Anti-tubercular treatment & Liver

A double whammy

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Antitubercular Drugs

Potential hepatotoxicity

- First-line Drugs
  - Rifampicin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol
- Second-line Drugs
  - Ethionamide
  - PAS
  - Cycloserine
  - Fluoroquinolones
  - Amikacin/kanamycin/Strepto
  - Terizidone

INH, RIF & Hepatotoxicity

Drug(s)	Clinical hepatitis (%)
INH	0.6
INH plus other drugs but not RIF	1.6
INH plus RIF	2.73
RIF plus other drugs but not INH	1.1
RIF	0

ATS, CDC. MMWR Recomm Rep. 2003

TB in Cirrhosis

- Prevalence of infection
  - 30%
  - 34%
  - Age > 50 yr – 60%
- Prevalence of disease
  - 0.4%
- Incidence
  - 1-2%

WHO Data 1994
Chakraborty AK, IJMR 2004

- Prevalence of disease in cirrhosis
  - 15 times gen population

Baijal R, Trop Doctor 2010

- Incidence in cirrhosis
  - 168 per 100,000 person yrs
  - Gen Population – 10 per 100,000 person years

Thulstrup AM, Epidem Infect 2000

Clinical Manifestations

Patients with cirrhosis

- Unexplained Fever
- Extrapulmonary TB more common in cirrhosis
- Radiographic features
  - Upper lobe involvement and cavitation less common
  - Pulmonary nodules, lymphadenopathy
  - Miliary TB

Yehia BR, Liver Transpl 2010
Cho YJ. Respirology 2007

Clinical Manifestations

- Adenosine deaminase level in peritoneal fluid
  - Useful in the detection in patients without cirrhosis
  - In presence of cirrhosis – Sensitivity is 30%
- Laparoscopic biopsies and ultrasound or CT-guided FNB are often required

Wu HP et al. Respirology 2007
Kim NJ et al. Scan J Infect Dis 2009

Issues

- Liver dysfunction in patients on ATT
  - Define ATT induced hepatotoxicity
  - Guidelines to Stop/modify ATT
  - Risk factors
  - Reintroduction of ATT
- ATT in patients with chronic liver disease (cirrhosis)

ATT induced hepatotoxicity

Definition (ATS/BTS) - Stop rule

- AST/ALT > 5 times ULN irrespective of symptoms

or

- AST/ALT > 3 times ULN with symptoms

or

- Total bilirubin > 2 with AST/ALT > 2 times ULN

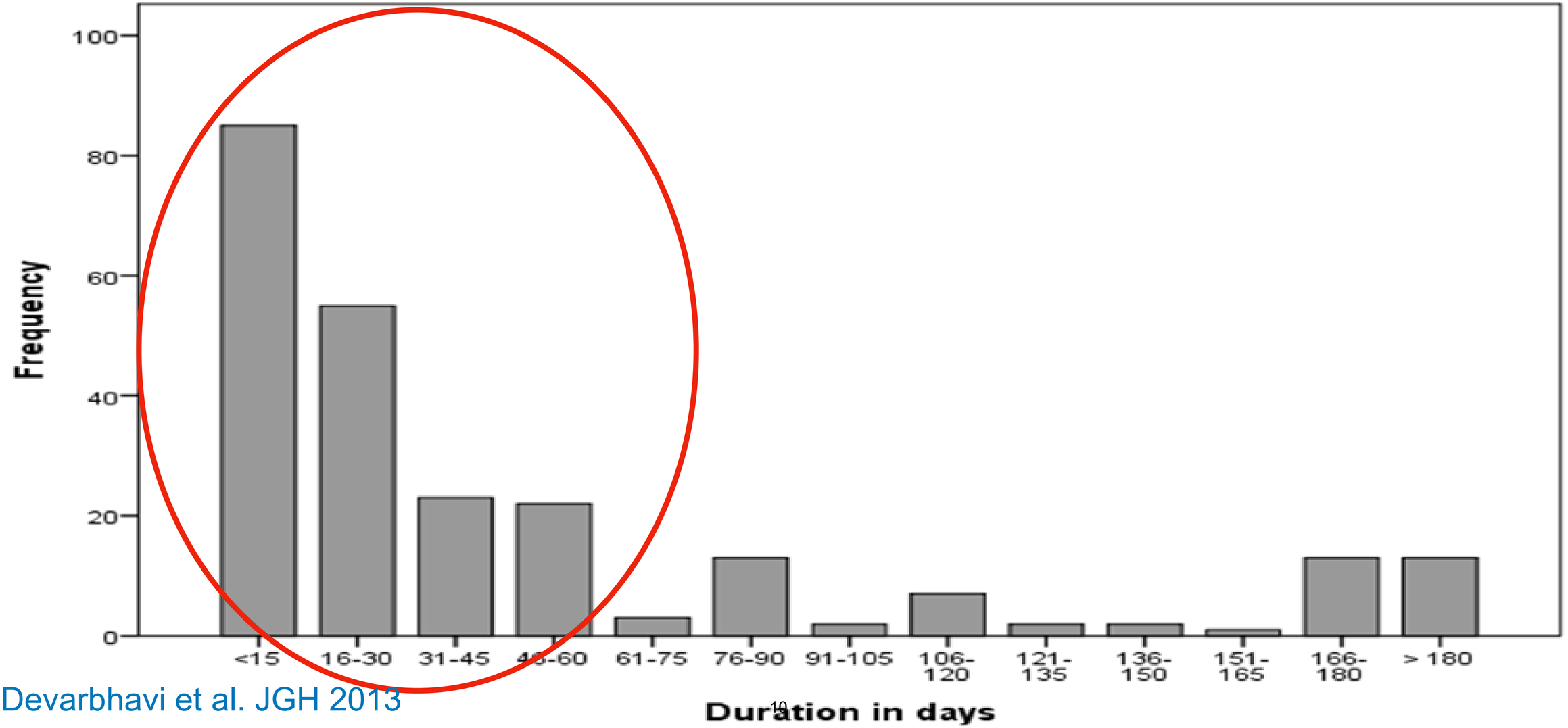
ATT induced hepatoxicity in RHZ regimens

