Hepatic Adverse Reactions of First Line Anti-TB Drugs

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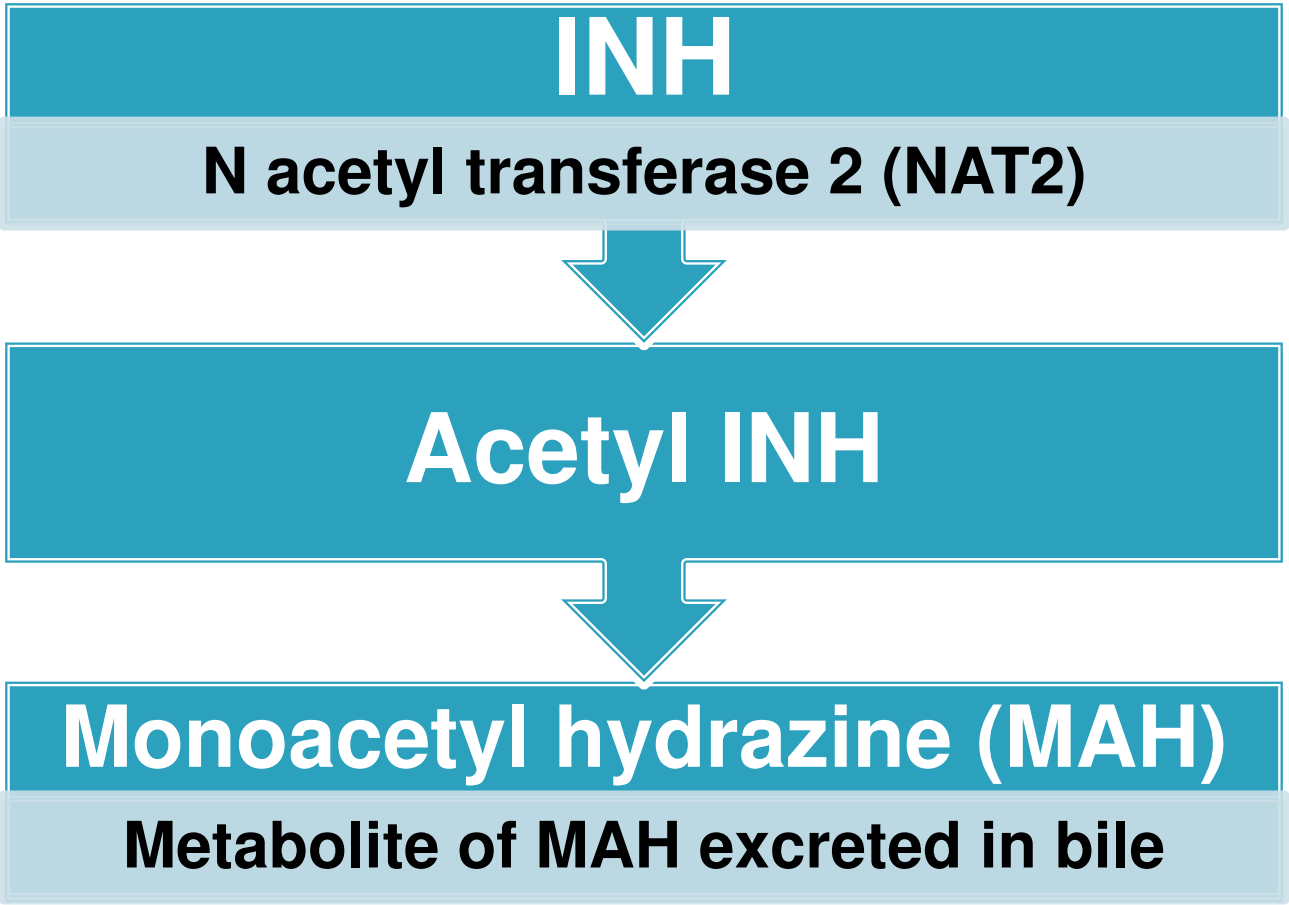
Objectives

- To review the metabolism of first line anti-TB drugs: INH, RMP, PZA
- To describe how hepatotoxicity may occur with the use of these drugs
- To discuss manifestations and incidence of hepatotoxicity
- To elucidate suggested management of patients who develops hepatotoxicity

Metabolism of INH



Huang YS. *Hepatology* 2002; 35

Acetylator status and INH hepatotoxicity

- Acetylator status determined by NAT-2 genotype
- Slow, intermediate, fast
- Fast acetylators: clear MAH more rapidly
- Slow acetylators: greater cumulative MAH
- 3x ALT increase more common in slow than fast acetylators (26% vs 11%)
- INH rechallenge frequently causes increase in ALT in slow than fast acetylators

Hiratsuka M. *Drug Metabol Pharmacokin* 2002; Huang YS. *Hepatology* 2002; Ohno M. *Int J Tuberc Lung Dis* 2000

Acetylator Status of Filipinos

- 93% of Filipinos considered fast acetylators based on an arbitrary INH plasma level <2.5 µg/ml
- Study did not consider confounding factors that may affect INH levels: nutritional status, alcohol consumption, concomitant use of other hepatotoxic drugs, co-morbid illnesses

Maramba NC. *Chest Diseases* 1977; 12

Acetylator Status of Filipinos

- 24 Filipino children with PTB on first line anti-TB meds
- 39% and 22% had slow acetylator status based on presence of 590G to A (NAT2*6) and 857G to A (NAT2*7)
- None developed hepatotoxicity

