Bulletin Pharmacy Hospital Segamat

TUBERCULOSIS

Bulletin Pharmacy Hospital **Bil 1/2015**

What is Tuberculosis (TB)?

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, is second only to HIV/AIDS as the greatest killer worldwide due to single infectious agent. In 2013, 9 million people, including 550,000 children were suffered from TB ,1.5 million is died from the disease and 480,000 people developed multidrug resistant TB (MDR-TB). Over 95% of TB deaths occur in low– and middle-income countries, and it is among the top 5 causes of death for women aged 15 to 44. It is also a leading killer of HIV-positive people causing one fourth of all HIV-related deaths. Among 1.5 million people died from TB, 360,000 were people HIV positive. In Malaysia, there are 24,071 notified TB cases in 2013. Among 23,417 new and relapse cases, 644 (3%) are people who aged under 15 years old and the male to female ratio are 1:8. There are estimated 1,700 thousand non-HIV positive TB patients and 440 hundred HIV positive TB patient died from TB in 2013. Furthermore, among 13,198 cases tested for MDR-TB, 277 cases were confirmed by laboratory test while only 49 patients started on MDR-TB treatment.[1]

ToBe Continued World TB Day on 24 March 2015

To Be Continued is an original concert lasting 24 hours, during which musician from many parts of the World will be connected to a website that will broadcast their concerts. During this un-uninterrupted 24 hour marathon, each musician has at disposal a 30 minute window, thus creating a relay of sounds and rhythms that will range from the different streams of the 'new music'. The event, that will cover the 24th of March, World TB Day, in its entirely coordinated by Antonio Della Marina, musician and computer music composer, and by Moreno Miorelli, artistic director of the annual gathering 'Stazione di Topolò/Postaja Topolove'. The whole initiative is under aegis of the Global Health Incubator, to create links between the world creativity and that if science.[2]

ToBe Continued… 2015 (left) is held on 24th of March, the World TB Day.

The End TB Strategy by WHO

The World Health Assembly, convened annually by WHO at the UN Palais des Nations in Geneva, passed a resolution in May 2014 approving full support with new post-2015 Global TB Strategy. The strategy aims to end the global TB epidermic, with targers to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB.[3]

Vision
A world free of tuberculosis

Goal
End the global tuberculosis epidermic

Pillars and Components

1. Integrated, patient-centred care and prevention
2. Bold policies and supportive systems
3. Intensified research and

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Treatment Regimen for New Cases

A six-month regimen consisting of 2 months of daily EHRZ (2EHRZ) followed by 4 months of daily HR (4HR) is recommended for newly-diagnosed TB. Table below shows the dosages of First-Line Antituberculosis (AntiTB) Drug. [4,5]

Drug	Recommended dose			
	Daily		3 times per week	
	Dose (range) in mg/kg body weight	Maximum in mg	Dose (range) mg/kg body weight	Daily maximum in mg
Isoniazid (H)	5 (4-6)	300	10 (8-12)	900
Rifampicin (R)	10 (8-12)	600	10 (8-12)	600
Pyrazinamide (Z)	25 (20-30)	2000	35 (30-40)*	3000*
Ethambutol (E)	15 (15-20)	1600	30 (25-35)*	2400*
Streptomicin (S)	15 (12-18)	1000	15 (1218)*	1500*

Pyridoxine 10-50mg daily needs to be added if isoniazid is prescribed.
* Daily treatment is the preferred regimen.

The regimen should contain six months of rifampicin and it should be rounded to higher recommended dose if tolerated. Ethambutol is contraindicated in patients who are hypersensitivity towards ethambutol or patients with known optic neuritis and poor vision. Therefore, streptomycin can be used to replace ethambutol. Full ophthalmology examination should be carried out before starting ethambutol and patients should be counselled on the possibility of visual abnormalities. Pyrazinamide, isoniazid and rifampicin are associated with hepatotoxicity and cutaneous ADRs. Pyrazinamide is the most hepatotoxic while rifampicin being the least. Therefore, liver function should be monitored closely. Furthermore, pyrazinamide will induce hyperuricemia. Hence, monitoring of serum uric acid is crucial in TB patients.[4,5]

Tuberculosis in Renal Impairment

The TB treatment regimen should be adjusted in renal failure or severe renal insufficiency patients. The table below shows the recommended dose in renal impairment patient.