Proportion ATDH (%)	Definition of hepatotoxicity	Risk factors	Population†
2.0[10]	AST > 6× ULN and confirmation by re-challenge	Female sex, advanced age	E 78%, As 17%, Af 4%, NA + SA 1%
2.3[11]	ALT > 5× pretreatment level	Advanced age	As (India, Pakistan) 70%, E 30%
2.6[12]	ALT/AST > 10× ULN	Alcoholism, hepatitis B carriage, other hepatotoxic drugs	E (Spain) 86%, C/SA 14%
3.0[13]	ALT > 3× ULN	Advanced age, female sex, HIV-status, Asian	As 42%, E +C/SA 29%, Af 16%, NA 12%
3.4[14]	ALT > 5× ULN	Female sex	Dutch (94%), non-Dutch (6%)
5.3[15‡]	ALT/AST > 3× ULN	Abnormal baseline values, female sex, advanced age	As (Singapore)
8.1[16]	ALT/AST > 5× ULN	Abnormal baseline liver function, low BMI, hepatitis B/C, other drugs	Not mentioned
10.7[17§]	ALT > 5× ULN	Fluconazole exposure, baseline CD4 < 100 cells/mL, bilirubin >13 mmol/L or ALT >51 U/L	E 60%, Af 34%, other 5%
11.0[18]	ALT/AST > 3× ULN	Advanced age, history of hepatitis, female sex	E 90%, As 6%, Af 3%, SA 1%
13.0[19]	ALT/AST > 5× ULN	HIV infection, Asian	Af 60%, As 15%, E 24%, other 3%
15.0[20,55¶]	ALT > 3× ULN	Advanced age, low BMI, slow acetylator status, CYP2E1 c1/c1 genotype	As (Taiwan)
16.1[21]	ALT/AST > 5× ULN, or any increase + symptoms	Advanced age	As (India)
19.0[22]	ALT/AST > 3× ULN	HIV or hepatitis C infection	Not mentioned
27.7[23]	ALT > 3× ULN with or > 5× ULN without symptoms	No significant risk factors	Iran
ND[24††]	AST > 3× ULN	Advanced age, high alcohol intake, slow acetylators	As (India)