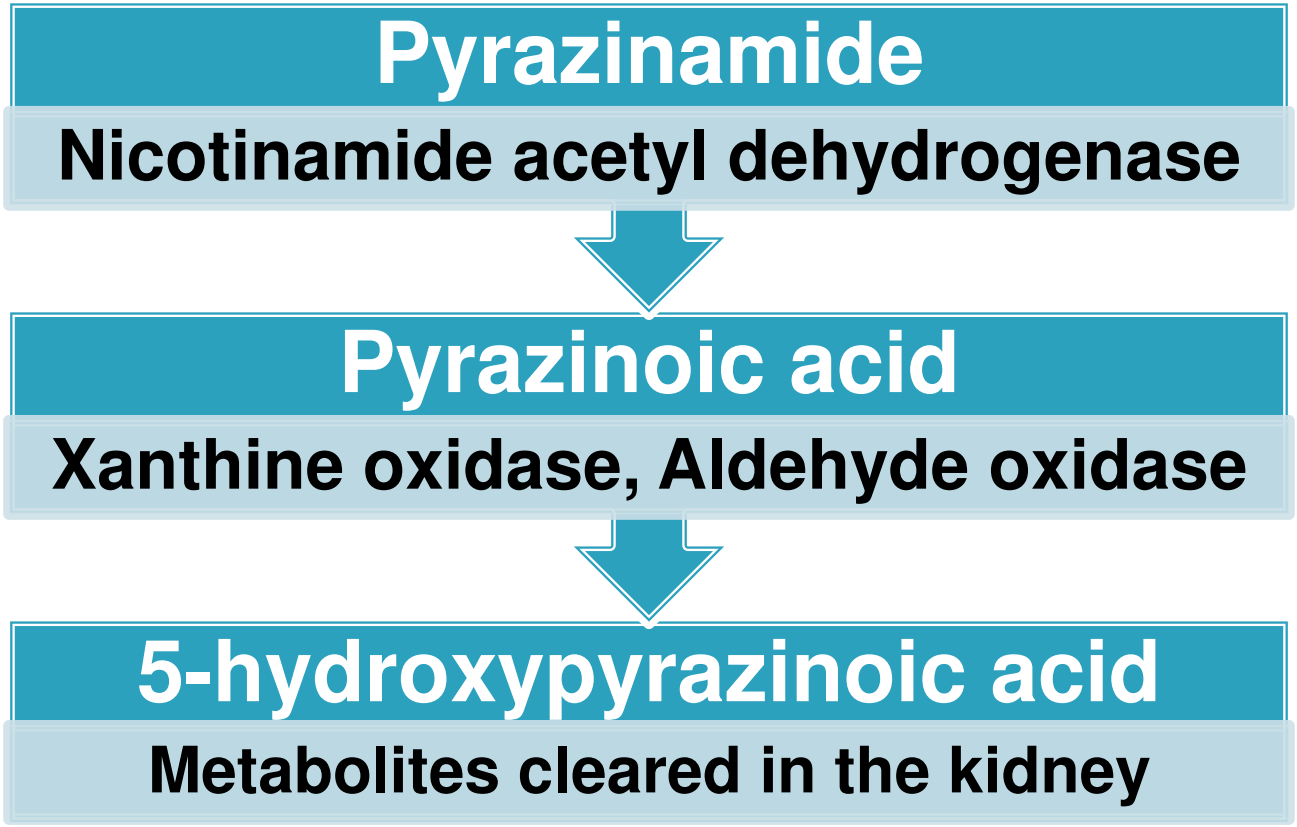
Gregorio GV, Cutiongco-dela Paz E, Gonzales MLM. Acta Medica Philippina 2011; 45

RMP Metabolism & Hepatotoxicity

- RMP interferes with bilirubin uptake or competes with the major bile salt exporter pump for clearance causing jaundice
- RMP induces several enzymes involved in drug metabolism, i.e., cytochrome p450 and UDPG transferases
- Hepatocellular damage may occur when used with INH & PZA

Capelle P *Gut 1972;13*; Grosset *J Rev Infect Dis* 1983;5

PZA Metabolism



Yamamoto T. *Anal Biochem 1987;160*

PZA Metabolism & Hepatotoxicity

- Causes both dose-dependent and idiosyncratic hepatotoxicity
- Alters nicotinamide acetyl dehydrogenase which results in generation of free radical species
- May induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis

Knobel B. *J Clin Gastroenterol* 1997;24

Manifestations of Drug Induced Liver Injury

- Asymptomatic increase in transaminase levels (>3x ULN)
- Acute hepatocellular injury: fever, jaundice, nausea, vomiting, anorexia, lethargy; increase bilirubin and ALT
- Fulminant Liver Failure

WHO Adverse Drug Reaction

Table 1 Definition of hepatotoxicity according to the WHO Adverse Drug Reaction Terminology

WHO definition of hepatotoxicity	
Grade 1 (mild)	<2.5 times ULN (ALT 51–125 U/L)
Grade 2 (mild)	2.5–5 times ULN (ALT 126–250 U/L)
Grade 3 (moderate)	5–10 times ULN (ALT 251–500 U/L)
Grade 4 (severe)	>10 times ULN (ALT > 500 U/L)

ALT, alanine aminotransferase; ULN, upper limit of normal, i.e. 50 U/L.

INH Used As Prophylaxis

- Asymptomatic increase in ALT: 5-10%
- Acute hepatocellular injury: 2/1451 (0.14%) from four studies at INH 10 mg/kg

Beaudry PH 1974; Litt IF1976; Nakajo MM 1989; Palusci VJ 1995; Rapp RS 1978; Spyridis NP1979; Magdorf K1994

INH & RMP at 10mg/kg/day

- Asymptomatic increase in ALT: 12/733 (1.6%) from two studies
- Acute hepatocellular injury: 14/430 (3.3%) in a study in India

O'Brien RJ *Pediatrics* 1983; Ormerod LP *Tuber Lung Dis* 1987; Padmini *J Trop Pediatr* 1993

INH, RMP & PZA

Setting	N	Doses (mg/kg/day)			Duration (months)	Hepatic Adverse Reactions, n(%)
		INH	RMP	PZA		
South Africa	206	10	10	25	6	None
Lucknow India	76	10–15	10–15	20–30		None
Papua NG	639	10–15	10–15	25–35	4	2 (0.3)
Japan	99	4–10	10–20	20–30		8 (8)
South India	1686	12–20	12–20	25–30	Variable	TB men: 39% (with Strep) Spine TB: 10% (with Strep) PTB: 8%

Te Water Naude 2000; Kumar1990; Biddulph 1990; Ohkawa K 2002; c R 1986

Risk Factors for Hepatotoxicity

- Identification of high-risk patients is useful to allow early detection of hepatotoxicity and reduce morbidity and mortality