Drug	Dose (Range) in mg/kg	Max dose in mg	Frequency
Isoniazid	5 (4-6)	300	Daily
Rifampicin	10 (8-12)	600	Daily
Pyrazinamide	25-30	2000	Thrice a week
Ethambutol	15-25	1600	Thrice a week
Streptomycin **avoid if possible*	*If needed:* 15	1000	Twice/Thrice a week

Pyridoxine 10-50mg daily needs to be added if isoniazid is prescribed.

Pyrazinamide and ethambutol are recommended to administer three times a week in order to provide adequate maximum plasma concentration (Cmax) of the drug and avoid accumulation of the drugs. All antiTB drugs are advised to be administered after hemodialysis.[4]

Tuberculosis in Liver Impairment

The use of hepatotoxic drugs such as pyrazinamide, isoniazid and rifampicin should be reviewed in patients with unstable or advanced liver disease. If baseline liver enzyme, alanine aminotransferase (ALT), is more than three times upper limit of normal before the initiation of treatment, different treatment regimen should be started. The table below shows different treatment regimens in liver impairment patients.[4]

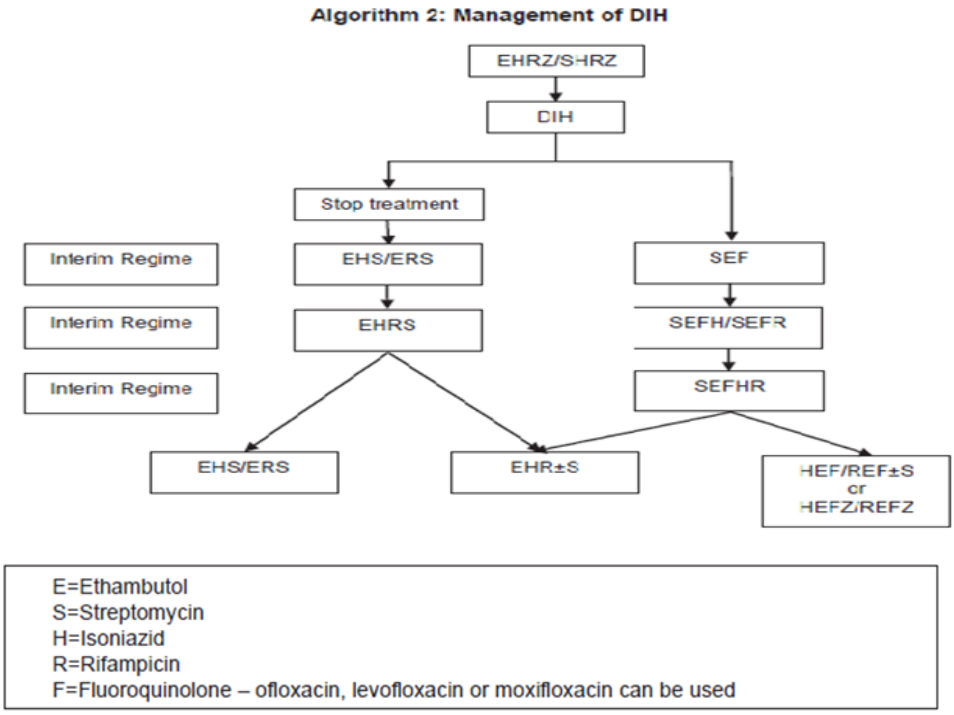
Rationale	Regime
Two hepatotoxic drugs (rather than three in the standard regimen)	- 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented)
	- 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin
	- 6-9 months of rifampicin, pyrazinamide and ethambutol
One hepatotoxic drug	2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol
No hepatotoxic drug	18-24 months of streptomycin, ethambutol and fluoroquinolones* *Newer fluoroquinolones such as levofloxacin and moxifloxacin are preferred over the older generations

Drug-Induced Hepatitis (DIH)

DIH usually occurs within the initial two months of treatment. It is recommended to stop antiTB drugs when the serum transaminase level reaches three times the upper limit of normal for patients with symptoms suggestive of hepatitis or five times upper limit for those without symptoms. Subsequently, if the TB disease is of low severity in terms of radiographic extent, bacillary load and infectiousness, antiTB treatment can be withheld until liver chemistry recovers and patients symptoms resolve. Timing of restarting treatment depends on whether hepatotoxicity sets in during the initial or the continuation phase of treatment, and the amount of treatment received prior to the onset of such toxicity. [4]