Tostmann et al. J Gastoenterol Hepatol 2008

ATT induced hepatotoxicity

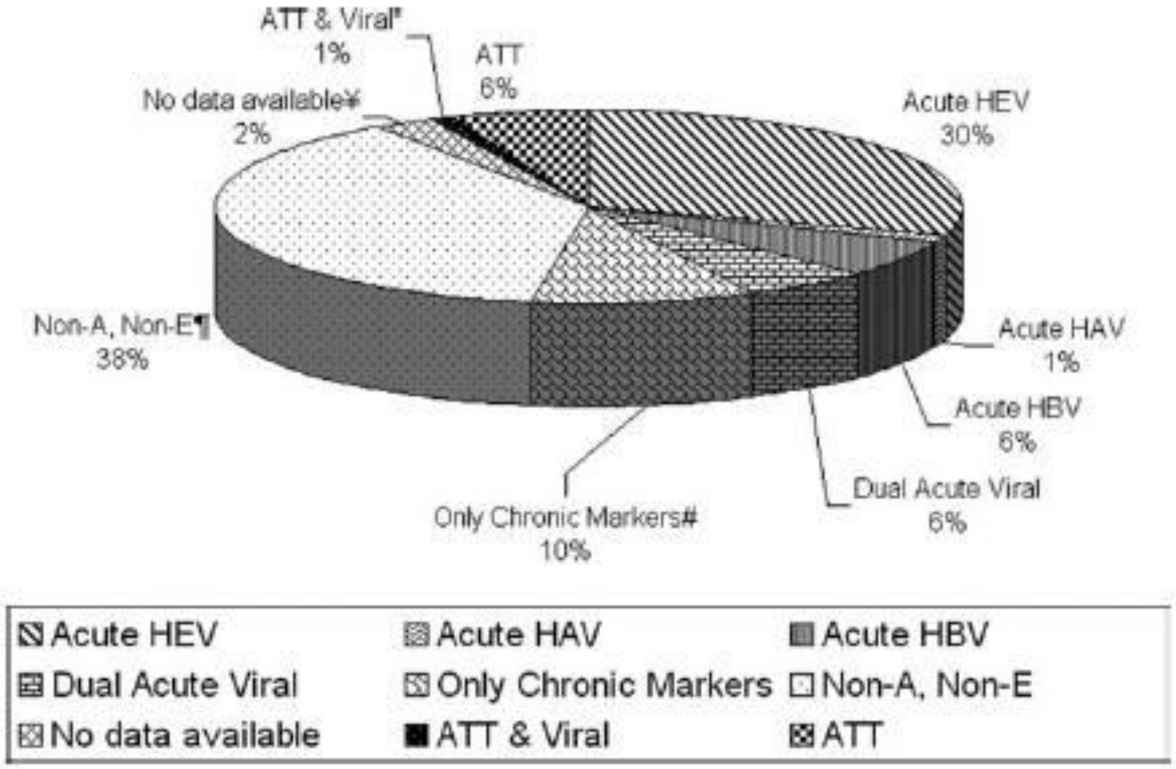
Timing



Devarbhavi et al. JGH 2013

Antituberculosis Therapy–Induced Acute Liver Failure: Magnitude, Profile, Prognosis, and Predictors of Outcome

Ramesh Kumar,[1] Shalimar,[1] Vikram Bhatia,[1] Shankar Khanal,[2] V. Sreenivas,[2] S. Datta Gupta,[3] Subrat K. Panda,[3] and Subrat K. Acharya[1]

