Farmakoterapi

Obat Tuberkulosis

Fathiyah Safithri

klasifikasi TB PARU

TB PARU dengan BTA POSITIF

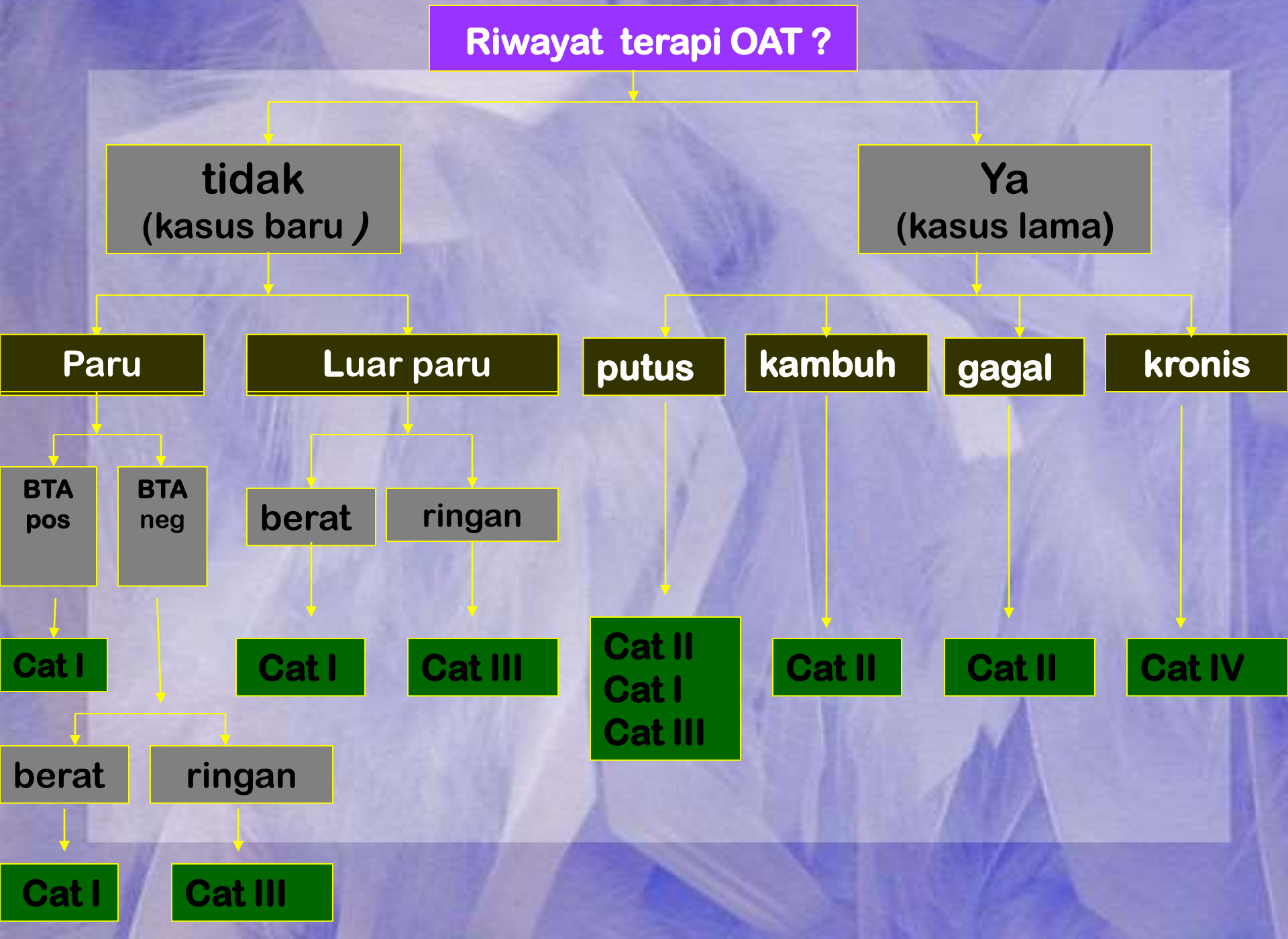
a. 2 atau lebih hasil pemeriksaan awal BTA (+) ,
b. 1 pemeriksaan awal BTA (+) plus gamb.radiologis TB aktif
c. 1 sputum BTA (+) plus biakan sputum (+)

TB PARU dengan BTA NEGATIF

3 pemeriksaan awal BTA (-) , *dan*
gambaran radiologis TB aktif , *dan* tidak ada respon antibiotik spektrum luas, *dan* pertimbangan klinis.