Retreatment regimen can contain fewer potentially hepatotoxic drugs such as streptomycin, ethambutol and isoniazid. Fluoroquinolones have low hepatotoxicity. It should be included if co-administration of isoniazid and rifampicin cannot be prescribed. Attempt should be made to resume the use of both isoniazid and rifampicin by slow sequential introduction to shorten the total duration of treatment. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped.[4]

Rifampicin can be introduced first as it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective drug. In patients who have DIH but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide. After 3 - 7 days, isoniazid may be reintroduced. If pyrazinamide is not included in the intensive phase, the total duration of treatment should be extended to nine months.[4]
A suggested algorithm for treatment of patients with DIH is shown below:



TB-HIV Co-infection

The treatment for TB-HIV co-infected patients is similar to those for HIV-uninfected patients. The regimen contains 2 months of EHRZ and 4 months of HR. If there is evidence of a slow or suboptimal response, prolongation of the continuation phase to seven months (a total of nine months treatment) should be considered. All HIV patients should receive daily treatment in maintenance phase. The initiation of HAART in TB-HIV co-infected patients should be carefully consider based on CD4 counts due to adverse effects, Immune Reconstitution Inflammatory Syndrome (IRIS) and drug interaction. The recommendation of the timing to initiate HAART is shown as table below:

CD4 count	Plan
If CD4 <50 cells/ul	Initiate HAART two weeks after starting intensive phase of antiTB treatment
If CD4 >50 cells/ul	Defer initiating HAART until completion of intensive phase of antiTB treatment
If CD4 >350 cells/ul	Complete antiTB treatment and consider HAART if CD4 drops below 350 cells/ul

Apart from the timing of initiation, the drug of choice of HAART is also very important due to drug interactions and additives toxicities. For NRTIs, zidovudine is the preferred drug option. Stavudine and tenofovir –based regimen are alternative options as they can cause peripheral neuropathy. Among the drugs from NNRTIs, efavirenz showed superior virological outcomes when compared to nevirapine. However, if nevirapine is to be initiated due to adverse effects of efavirenz, the dose of 200mg BD is preferred if rifampicin has been given for more than one week. Rifampicin is a potent inducer of CYP450 system and if use together with indinavir and ritonavir could lead to subtherapeutic concentrations of indinavir. Rifabutin is a weaker enzyme inducer, which has much less effect on drugs metabolism through the CYP3A system. It is also as effective as rifampicin. Therefore, the combination of rifabutin with PI-based ARV therapy is the preferred form of therapy for patients who are unable to take NNRTI-based ARV therapy.[4]

**Rifabutin is not registered in Malaysia*

The Five Elements of Direct-Observed Treatment, Short-Course (DOTS) by WHO[6]

- Political commitment with increased and sustained financing
- Case detection through quality-assured bacteriology
- Standardized treatment, with supervision and patient support
- An effective drug supple and management system
- Monitoring and evaluation system, and impact measurement

Suggested First Line AntiTB Medication Side Effects[4]

Drug	Common Side Effects	Drug-drug Interactions	AntiTB & HAART Concern
Isoniazid	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning,, numbness or tingling sensation in the hands or feet	• Reduction in phenytoin & diazepam levels • Increase the toxicity of carbamazepine, benzodiazepines, paracetamol, serotonergic antidepressants, warfarin & theophylline	Care is needed when taking with HAART medications that can cause peripheral neuropathy, particularly stavudine & didanosine
Rifampicin	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange or red urine, flu syndrome (fever, chills, malaise, headache, bone pain)	Reduction in plasma level of: • Anti-infectives • Hormone therapy, including ethinylestradiol, norethindrone, tamoxifen, levothyroxine • Methadone • Warfarin • Cyclosporine • Corticosteroid • Anticonvulsants • Cardiovascular agents • HMG-CoA reductase inhibitors • Antipsychotics • Azole antifungal drug	• Reduces levels of protease inhibitors & NNRTIs in the blood
Pyrazinamide	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain & joint pains	Excretion may be blocked by probenecid	Should be taken two hours before didanosine
Ethambutol	Visual impairment	Absorption delayed or reduced by aluminium hydroxide	-
Streptomycin	Skin rash, deafness (no wax on otoscopy), dizziness (vertigo & nystagmus), decreased urine output	May increase ototoxicity & nephrotoxicity when use with: • Aminoglycoside • Amphoterin B • Cephalosporins • Cyclosporin • Cisplatin • Furosemide • Vancomycin	-