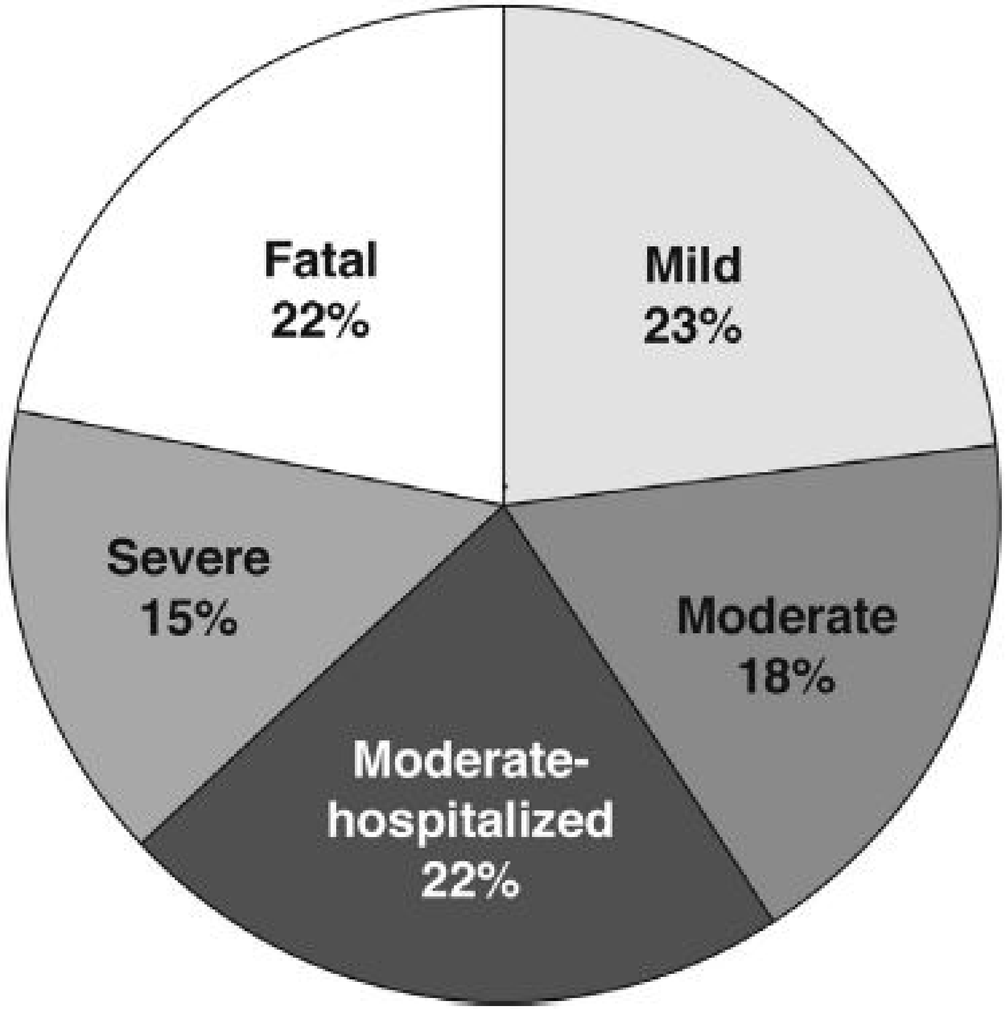


- n= 1223 cases of ALF
  - ATT alone as a cause in 70 (5.7%)
  - ATT + viral hepatitis in 15 (1.2%)
- Median duration of ATT before ALF: 30 (7-350) days
- Mortality 67.1%, (n=5 47)

Hepatology 2010;51: 1665-74

Under-reporting and Poor Adherence to Monitoring Guidelines for Severe Cases of Isoniazid Hepatotoxicity

Paul H. Hayashi,* Robert J. Fontana,‡ Naga P. Chalasani,§ Andrew A. Stolz,‖



- 60 pts who developed liver injury during INH therapy for latent TB
- 13 (22%) developed ALF
- Delay in stopping INH carries a more severe outcome
- 9/13 pts who continued to take INH for >7 days after meeting ATS criteria for stopping died died