BATASAN KASUS ~ RIWAYAT TX SEBELUMNYA

Kasus baru	belum pernah tx atau tx < 1 bulan
Kambuh	telah di tx & sembuh, sekarang kembali dg dahak (+)
Gagal Tx	TB paru baru dg dahak tetap (+) setelah di tx > 5 bulan
Putus obat	Berhenti berobat ≥ 2 bulan, kembali (+)
Kronik	Dahak tetap (+) walau telah menjalani tx ulang


Riwayat terapi OAT ?
tidak
(kasus baru)
Ya
(kasus lama)
Paru
Luar paru
putus
kambuh
gagal
kronis
BTA pos
BTA neg
berat
ringan
Cat I
Cat I
Cat III
Cat II
Cat I
Cat III
Cat II
Cat II
Cat IV
berat
ringan
Cat I
Cat III

STANDARDISASI KATEGORI PENGOBATAN

Kategori Terapi	Penderita TB
• Kategori 1 …	• Kasus baru dahak BTA + • Kasus baru dahak BTA - dg kelainan parenkim paru luas • Kasus baru pd TB di luar PARU yg berat
• Kategori 2 …	• Kambuh ; Gagal terapi • Putus berobat
• Kategori 3 …	• Kasus baru dahak (-) dg kelainan parenkim paru yg tidak luas • Kasus TB di luar yg tidak berat
• Kategori 4 …	▪ Kasus kronik

Regimen Terapi Standard WHO

Kategori terapi	Penderita	Regimen terapi TB
I	Kasus baru : - sputum BTA (+) - sputum BTA (-) dgn kelainan radiologis luas - TB diluar paru berat	2HRZE (S) / $4H_3R_3$ / 4HR / 6HE
II	kasus lama : sputum BTA (+) : kambuh, gagal, putus	2HRZES-1HRZE/ $5H_3R_3E_3$ / 5HRE
III	Kasus baru : - sputum BTA (-) dgn kelainan radiologi minimal - TB diluar paru ringan	2HRZ / $4H_3R_3$ / 4HR / 6HE
IV	kasus kronis	Refer. to specialized center

Kriteria Berat dan Ringannya Penyakit Tuberkulosis

TUBERKULOSIS EXTRA PARU		TUBERKULOSIS PARU (SAKIT BERAT)
Sakit Berat	**Sakit Ringan**	
Meningitis	Kelenjar limfe	Proses Milier
Proses Milier	Efusi Pelura unilateral dan tidak exentsif	Gambaran Rontgen “far advanced” (lesi luas)
Perikarditis	Tulang (kecuali tulang belakang)	
Efusi pleura bilateral atau extensif	Persandian	
Tulang belakang		
usus		

TUJUAN TERAPI

- menyembuhkan
- mencegah kematian
- mencegah kekambuhan
- mencegah resistensi terhadap OAT
- memutuskan mata rantai penularan

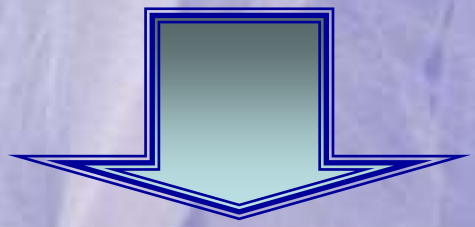
Dua Fase Pengobatan Tuberkulosis

Fase intensif
2-3 BULAN

Membunuh kuman yang aktif berkembang

Fase lanjutan
4-7 BULAN

Membunuh kuman yang tersembunyi dan tumbuh sangat lambat (Dorman)



GAGAL

SEMBUH

KAMBUH

Apa yang harus diketahui dari FarmakoTx TB ?

- First line / Second line
- Kenapa harus kombinasi ?
- Kenapa 6bulan
- Bagaimana aturan pakai (waktu paruh)
- Hati-hati interaksi obat (apa saja)
- Apa yang harus dimonitor ?
  - ✓ efek samping masing-masing
  - ✓ LFT
  - ✓ tanda perbaikan : BB, nafsu makan, gejala klinis lain.
- Tindak lanjut bds hasil monitoring ?

TB Medications

- First-Line Anti-TB Medications
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Rifabutin (RFB)
  - Rifapentine (RPT)
  - Ethambutol (EMB)
  - Pyrazinamide (PZA)
- Second-Line Anti-TB Medications

Second-Line Anti-TB Medications

- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- Gatifloxacin
- *p*-Aminosalicylic acid (PAS)
- Streptomycin
- Amikacin/Kanamycin
- Capreomycin

JENIS DAN DOSIS OAT

ISONIASID (H)

- BAKTERISID
- MEMBUNUH 90 % POP.KUMAN BBRP.HARI PENGOBATAN
- UNTUK KUMAN YG.SEDANG BERKEMBANG
- DOSIS 5 mg/kg BB pada fase INTENSIF
- DOSIS 10 mg/kg BB pada fase INTERMITEN 3 x/minggu

RIFAMPISIN (R)

- BAKTERISID

  MEMBUNUH KUMAN SEMI DORMANT (PERSISTEN) YG.TDK DAPAT DIBUNUH DGN. INH
- DOSIS 10 mg/kg BB pada fase INTENSIF atau fase INTERMITEN

Isoniazid (INH)