- Variation in risk factors among different population may explain the observed differences in prevalence of adverse drug reactions

Risk Factors for Hepatotoxicity in Adults

- 421 adult patients with PTB III at PGH
- HRZE treatment
- 41 (9.7%) developed acute hepatocellular injury
- Other side effects: pruritus/exanthema (54%), vomiting (24%), headache (8%)
- Risk factors: age >60yo, history of hepatitis, fixed dose

Fernandez LC Phil J Chest Disease 2003

Risk Factors for Hepatotoxicity in Adults

- 342 patients with PTB III at Veterans Medical Center
- HRZ treatment
- 51 (15%) developed hepatotoxicity
- Risk factor: age >65yo

Anin-Bringas B. Phil J Chest Disease 2003

Risk Factors for Children

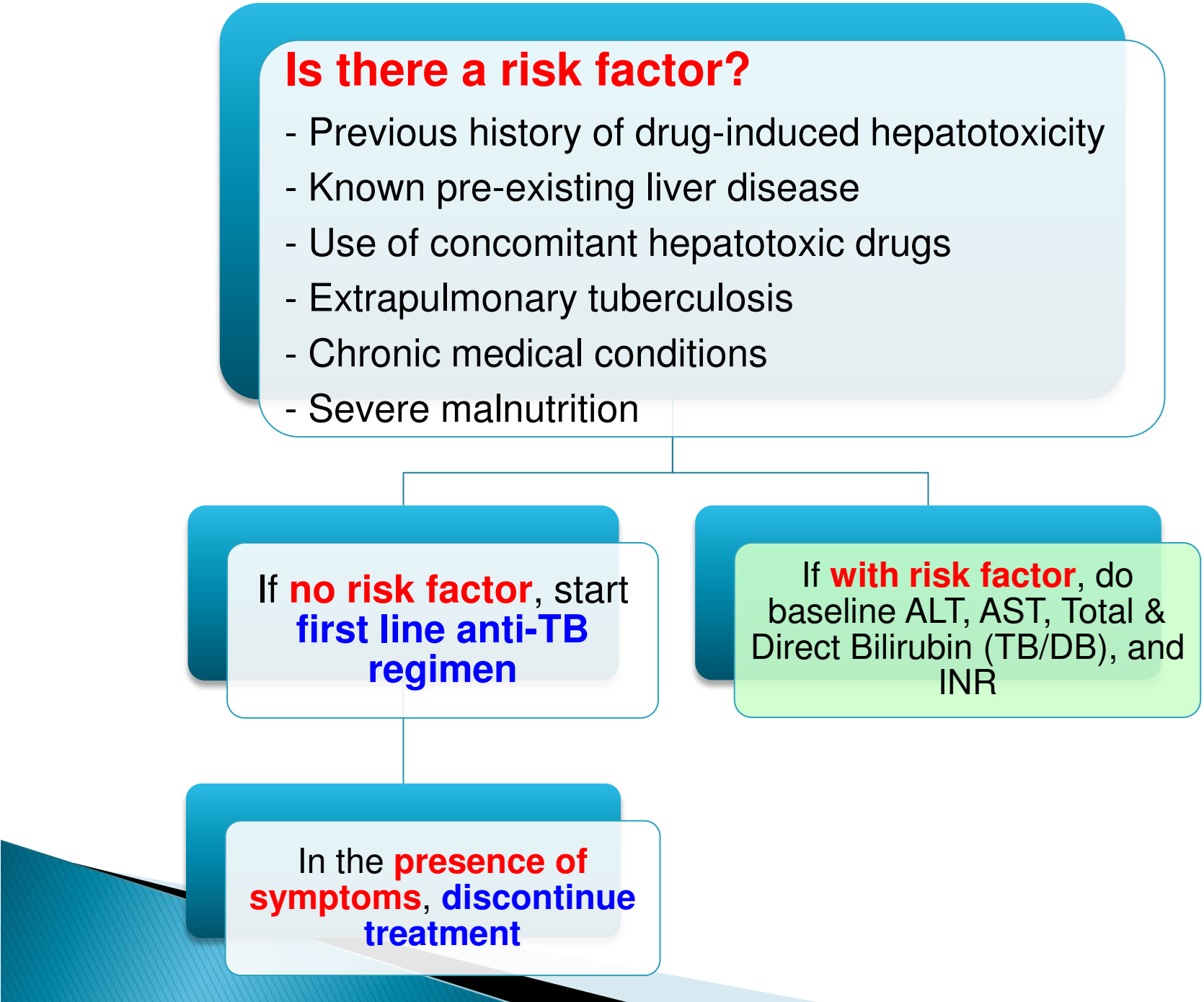
Setting	Study type	Hepatotoxicity, n(%)	Risk factor(s) for Hepatic adverse reactions
Japan	Retrospective	8%	Age<5 years Extrapulmonary TB PZA intake
South India	Prospective	16-39%	TB Meningitis as compared to patients with Spinal or Pulmonary TB
USA	Retrospective	3.3%	Use of INH>15mg/kg/day