Multidrug Resistance Tuberculosis (MDR-TB)

MDR-TB is defined as Mycobacterium tuberculosis infection resistant to both isoniazid and rifampicin with or without resistance to other drugs. The antiTB drugs for MDR-TB is shown in the table below:

Group Name	AntiTB Drug	Description
Group 1	Pyrazinamide Ethambutol Rifabutin	Group 1 drugs are the most potent and best tolerated. If laboratory evidence and clinical history suggests that a drug from this group is effective, it should be used. If a Group 1 drug was used in a previous regimen that fails, its efficacy should be questioned even if the DST result suggests susceptibility. The newer rifamycins, such as rifabutin, have very high rates of cross-resistance to rifampicin.
Group 2 - Injectable drugs	kanamycin amikacin	Group 2 - 5 (except streptomycin) are second line or reserve drugs. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Kanamycin or amikacin is the first choice of an injectable agent. Amikacin and kanamycin have high frequency of cross resistance. Hence if there is a resistance to both streptomycin and kanamycin, capreomycin should be used.
Group 3	levofloxacin moxifloxacin ofloxacin	The newer generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice
Group 4	ethionamide cycloserine p-aminosalicylic acid (PAS)*	Drugs in this group can be added
Group 5	clofazimine linezolid amoxicillin/ clavulanate clarithromycin imipenem	Group 5 drugs are not used routinely as their efficacy is uncertain. They may be needed in patients with extensively drug resistant-TB

**Drug is not registered in Malaysia*

Once patient is confirmed with MDR-TB, a standard MDR-TB regime or an individually tailored regimen based on drug sensitivity testing of additional drugs can be given. In a standard regimen, it should includes at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide and either cycloserine or PAS (if cycloserine cannot be used). The 8 months of intensive phase is suggested for most patient, which includes injectable agent. A total treatment of 20 months is suggested for most newly diagnosed patients.[4]

Suggested Second-Line AntiTB Medication Dosages & Side Effects[4]

Drug	Adult			Common Side Effects
	Daily Dose (mg/kg body weight)	Max Dose (mg)	Frequency	
Kanamycin	15-20	1000	Daily	Nephrotoxicity, peripheral neuropathy, rash, auditory damage
Amikacin	15-20	1000	Daily	
Capreomycin	15-20	1000	Daily	Nephrotoxicity, tubular dysfunction, azotaemia, proteinuria, urticaria or maculopapular rash
Cyloserine*	15-20	1000	Twice Daily	Neurological and psychiatric disturbances including headaches, irritability, sleep disturbances, aggression and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness
Ethionamide	15-20	1000	Daily	Severe gastrointestinal intolerance, psychotic disturbances, neurotoxicity, gynecomastia
P-aminosalicylic acid (PAS)	150	12000	2-3 equally divided doses	Gastrointestinal intolerance, careful use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
Clofazimine	100-300mg daily (not in mg/kg)	300	Daily	Ichthyosis, dry skin; pink to brownish-black discolouration of skin, cornea, retina and urine; anorexia, abdominal pain
Ofloxacin	15-20	1000	Twice daily (common dose is 400mg twice daily)	Gastrointestinal intolerance, headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhea, photosensitivity
Levofloxacin	7.5-10	1000	Daily (common dose is 750mg daily)	
Moxifloxacin	7.5-10	400	Daily	

*All patients receiving cycloserine should be given 50mg pyridoxine for every 250mg of cycloserine

Read more on:

1. Fact Sheet Tuberculosis. World Health Organization. Available at http://www.who.int/mediacentre/factsheets/fs104/en/ (accessed 21April 2015)

2. ToBeContinued…2015. Stazione Topolò. Available at http://www.stazioneditopolo.it/24h-2015/ (accessed 23 April 2015)

3. World Health Organization. The End TB Strategy. Geneva: WHO; 2015

4. Ministry of Health Malaysia. Clinical Practice Guidelines: Management of Tuberculosis 3rd Edition. Malaysia: MOH; 2012

5. www.mimsgateway.com.my

6. The Five Elements of DOTS. World Health Organization. Available at http://www.who.int/tb/dots/whatisdots/en/ (accessed 19 April 2015)