- Adverse effects:
  - Hepatic enzyme elevation
  - Hepatitis
  - Peripheral neuropathy
  - CNS effects
  - SLE-like symptoms
  - Hypersensitivity reaction
  - Monoamine (Histamine/tyramine poisoning)
  - Diarrhea

INH Drug Interactions & Monitoring

- Drug Interaction
  - Phenytoin
- Monitoring
  - Routine monitoring is not necessary
  - For patients with pre-existing liver disease or who develop abnormal liver function test should be measured monthly and when symptoms occur
- Prevention
  - Vitamin B6 may prevent peripheral neuropathy and CNS effects

Rifampin (RIF)

- Adverse effects:
  - Cutaneous reactions
  - Gastrointestinal reactions
  - Flu-like syndrome
  - Hepatotoxicity
  - Severe immunologic reactions
  - Orange discoloration of bodily fluids
    - Patients should be informed in advance of urine and contact lens discoloration

RIF Drug Interactions

- Drug Interactions
  - Antiinfectives
  - Hormone therapy
  - Narcotics
  - Anticoagulants
  - Immunosuppressive agents
  - Anticonvulsants
  - Cardiovascular agents
  - Bronchodilators
  - Sulfonylurea hypoglycemics
  - Hypolipidemics
  - Psychotropic drugs

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins (References)	Comments
Antiinfectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir/ritonavir)	Can be used with rifabutin. Ritonavir, 400–600 mg twice daily, probably can be used with rifampin. The combination of saquinavir and ritonavir can also be used with rifampin.
	Nonnucleoside reverse transcriptase inhibitors Delavirdine Nevirapine Efavirenz	Delavirdine should not be used with any rifamycin. Doses of nevirapine and efavirenz need to be increased if given with rifampin, no dose increase needed if given with rifabutin.
	Macrolide antibiotics (clarithromycin, erythromycin)	Azithromycin has no significant interaction with rifamycins.
	Doxycycline	May require use of a drug other than doxycycline.
	Azole antifungal agents (ketoconazole, itraconazole, voriconazole)	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased.
	Atovaquone	Consider alternate form of *Pneumocystis carinii* treatment or prophylaxis.
	Chloramphenicol	Consider an alternative antibiotic.
	Mefloquine	Consider alternate form of malaria prophylaxis.
Hormone therapy	Ethinylestradlol, norethindrone	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when taking a rifamycin.
	Tamoxifen	May require alternate therapy or use of a nonrifamycin-containing regimen.
	Levothyroxine	Monitoring of serum TSH recommended; may require increased dose of levothyroxine.

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins (References)	Comments
Narcotics	Methadone	Rifampin and rifapentine use may require methadone dose increase; rifabutin infrequently causes methadone withdrawal.
Anticoagulants	Warfarin	Monitor prothrombin time; may require two- to threefold dose increase.
Immunosuppressive agents	Cyclosporine, tacrolimus	Rifabutin may allow concomitant use of cyclosporine and a rifamycin; monitoring of cyclosporine serum concentrations may assist with dosing.
	Corticosteroids	Monitor clinically; may require two- to threefold increase in corticosteroid dose.
Anticonvulsants	Phenytoin, lamotrigine	Therapeutic drug monitoring recommended; may require anticonvulsant dose increase.
Cardiovascular agents	Verapamil, nifedipine, diltiazem (a similar interaction is also predicted for felodipine and nisoldipine)	Clinical monitoring recommended; may require change to an alternate cardiovascular agent.
	Propranolol, metoporol	Clinical monitoring recommended; may require dose increase or change to an alternate cardiovascular drug.
	Enalapril, losartan	Monitor clinically; may require a dose increase or use of an alternate cardiovascular drug.
	Digoxin (among patients with renal insufficiency), digitoxin	Therapeutic drug monitoring recommended; may require digoxin or digitoxin dose increase.
	Quinidine	Therapeutic drug monitoring recommended; may require quinidine dose increase.
	Mexilitine, tocainide, propafenone	Clinical monitoring recommended; may require change to an alternate cardiovascular drug.
Bronchodilators	Theophylline	Therapeutic drug monitoring recommended; may require theophylline dose increase.

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins (References)	Comments
Sulfonylurea hypoglycemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide	Monitor blood glucose; may require dose increase or change to an alternate hypoglycemic drug.
Hypolipidemics	Simvastatin, fluvastatin	Monitor hypolipidemic effect; may require use of an alternate hypolipidemic drug.
Psychotropic drugs	Nortriptyline	Therapeutic drug monitoring recommended; may require dose increase or change to alternate psychotropic drug.
	Haloperidol, quetiapine	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.
	Benzodiazepines (e.g., diazepam, triazolam), zolpidem, buspirone	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.