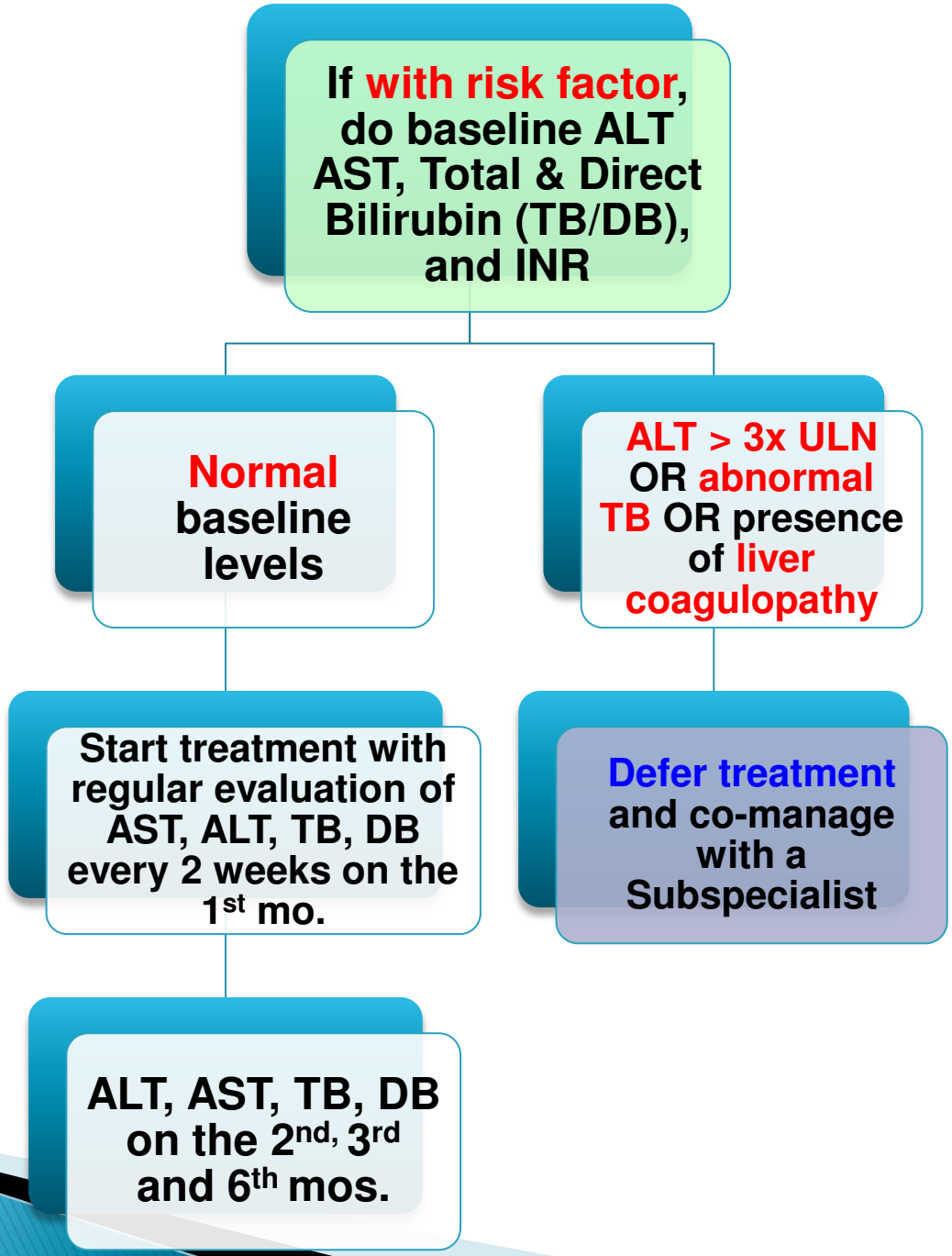
Ohkawa K 2002; Parthasarathy R 1986; O'Brien RJ 1983

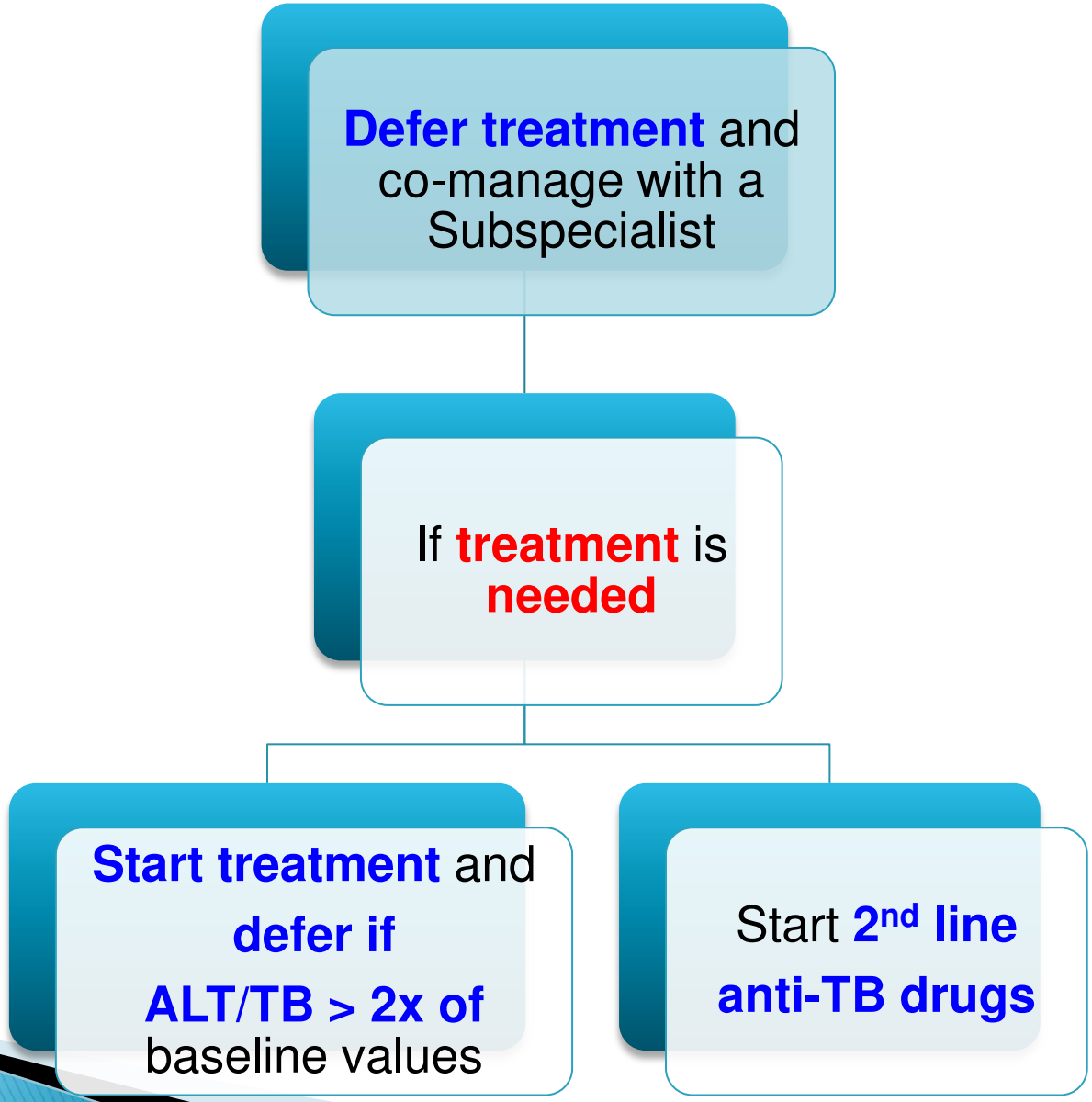
Case Scenario #1

- A previously well 4 year old boy was diagnosed to have TB infection and was prescribed INH at 11 mg/kg/day. On the 3rd month of treatment, he developed fever, abdominal pain, nausea and jaundice. What will you do?