Adverse Drug Reaction Report Hospital Segamat Jan-Mar 2015

No	DATE	MEDICATIONS	ADR
1	22.1.2015	Insuman® Rapid & Insuman® Basal	urticaria & pruritis all over the body after switching from Novo Nordisk® to Insuman®
2	26.1.2015	Pizotifen 0.5mg	nausea & vomiting
3	12.2.2015	Phenoxymethylpenicilin suspension	generalised rashes, more at face, itchiness
4	26.3.2015	Insuman Comb	Itchiness (Whole body)

Malaysian Adverse Drug Reactions Newsletter August 2014

Implanon NXT® (Etonogestrel): Drug Interaction with Rifampicin

It is documented that concurrent use of rifampicin and contraceptives may decrease the plasma concentration of estrogens and thus decrease contraceptive effectiveness. This is due to the cytochrome P450 enzyme-inducing effect of rifampicin. There is no documented interaction between isoniazid and contraceptive drugs.

Since the year 2000, NPCB has received 48 ADR reports related to Implanon NXT®, with seven (7) of these possibly indicating inefficacy (reported ADR terms: medicine ineffective, pregnancy, pregnancy unintended). Six of these reports were given the causality C3 (possibly-related to the drug) while the remaining one report was assigned causality C5 (insufficient information to analyse report). Other frequently reported ADRs related to Implanon NXT® were menstrual disorders, implant site reactions , and skin reactions such as rash, cellulitis or pruritus.

Advice to Healthcare Professionals:

- If rifampicin is co-administered with a combination or progestin-only contraceptive, the patient should be advised to use an **alternate non-hormonal contraceptive** method of birth control.
- The patient should be monitored closely for signs of breakthrough bleeding and/or pregnancy.
- Patients who are started on Implanon NXT® should be **counselled to inform** their healthcare professionals of the implant use before taking any other medication.
- During drug history taking, patients should be **specifically asked** about any concomitant use of contraceptive medication, including implants.
- Please report any ADRs suspected to be due to Implanon NXT® to the Drug Safety Monitoring Centre, NPCB.

Reaksi Drug Safety News March 2015, No 22

Chlorhexidine Solutions: Risk of Chemical Burns to Skins in Premature Infants

Since year 2000, the NPCB Drug Safety Monitoring Centre has received 12 reports related to chlorhexidine with 22 adverse events. However, none of the reports were related to topical use in paediatric patients. All the reports involved chlorhexidine used as a gargle, skin disinfectant before vaginal examination, hand rub, or body wash in patients aged 13 years and above. The adverse events reported were mainly allergy-related reactions such as rash, itching, eczema, contact dermatitis, sore throat, and facial swelling.

Advice for Healthcare Professionals:

- When using alcohol-based or water-based chlorhexidine solutions on premature infants, bear in mind the risk of severe chemical burns, while still considering any impact on antisepsis and preventing catheter-related sepsis.
- Use the minimum amount of chlorhexidine solution required and do not allow the solution to pool. Remove any excess solution, especially in skin folds, and any soaked materials, drapes, or gowns before proceeding with catheter insertion.
- Monitor patients frequently to detect and manage cutaneous side effects at an early stage.
- All adverse events associated with chlorhexidine-containing products should be reported to the NPCB Drug Safety Monitoring Centre.

