- **Paediatric:** The study of efficacy in children and adolescent below 1 years have not yet been established.
- **Pregnancy:** Contraindicated. Do not consume Macitentan if currently pregnant or planning to become pregnant as it may harm unborn babies conceived before, during or soon after treatment.
- **Lactation:** It is not known if Macitentan is transferred to breast milk. Infant risk cannot be ruled out.
- **Fertility:** Macitentan may lower man sperm count.
- **Elderly:** No dose adjustment is required in patients over the age 65 years old.
- **Renal impairment:** Based on pharmacokinetic data, no dose adjustment is required. The use is not recommended in patients undergoing dialysis.
- **Hepatic impairment:** Based on pharmacokinetic data, no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. It must not be initiated in patients with severe hepatic impairment or clinically significant elevated hepatic aminotransferases.

N. PHARMACIST ROLE

- Counsel patient on common side effects such as headache, dizziness, anemia, UTI and URTI.
- Counsel patient/caregiver to report symptoms of serious cardiovascular effects.
- Counsel patient to use a reliable form of contraception before and while taking medication.
- Counsel patient to report symptoms of allergic reactions such as swelling around the eyes, face, lips, tongue or throat, itching and/or rash.
- Advise patient to avoid alcohol while using the drug.

O. REFERENCES

Product information leaflet, FUKKM, QUEST3+, MIMS Gateway, Micromedex

By: Wan Muhammad Syahir Bin W Mustappa

EVALUATION OF PHARMACEUTICAL INTERVENTION IN OPTIMIZING DIRECT ACTING ANTIVIRAL TREATMENT AMONG CHRONIC HEPATITIS C PATIENTS

Authors: Liyana Hamiza, Kwan Ee Wei, Nasreen Nazmi, Tan Chung Han, Pang Zyu Wen, Hospital Tengku Ampuan Afzan, Kuantan.

Introduction

Direct antiviral agents (DAA) are the latest modern drug with demonstrated effectiveness and manageable side effects for treating hepatitis C viral (HCV) infection. However, continual research is essential to keep healthcare providers informed about DAA adverse effects and drug-drug interactions. SVR12 findings show that non-compliance due to side effects and missed dosage management may lead to unsuccessful Hepatitis C treatment. To optimize the beneficial effects of oral DAA medications, we provide comprehensive counselling as part of collaborative pharmaceutical care provided by a pharmacist and a physician. The counselling session included education about side effects and their management, screening for potential drug-drug interactions (DDI), and monitoring medication adherence levels. Therefore, this study aims to describe pharmaceutical interventions identified in HCV-infected patients receiving DAA therapy and assess the effectiveness of DAA based on sustained virologic response 12 weeks (SVR12) after treatment completion.

Materials and method

This was a cross-sectional, retrospective, and single-center study evaluating all patients with chronic HCV infection treated under DAA therapy in Hospital Tengku Ampuan Afzan, Kuantan (HTAA), starting from March 2018 to August 2020.

Results

A total of 293 patients were enrolled. However, 3 patients were excluded due to drug allergy and 1 blood sample was rejected. Majority of our patients are male, with mean age of 47 years old. Most were non-cirrhotic liver and had not been treated with any DAA before. All patients were treated with daclatasvir/sofosbuvir in 3-6 months. Drug-drug interaction screening was performed and a total of 125 (58.1%) DDI were reported among the patients. The most common concomitant drugs were HAART (39.2%), antihypertensive (28.0%), and cholesterol lowering (16.8%). The top three approaches for managing drug interactions between DAA and other drugs were dose adjustment (41.6%), side effects monitoring (21.6%), and discontinuing medications (16%). The overall rate of SVR12 achieved was 95.9%.

Conclusion

Patients infected with hepatitis C treated with direct-acting antivirals frequently have drug-drug interactions. However, the collaboration between physicians and pharmacists makes it feasible to identify, prevent, or clinically manage these drug-drug interactions to maintain the therapeutic safety and efficacy of direct-acting antivirals during the therapy.

AN OVERVIEW OF COST OF ALPHA BLOCKERS AND 5 ALPHA REDUCTASE INHIBITORS FOR BENIGN PROSTATE HYPERPLASIA/LOWER URINARY TRACT SYMPTOM TREATMENT IN A GENERAL HOSPITAL

Authors: Khairul Naim Zainal Abidin, Nurul Amira Zunaidi, Abdul Qayyum Mat Zaid, Darlia Syafika Darusalam, Norashikin Sumari, Nurul Wajihah Muhammad Zaki, Quek Xin Wei, Hospital Tengku Ampuan Afzan, Kuantan.

Introduction

The number of patient with BPH/LUTS receiving alpha blockers and 5-alpha reductase is still unknown. This information is crucial so that the stakeholders (Pharmacy Dept & Urology Dept) can make better decision regarding the control of medication prescribing or for purpose of request of additional budget. Thus, this study will be conducted to fill the gaps.