Pre-treatment evaluation


Is there a risk factor?
- Previous history of drug-induced hepatotoxicity
- Known pre-existing liver disease
- Use of concomitant hepatotoxic drugs
- Extrapulmonary tuberculosis
- Chronic medical conditions
- Severe malnutrition
If no risk factor, start first line anti-TB regimen
If with risk factor, do baseline ALT, AST, Total & Direct Bilirubin (TB/DB), and INR
In the presence of symptoms, discontinue treatment


If with risk factor, do baseline ALT AST, Total & Direct Bilirubin (TB/DB), and INR
Normal baseline levels
ALT > 3x ULN OR abnormal TB OR presence of liver coagulopathy
Start treatment with regular evaluation of AST, ALT, TB, DB every 2 weeks on the 1st mo.
Defer treatment and co-manage with a Subspecialist
ALT, AST, TB, DB on the 2nd, 3rd and 6th mos.


Defer treatment and co-manage with a Subspecialist
If treatment is needed
Start treatment and defer if ALT/TB > 2x of baseline values
Start 2nd line anti-TB drugs

Case Scenario #2

- 1/F was diagnosed to have TB Meningitis with communicating hydrocephalus and severe malnutrition
- Given daily doses of INH (15mg/kg), RIF (15mg/kg), PZA (30mg/kg), EMB (20mg/kg) and Phenobarbital (5mg/kg). No baseline LFT was done
- One week after treatment, noted to be jaundiced