Clin Gastroenterol Hepatol 2015

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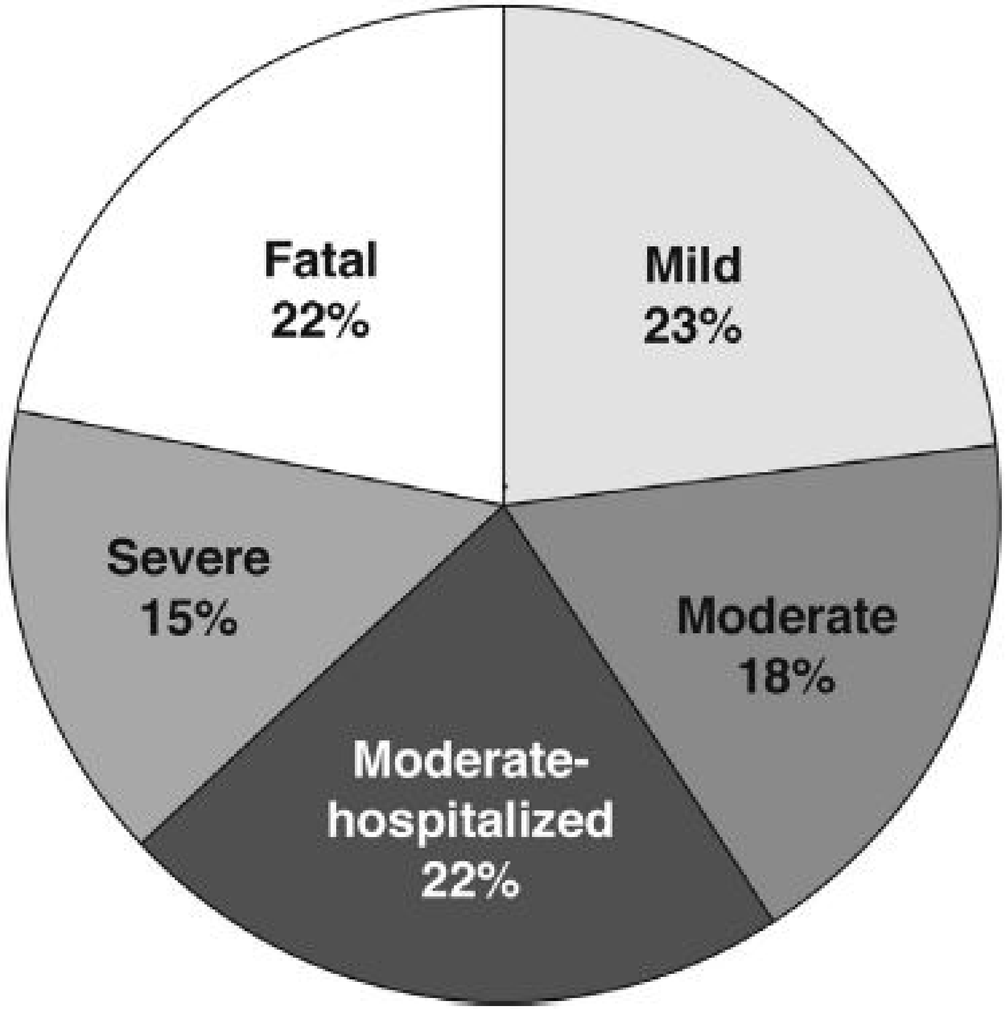

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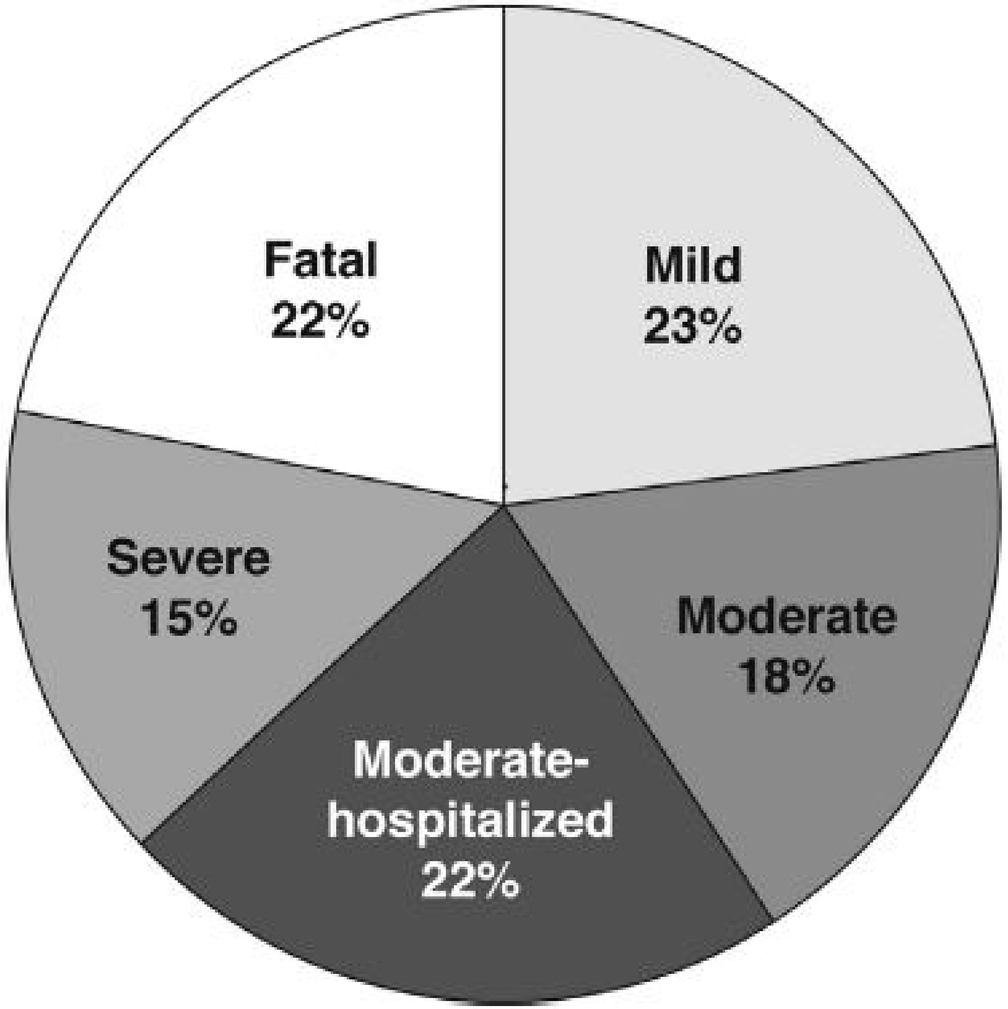