RIF Monitoring

- Monitoring
  - No routine monitoring required
  - When given with drugs that interact, may necessitate regular measurements of the serum concentrations of the drugs in question

Ethambutol (EMB)

- Adverse effect:
  - Optic neuritis (impaired perception of the red and green colors)
  - Cutaneous reactions
- Monitoring
  - Baseline and monthly tests of visual acuity and color vision
  - Educate patient about self monitoring their vision and reporting any visual changes to their physician immediately

Pyrazinamide (PZA)

- Adverse effects:
  - Hepatotoxicity
  - GI symptoms
  - Non-gouty polyarthralgia
  - Hyperuricemia
  - Acute gouty arthritis
  - Rash
- Monitoring
  - Serum uric acid measurements are not routinely recommended
  - Liver function tests should be performed when the drug is used in patients with underlying liver disease

Second-Line Anti-TB Medications

- Cycloserine
  - Psychosis, seizures
- Ethionamide and PAS
  - GI upset
- Fluoroquinolones
  - Tendon rupture
- Aminoglycosides
  - Deafness
  - Renal failure

Sediaan dan Dosis Obat TB

Drug	Preparation	Adults/Children	Daily
First-Line Drugs			
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/mL) for intravenous or intramuscular injection	Adults (max.) Children (max.)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults[c] (max.) Children (max.)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)
Rifabutin	Capsule (150 mg)	Adults[c] (max.) Children	5 mg/kg (300 mg) Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults Children	— The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg, scored)	Adults Children (max.)	1000 mg (40–55 kg) 1500 mg (56–75 kg) 2000 mg (76–90 kg)[k] 15–30 mg/kg (2.0 g)
Ethambutol	Tablet (100 mg, 400 mg)	Adults Children[d] (max.)	800 mg (40–55 kg) 1200 mg (56–75 kg) 1600 mg (76–90 kg)[k] 15–20 mg/kg daily (1.0 g)

Drug	Preparation	Adults/Children	Daily
Second-Line Drugs			
Cycloserine	Capsule (250 mg)	Adults (max.)	10–15 mg/kg/day (1.0 g in two doses), usually 500–750 mg/d in two doses[e]
		Children (max.)	10–15 mg/kg/day (1.0 g/day)
Ethionamide	Tablet (250 mg)	Adults[f] (max.)	15–20 mg/kg/day (1.0 g/day), usually 500–750 mg/day in a single daily dose or two divided doses[f]
		Children (max.)	15–20 mg/kg/day (1.0 g/day)
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	[g]
		Children (max.)	20–40 mg/kg/day (1 g)
Amikacin/ kanamycin	Aqueous solution (500-mg and 1-g vials) for intravenous or intramuscular administration	Adults (max.)	[g]
		Children (max.)	15–30 mg/kg/day (1 g) intravenous or intramuscular as a single daily dose
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max.)	[g]
		Children (max.)	15–30 mg/kg/day (1 g) as a single daily dose