Case Scenario #2

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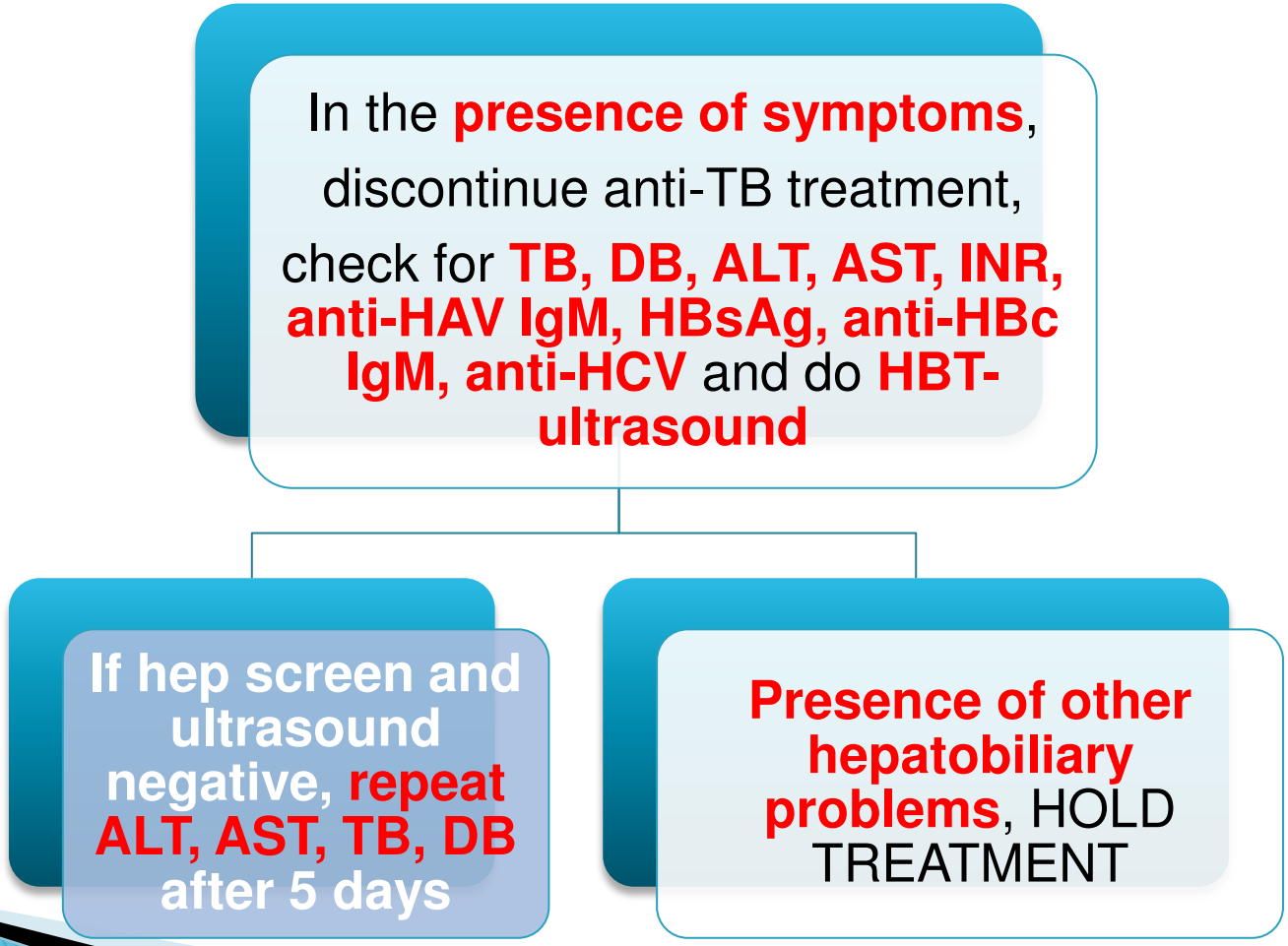
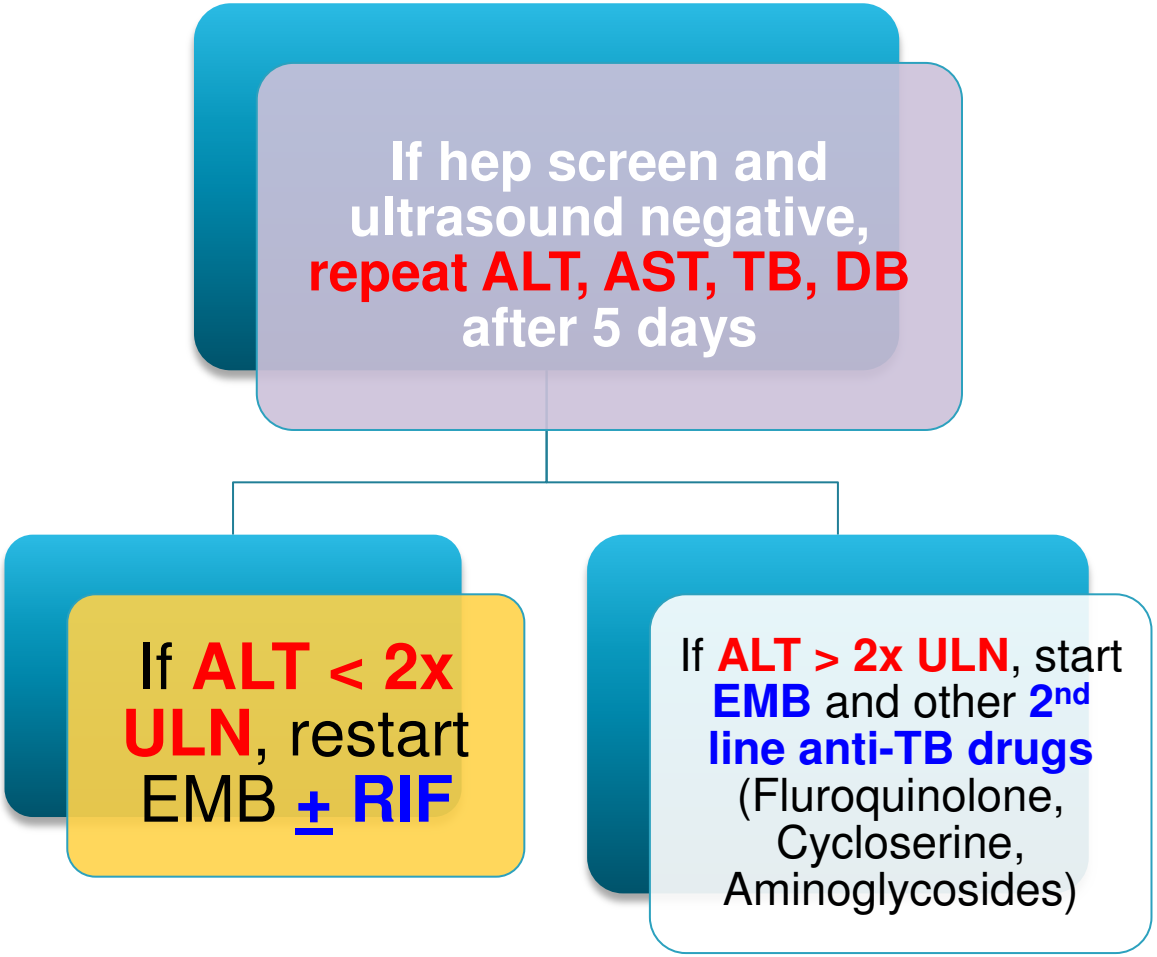