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ATT induced hepatotoxicity

Clinical risk factors

- Demographic factors
  - Advanced age >60 years
  - Female gender
- HIV coinfection
  - Altered drug metabolism
  - ART drugs like Nevirapine
  - Coexistent Fatty liver (HAART)
- Malnutrition
- Alcoholism
- Pre-existing liver disease
  - Lower hepatic metabolism
  - HBV and HCV coinfection

ATT induced hepatotoxicity

Molecular risk factors

- NAT2 slow acetylators
- CYP 450 polymorphisms
- Glutathione -S-transferase M1 null mutation
- Glutathione -S-transferase T1 null mutation

ATT induced hepatotoxicity

Prevention

- Identify patients with high risk factors
- Avoid PZA (add floxacin instead)

ATT induced hepatotoxicity

Restarting ATT

- When to reintroduce - AST/ALT < 2 ULN
- How to reintroduce
  - Different guidelines from ATS, BTS & Task Force of European Respiratory society

BTS Guidelines

Reintroduction of ATT

INH 50mg/day→ 300 x 2-3 days

↓

Rifampicin 75 →450/600

↓

Pyrazinamide 250 →1.5 g(<50 kg)/2 g(>50 kg)

British Thoracic Society *Thorax* 1998;**53**:536–548

American Thoracic Society Documents

American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis

- Restart when AST < 2 times
- R→ after 1 week H → after 1 week PZA
- If pt had severe hepatitis→ avoid PZA
- If symptoms recur or AST increases, the last drug added should be stopped.

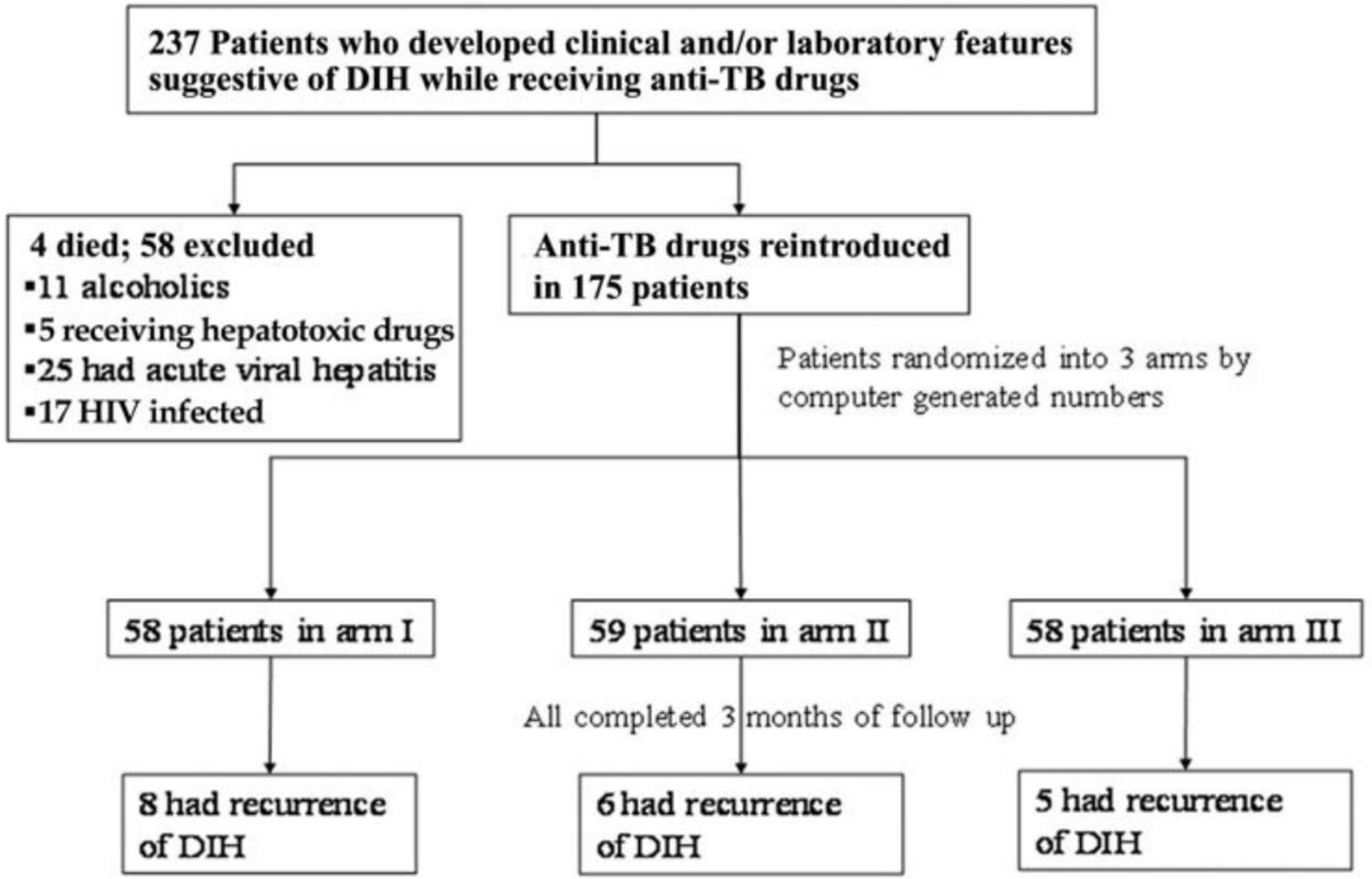
American Thoracic Society guidelines 2003