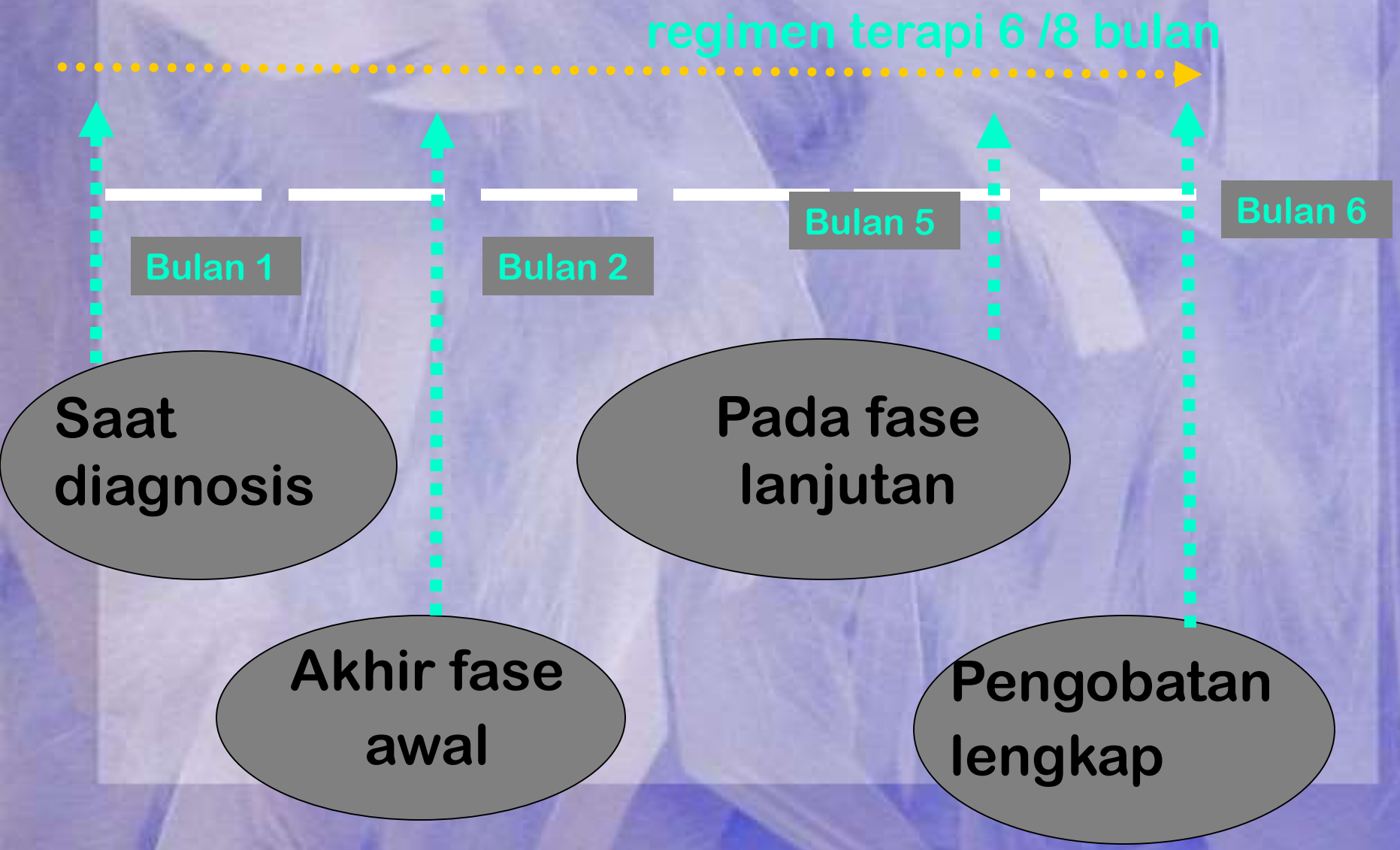
MONITORING / EVALUASI SELAMA PENGOBATAN

- klinis
- radiologis
- bakteriologik
- efek samping
- keteraturan minum obat

EVALUASI BAKTERIOLOGIS

- Tuj. mendeteksi konversi dahak :
  - BTA POSITIF menjadi NEGATIF
- Jadwal pem. bakteriologik :
  - Sebelum pengobatan dimulai
  - Setelah 2 bulan pengobatan
  - Akhir pengobatan

KAPAN MONITOR BTA SPUTUM ?



HASIL PENGOBATAN

- Sembuh :

  Bila hasil hasil pem. ulang dahak (follow up) paling sedikit 2 kali berturut-turut negatif, salah satu diantaranya haruslah pemeriksaan pada akhir pengobatan.

- Pengobatan Lengkap :

  Penderita telah selesai pengobatan secara lengkap, tapi tidak ada pemeriksaan ulang dahak, khususnya pada akhir pengobatan.

HASIL PENGOBATAN

- **Gagal:**
  - Px dahak (+) yg tetap (+) atau kembali (+) pd akhir bl ke-5 atau lbh.
  - Px dahak (-) Rö (+) menjadi dahak (+) pada akhir bl ke-2 pengobatan
- **Drop-out :**
  - Penderita yang tidak mengambil/meminum obat 2 bulan berturut-turut atau lebih sebelum masa pengobatannya selesai

EVALUASI KLINIS

- Setiap 2 minggu pada bulan pertama pengobatan selanjutnya setiap bulan
- Evaluasi : respons pengobatan, efek samping & komplikasi penyakit
- Meliputi : keluhan, berat badan, pemeriksaan fisik.

EVALUASI RADIOLOGIK

Evaluasi foto toraks dilakukan pada :

- Sebelum pengobatan
- Setelah 2 bulan pengobatan
- Pada akhir pengobatan

PARAMETER MENILAI HASIL TERAPI

PENDERITA TB PARU BTA (+)

SERIAL PEM. BAKTERIOLOGIS MUTLAK !

SERIAL KLINIS & RADIOLOGIS BERGUNA PADA FASE AWAL TERAPI

YANG PERLU DIPANTAU

PENDERITA TB PARU BTA (-)

KLINIS & RADIOLOGIS

MERUPAKAN INDIKATOR UTAMA

MONITORING EFEK SAMPING & PENANGANANNYA

RINGAN

JENIS EFEK SAMPING ?

BERAT

OAT

YANG MANA?