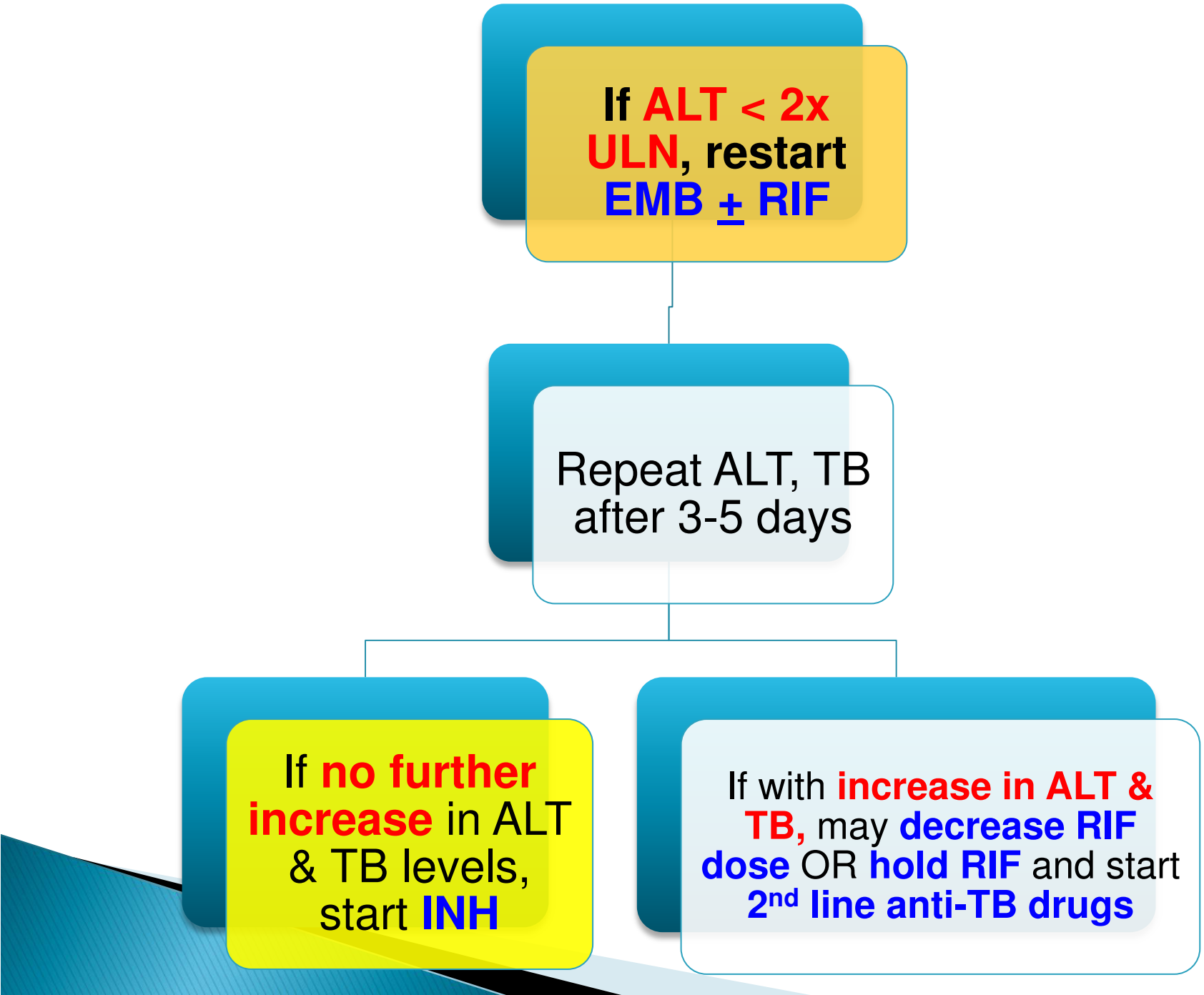
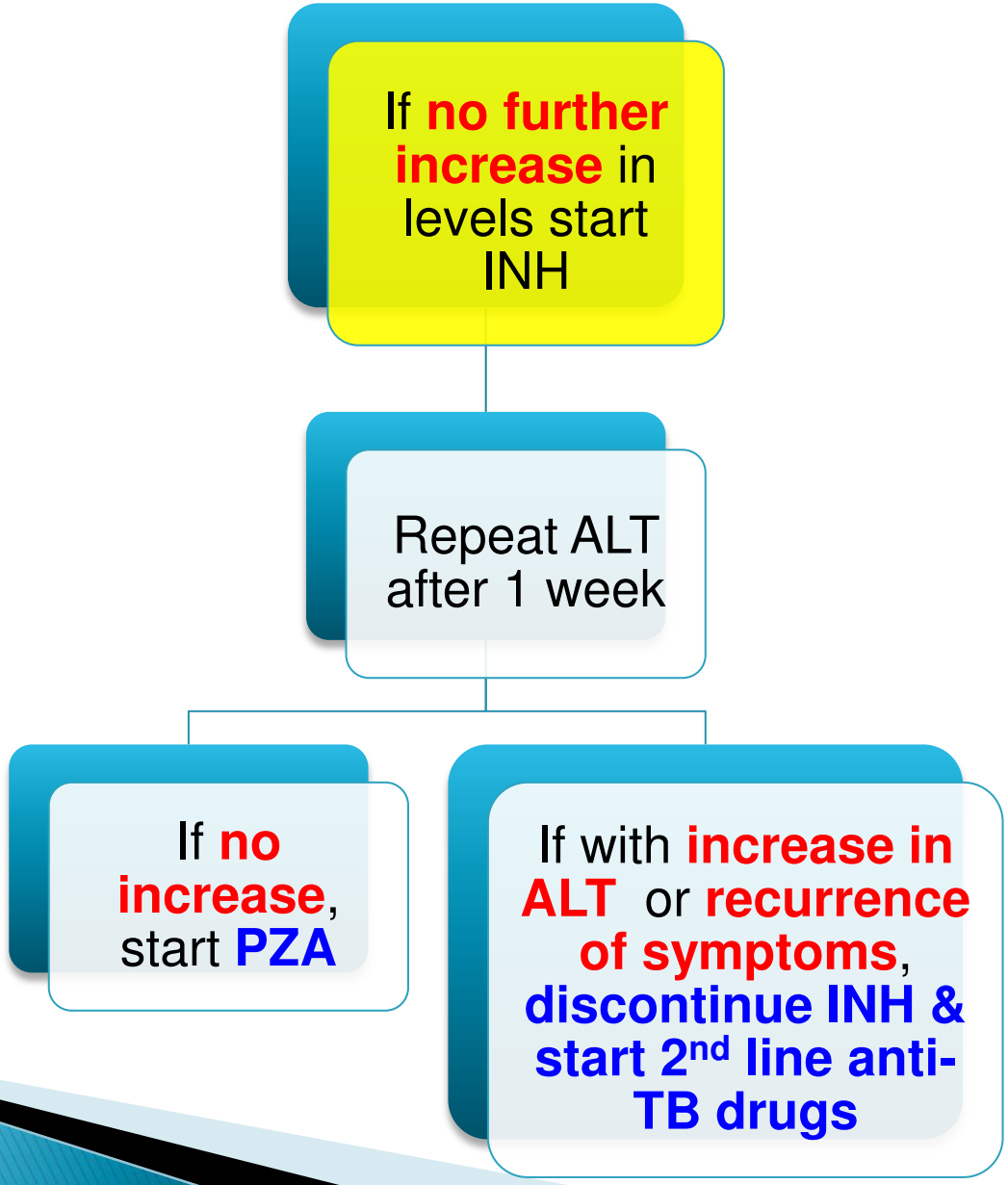
- One week after treatment, noted to be jaundiced