Safety of 3 Different Reintroduction Regimens of Antituberculosis Drugs after Development of Antituberculosis Treatment–Induced Hepatotoxicity

Surendra K. Sharma,[1] Rohit Singla,[1] Pawan Sarda,[1] Alladi Mohan,[6] Govind Makharia,[2] Arvind Jayaswal,[3] Vishnubhatla Sreenivas,[4] and Sarman Singh[5]

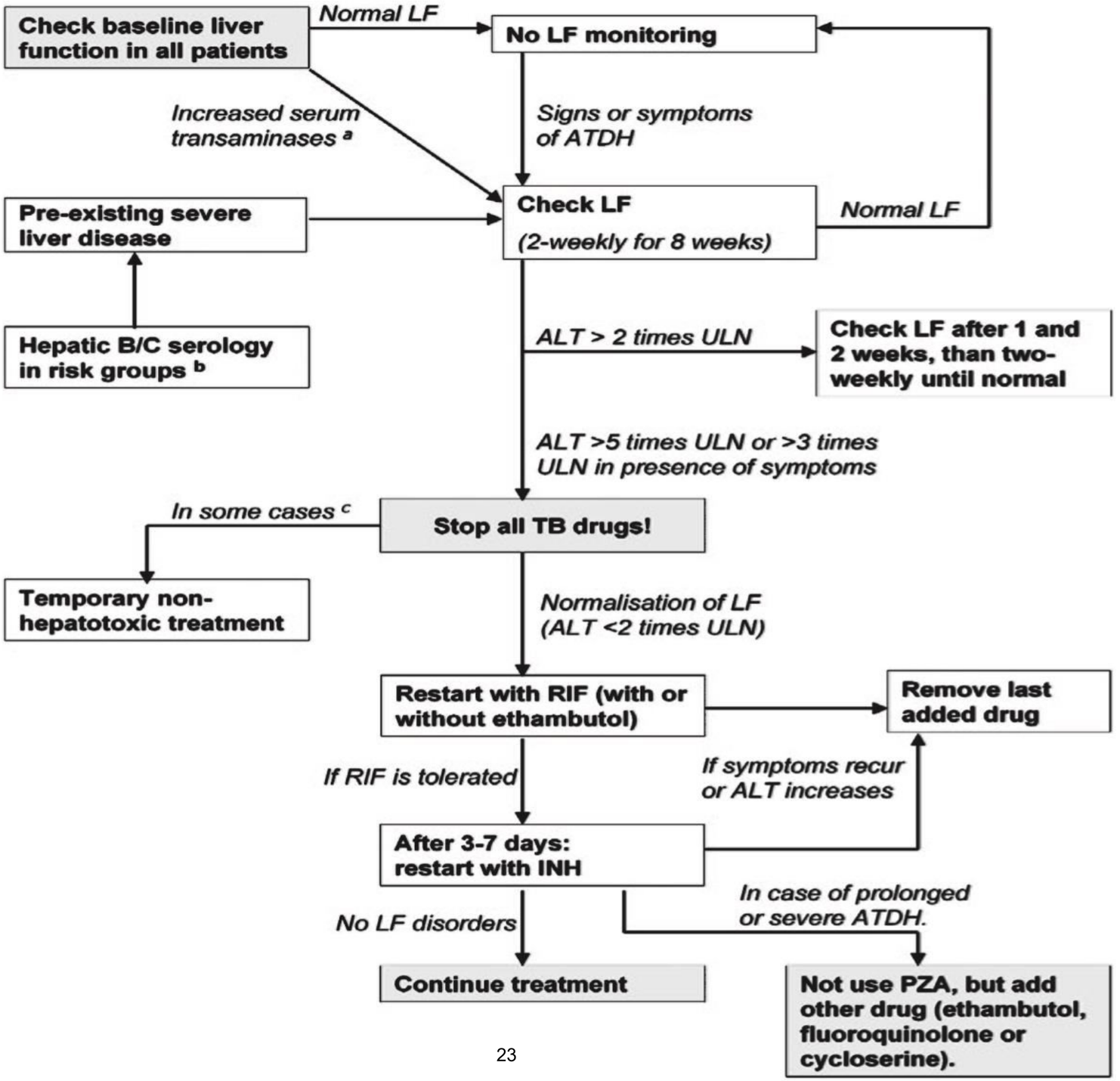
- n=175 patients with ATT hepatitis
- Three different regimen for reintroduction of ATT drugs
  - Arm I: H,R and Z at max doses on day 1
  - Arm II: R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15
  - Arm III: H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18