TETAP LANJUTKAN OAT

PENANGANAN

STOP OAT

- SEMENTARA
- SETERUSNYA

MENGATASI EFEK SAMPING RINGAN

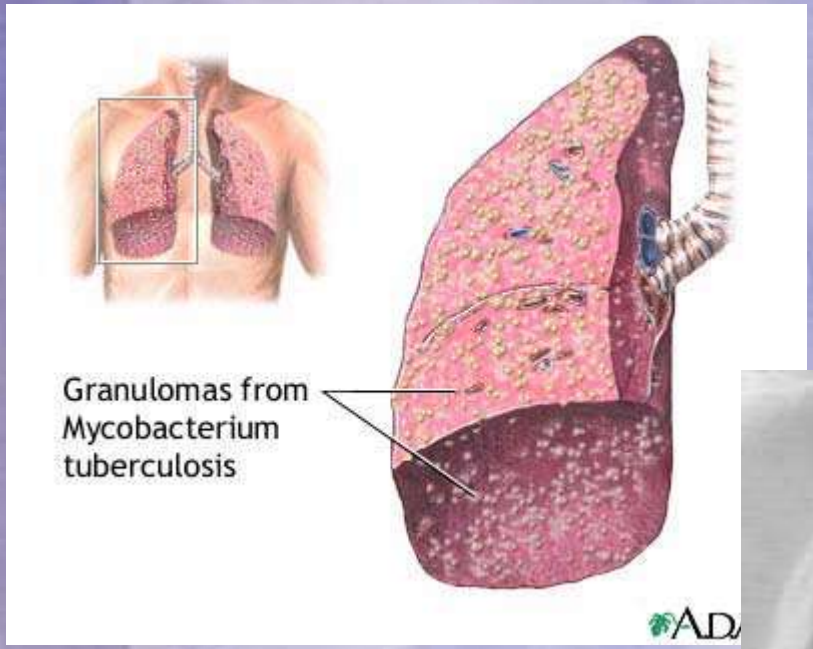
EFEK SAMPING	PENYEBAB	PENANGANAN
Tdk nafsu makan, mual, sakit perut	Rifampisin	Obat diminum malam sebelum tidur
Nyeri sendi	pyrazinamid	Beri aspirin
Kesemutan s/d rasa terbakar di kaki	INH	Beri Vit. B6 (piridoksin) 100 mg per hari
Warna kemerahan pada kulit	Rifampisin	Beri penjelasan, tidak perlu diberi apa-apa

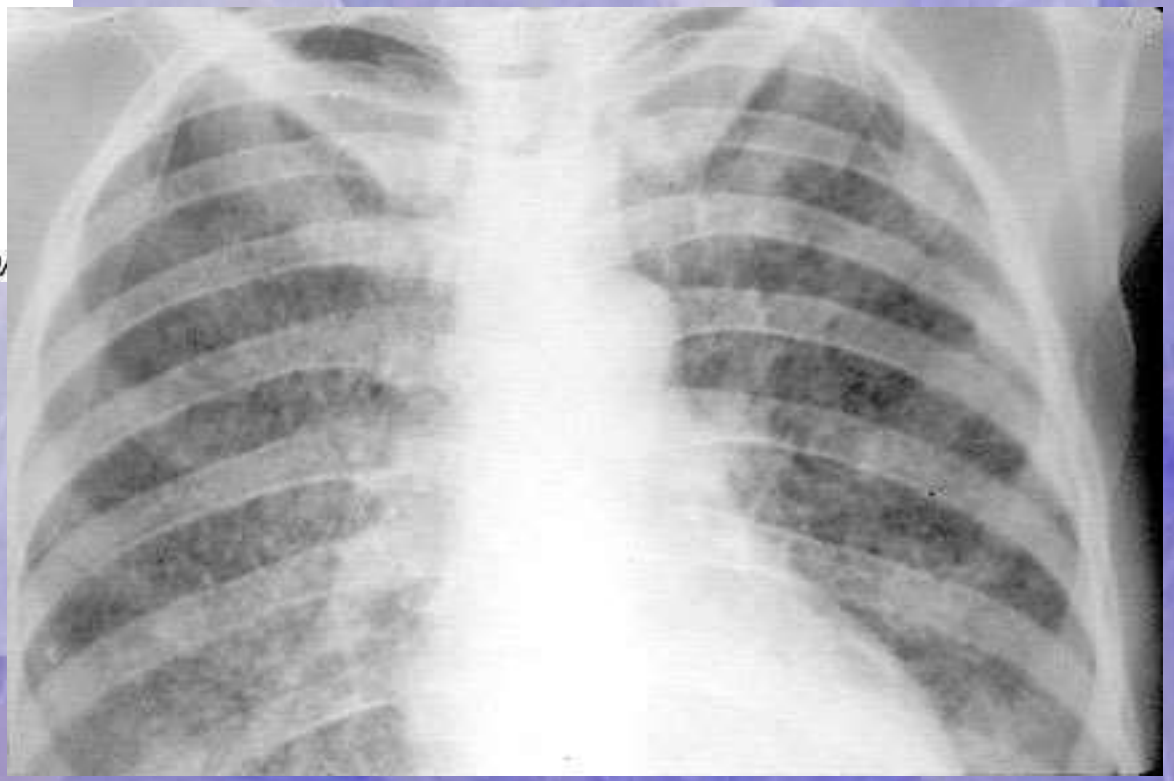
MENGATASI EFEK SAMPING BERAT

EFEK SAMPING	PENYEBAB	PENANGANAN
Gatal dan kemerahan pada kulit	Semua jenis OAT	Beri antihistamin & dievaluasi ketat
Tuli	Streptomisin	Streptomisin dihentikan
Gangguan keseimbangan	Streptomisin	Streptomisin dihentikan
Ikterik	Hampir semua OAT	Hentikan semua OAT sampai ikterik hilang
Bingung & muntah-muntah	Hampir semua obat	Hentikan semua OAT & lakukan uji fungsi hati
Gangguan penglihatan	Ethambutol	Hentikan Ethambutol
Purpura dan renjatan (syok)	Rifampisin	Hentikan Rifampisin