Re-challenge with First Line Anti-TB Drugs




If hep screen and ultrasound negative, repeat ALT, AST, TB, DB after 5 days
If ALT < 2x ULN, restart EMB ± RIF
If ALT > 2x ULN, start EMB and other 2nd line anti-TB drugs (Fluroquinolone, Cycloserine, Aminoglycosides)


If ALT < 2x ULN, restart EMB ± RIF
Repeat ALT, TB after 3-5 days
If no further increase in ALT & TB levels, start INH
If with increase in ALT & TB, may decrease RIF dose OR hold RIF and start 2nd line anti-TB drugs


If no further increase in levels start INH
Repeat ALT after 1 week
If no increase, start PZA
If with increase in ALT or recurrence of symptoms, discontinue INH & start 2nd line anti-TB drugs

Case Scenario #2

- 1/F was diagnosed to have TB Meningitis with communicating hydrocephalus and severe malnutrition
- Given daily doses of INH (15mg/kg), RIF (15mg/kg), PZA (30mg/kg), EMB (20mg/kg) and Phenobarbital (5mg/kg). No baseline LFT was done
- One week after treatment, noted to be jaundiced

- Labs done showed: AST 1231 IU/L (22-58); ALT 280 (10-32) ; TB 2.6mg% (0-2); DB 1.4mg%.
- US of liver and HBT: Normal US of liver, GB, hepatobiliary tract
- HBsAg, anti-HAV IgM, anti-HCV: non-reactive

Hosp Day	1-6
INH	√
RIF	√
PZA	√
EMB	√
Pb	√
ALT	
AST	
TB/DB	

⇩Jaundice

Hosp Day	**1-6**	**7-10**
INH	√	STOP
RIF	√	STOP
PZA	√	STOP
EMB	√	STOP
Pb	√	√
ALT		280
AST		1231
TB/DB		2.6/1.4

⇩Jaundice

Hosp Day	**1-6**	**7-10**	**11**
INH	√	STOP	
RIF	√	STOP	
PZA	√	STOP	
EMB	√	STOP	
Pb	√	√	√
ALT		280	183
AST		1231	211
TB/DB		2.6/1.4	

⇩ Jaundice

Hosp Day	**1-6**	**7-10**	**11**	**15**
INH	√	STOP		
RIF	√	STOP		
PZA	√	STOP		
EMB	√	STOP		
Pb	√	√	√	√
ALT		280	183	74
AST		1231	211	52
TB/DB		2.6/1.4		

⇩ Jaundice

Hosp Day	**1-6**	**7-10**	**11**	**15**	**16-18**
INH	√	STOP			
RIF	√	STOP			
PZA	√	STOP			
EMB	√	STOP			√
Pb	√	√	√	√	√
ALT		280	183	74	
AST		1231	211	52	
TB/DB		2.6/1.4			

⇩ Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19
INH	√	STOP				
RIF	√	STOP				
PZA	√	STOP				
EMB	√	STOP			√	
Pb	√	√	√	√	√	
ALT		280	183	74		37
AST		1231	211	52		22
TB/DB		2.6/1.4				

Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22
INH	√	STOP					
RIF	√	STOP					√
PZA	√	STOP					
EMB	√	STOP			√		√
Pb	√	√	√	√	√		√
ALT		280	183	74		37	
AST		1231	211	52		22	
TB/DB		2.6/1.4					

⇩ Jaundiced

Hosp Day	**1-6**	**7-10**	**11**	**15**	**16 to 19**	**19**	**19 to 22**	**22**
INH	√	STOP						
RIF	√	STOP					√	
PZA	√	STOP						
EMB	√	STOP			√		√	
Pb	√	√	√	√	√		√	
ALT		280	183	74		37		30
AST		1231	211	52		22		13
TB/DB		2.6/1.4						

⇩ Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22	22	23 to 29
INH	√	STOP							√
RIF	√	STOP					√		√
PZA	√	STOP							
EMB	√	STOP			√		√		√
Pb	√	√	√	√	√		√		√
ALT		280	183	74		37		30	
AST		1231	211	52		22		13	
TB/DB		2.6/ 1.4							

⇩ Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22	22	23 to 29	30
INH	√	STOP							√	
RIF	√	STOP					√		√	
PZA	√	STOP								
EMB	√	STOP			√		√		√	
Pb	√	√	√	√	√		√		√	
ALT		280	183	74		37		30		23
AST		1231	211	52		22		13		30
TB/DB		2.6/1.4								

Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22	22	23 to 29	30	30 to 35
INH	√	STOP							√		√
RIF	√	STOP					√		√		√
PZA	√	STOP									√
EMB	√	STOP			√		√		√		√
Pb	√	√	√	√	√		√		√		√
ALT		280	183	74		37		30		23	
AST		1231	211	52		22		13		20	
TB/DB		2.6/ 1.4									

Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22	22	23 to 29	30	30 to 35	35
INH	√	STOP							√		√	√
RIF	√	STOP					√		√		√	√
PZA	√	STOP									√	√
EMB	√	STOP			√		√		√		√	√
Pb	√	√	√	√	√		√		√		√	√
ALT		280	183	74		37		30		23		80
AST		1231	211	52		22		13		20		90
TB/DB		2.6/ 1.4										

Jaundiced

Hosp Day	1-6	7-10	11	15	16 to 19	19	19 to 22	22	23 to 29	30	30 to 35	35
INH	√	STOP							√		√	√
RIF	√	STOP					√		√		√	√
PZA	√	STOP									√	√
EMB	√	STOP			√		√		√		√	√
Pb	√	√	√	√	√		√		√		√	√
ALT		280	183	74		37		30		23		80
AST		1231	211	52		22		13		20		90
TB/DB		2.6/ 1.4										

PZA rechallenge

- If with severe hepatotoxicity, risk of PZA rechallenge might outweigh benefit
- In a cohort of 765 Danish adult patients on HRZ, hepatotoxicity observed in 127 (17%)
- On rechallenge, hepatotoxicity recurred:
  - 6 with INH
  - 1 with INH/RMP
  - 7 with PZA

Dossing M. *Tubercle Lung Dis* 1996

PZA rechallenge

- May extend duration of drug administration of other drugs or give a second line anti-TB drug

Dossing M. *Tubercle Lung Dis* 1996

Summary

- HRZ, first line anti-TB drugs are all potentially hepatotoxic

- Manifestations of liver injury include asymptomatic increase in transaminase; acute hepatocellular injury; fulminant liver failure

- On the first sign or symptom of possible hepatotoxicity, discontinue treatment

Summary

- In the presence of hepatotoxicity, HRZ may be reintroduced individually or if not possible, a 2nd line anti-TB drug could be started
- It is recommended that baseline monitoring of high risk children is done for anticipatory care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