Materials and method

This is a retrospective observational study on the patients with BPH/LUTS under follow up of Department of Urology, HTAA between January 2018 until December 2020. Data obtained from PhIS, Excel data and any relevant database. All data were further analyzed and presented in table, graphs, and chart whenever applicable and necessary

Results

There is an increasing trend in total number of new patients for Alfuzosin, Duodart & Dutasteride from 2018 2020. Doxazosin and Finasteride shows fluctuation in number of patients from 2018-2020. Tamsulosin shows decreasing number of patients from 2018-2020. As a result, there is an increasing trend in drug expenditure for Alfuzosin, Duodart & Dutasteride while, Doxazosin and Finasteride shows fluctuation in drug expenditure from 2018-2020. Drug expenditure of Tamsulosin shows decreasing trending from 2018-2020. In term of budgetary, cost of alpha blockers & 5-AR inhibitors comprised of 75% from annual budget of Urology Dept in 2018, and 69.8% in 2019 and 80.5% in 2020.

Conclusion

Cost of alpha blockers & 5-AR inhibitors consist of 70%-80% out of annual budget, thus Urology Department must find a way to ensure proper budget is allocated and received by the department in order to carter their needs.

PHARMACY ACTIVITY

6-8 FEBRUARY 2024

CHINESE NEW YEAR

DEDICATION

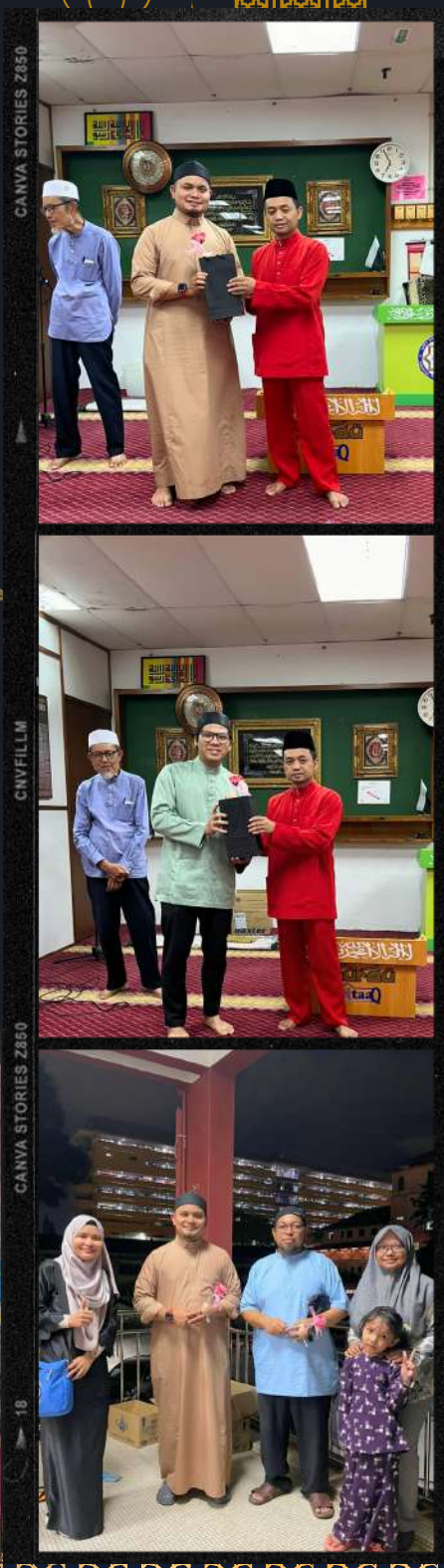
PharmCare
Hospital Tengku Ampuan Afzan

PROGRAM IHYA' RAMADAN 1445H

Tadarus Al-Quran

11 MAC - 3 APRIL 2024

Kolaberasi bersama Bahagian Perkhidmatan Farmasi, JKN Pahang



PHARMACY ACTIVITY

BIGGEST LOOSER CHALLENGE

WELLNESS CAMP

DATE: 27 APRIL 2024
TIME: 9 AM - 1 PM
VENUE: MAHKOTA VALLEY, KUANTAN

"EXERCISE IS MEDICINE"

En. Mohd Ridzwan bin Mohd Razali
Jurupulih Perubatan Fisioterapi

"IT'S NOT ABOUT EATING LESS, BUT EATING RIGHT"

En. Mohammad Basri bin Rusdu
Pegawai Dietetik

"OUR MENTAL HEALTH IS IN OUR HANDS"

Ms. Norasyikin Jane binti Mustafa Kamal
Pegawai Psikologi Klinikal

PharmCare
Hospital Tengku Ampuan Afzan

TABATA

Participants of the Day

PHARMACY BULLETIN BIL 1/2024