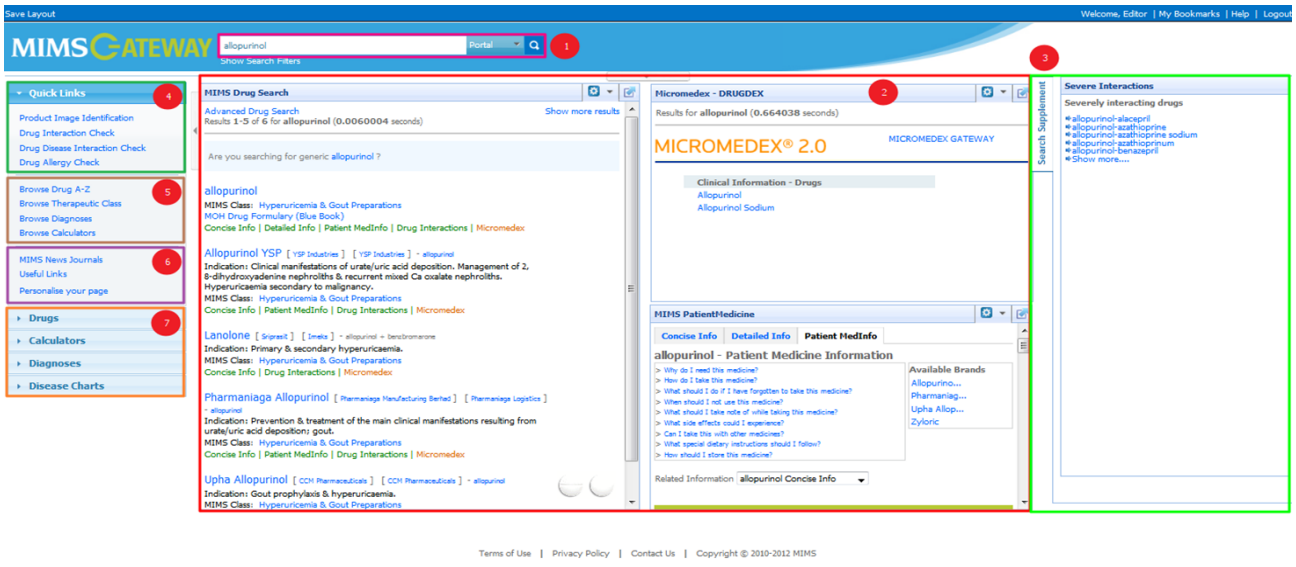
MIMS GATEWAY & MICROMEDEX

- Intelligent workflow-oriented resource designed specifically for healthcare professionals in their clinical practice needs

- High quality MIMS Drug Information integrated with clinical decision support tools and renowned international medical resources, delivering a convenient, comprehensive and seamlessly integrated suite of information through a single point of access

SYSTEM REQUIREMENTS

- INTERNET EXPLORER 8 AND ABOVE
- FIREFOX 13 AND ABOVE
- CHROME 19 AND ABOVE



Facility email address: farmasihsegamat@moh.gov.my
Password: password1

How to Log In

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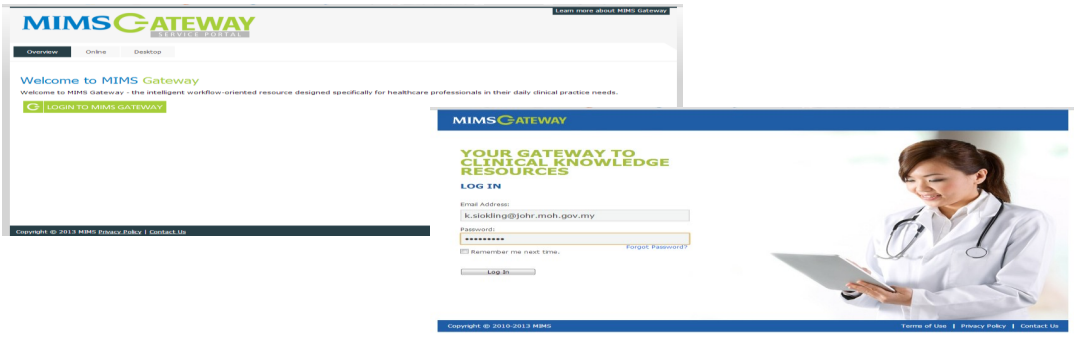
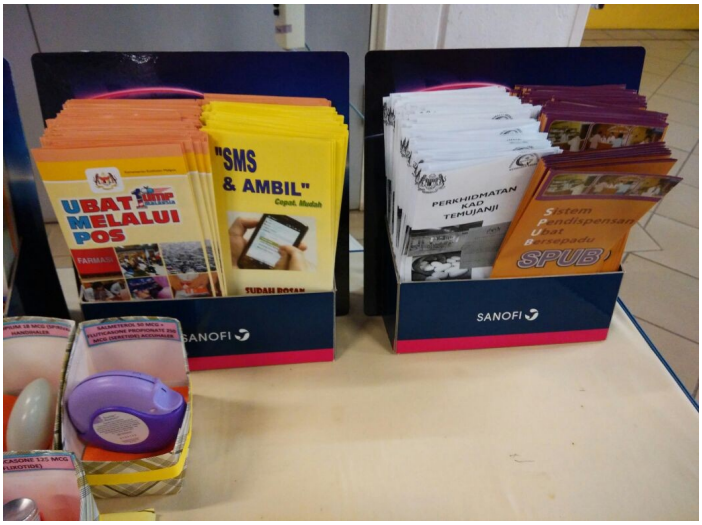


Hari Farmasi



Pharmacy Day was held on On 27th May 2015 by Pharmacy Department of Hospital Segamat. The activities include 'Kenali Ubat Anda' exhibition, medication counseling booth and talk.