PENGOBATAN TUBERKULOSIS PADA KEADAAN KHUSUS

TB MILIER

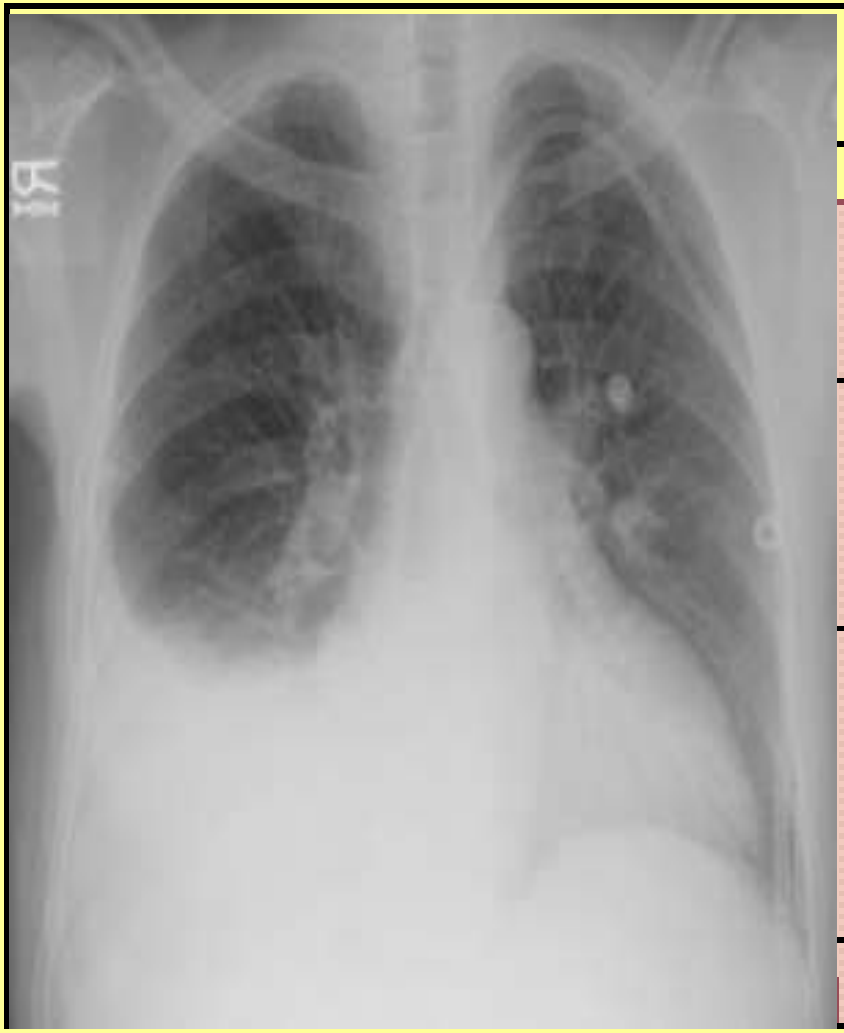


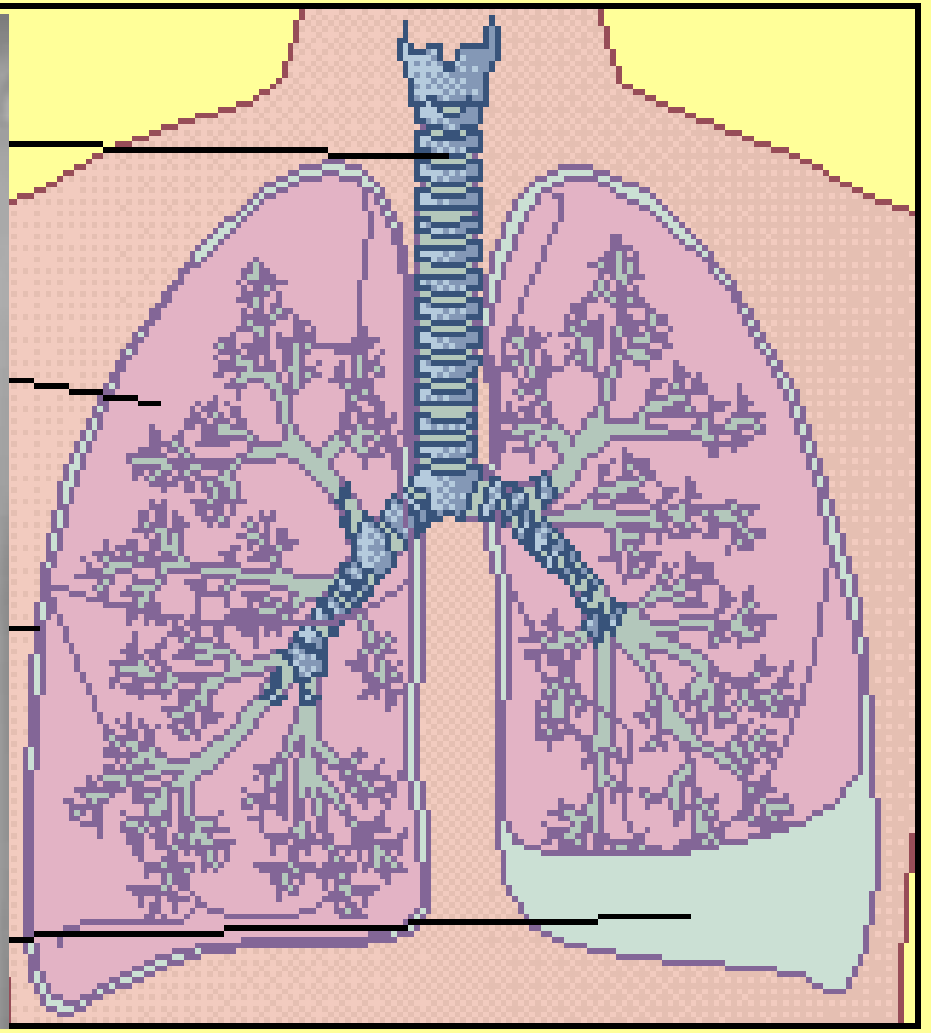


TB MILIER

- Rawat inap
- Paduan obat 2 RHZE/4RH
- Pada keadaan sakit berat, pengobatan dapat 2RHZE/7RH
- Pemberian kortikosteroid diberikan pada keadaan:
  - √ Tanda / gejala menigitis
  - √ Sesak napas
  - √ tanda/gejala toksik
  - √ Demam tinggi
- Prednison 30-40 mg/hari.
- Dosis diturunkan 5-10 mg/hari setiap 5-7 hari,
- lama pemberian 4-6 minggu

EFUSI PLEURA





EFUSI PLEURA

- Paduan obat 2RHZE/4RH atau RHZ/4RH
- Evakuasi cairan
- Dosis steroid prednison 30-40 mg/hari. Dosis diturunkan 5-10 mg/hari setiap 5-7 hari, lama pemberian 3-4 minggu

TB paru dengan DM

- Paduan OAT : 2 RHZ (E-S)/4 RH dg regulasi gula yang optimal
- Bila kdr gula tidak terkontrol → fase lanjutan 7 bulan : 2 RHZ(E-S)/ 7 RH
- Hati-hati dg etambutol → ES di mata
- Penggunaan rifampisin dpt me↘ efektiviti OAD (sulfonil urea), shg dosis perlu di↗kan

TB paru dengan HIV / AIDS

- **Paduan (ATS) : RHZE/RH 6-9 bulan setelah konversi dahak**

- **Men WHO :**

  paduan & lama pengobatan = TB paru tanpa HIV/AIDS

TB paru pada kehamilan & menyusui

- Tidak ada indikasi pengguguran kehamilan pd penderita TB dg kehamilan
- OAT tetap diberikan kecuali steptomisin
- Pend TB menyusui :
  - OAT & ASI tetap dpt diberikan.
  - Walau dpt tembus ke dalam ASI → konsentrasi kecil & tidak toksik pd bayi

TB paru & gagal ginjal

- Hindari penggunaan streptomisin.
- Hindari penggunaan etambutol → waktu paruh memanjang → akumulasi etambutol. Sedapat mungkin dosis disesuaikan dg faal ginjal
- Rujuk

TB paru dengan kelainan hati

- Pemeriksaan faal hati sebelum pengobatan
- Pyrazinamid tidak boleh diberikan
- Paduan OAT (WHO) :
  2 SHRE / 6 RH atau 2 SHE / 10 HE
- Pada hepatitis akut atau klinik ikterik :
  tunda OAT sampai sembuh.
  Bila diperlukan : beri E dan S maksimal 3 bulan sampai hepatitisnya sembuh & dilanjutkan 6 RH
- Sebaiknya dirujuk

Hepatitis imbas obat

- Bila klinik (+) ikterik (+), gejala / mual, muntah (+) → OAT stop
- Bila klinis (-), laboratorium tdp kelainan :
  - Bilirubin > 2 → OAT stop
  - SGOT, SGPT > 5 X → OAT stop
  - SGOT, SGPT ≥ 3 X, gejala (+) : OAT stop
  - SGOT, SGPT ≥ 3X, gejala (-) → teruskan pengobatan dg pengawasan

Hepatitis drug induced

- Stop OAT hepatotoksik (RHZ)
- monitor klinik & lab. :
  - Bila klinik & Lab normal → beri INH dg desensitisasi.
  - Bila klinik & lab tetap normal → tambahkan rifampisin dg desensitisasi
  - sampai paduan jadi kembali semula.

Terima Kasih ….