Sharma et al. CID 2010;50: 833



- The recurrence rate of hepatotoxicity similar in the 3 groups.
- All 3 of the potentially hepatotoxic drugs (HR & Z) can be reintroduced simultaneously at full dosage safely from day 1

Sharma et al. CID 2010;50: 833


Check baseline liver function in all patients
Normal LF
No LF monitoring
Increased serum transaminases a
Signs or symptoms of ATDH
Pre-existing severe liver disease
Check LF
(2-weekly for 8 weeks)
Normal LF
Hepatic B/C serology in risk groups b
ALT > 2 times ULN
Check LF after 1 and 2 weeks, than two-weekly until normal
ALT >5 times ULN or >3 times ULN in presence of symptoms
In some cases c
Stop all TB drugs!
Temporary non-hepatotoxic treatment
Normalisation of LF (ALT <2 times ULN)
Restart with RIF (with or without ethambutol)
Remove last added drug
If RIF is tolerated
If symptoms recur or ALT increases
After 3-7 days: restart with INH
In case of prolonged or severe ATDH.
No LF disorders
Continue treatment
Not use PZA, but add other drug (ethambutol, fluoroquinolone or cycloserine).

ATT in cirrhosis

Basic principles

- Altered handling & clearance of ATT is expected in cirrhosis
- Increased risk of drug induced hepatitis
- Higher DILI with INH/RIF/PZA in advanced liver disease.
- PZA is considered to be the most hepatotoxic. (frequency is less than INH or RIF, but more severe and prolonged)
- Isoniazid and rifampicin combination is more toxic than either drug alone

Recommendations

Prevention in cirrhosis

CTP	Treatment	Duration
≤7	2 hepatotoxic drugs (No PZA)	9 months
7-11	1 hepatotoxic drugs (RIF>>INH)	12-18 months
≥11	No hepatotoxic drug	18-24 months

Dhiman RK et al. JCEH 2012

ATT induced hepatotoxicity

Definition in cirrhosis

- Schenker et al[1]: AST, ALT levels > 50-100
- Saigal et al[2]: AST, ALT > 5 times of baseline or > 400 IU/L or Bil ↑ > 2.5
- Sharma et al[3]:
  - If baseline normal: AST, ALT > 3 times
  - If baseline abnormal: AST, ALT > 2 times or an absolute ↑ of Bil > 2 mg/dl from baseline

1. Schenker et al. J Hepatol 1999; 31: 1088-97
2. Saigal et al. J Gastroenterol Hepatol 2001; 16: 1028-32
3. Sharma et al. J CEH 2015; 5: 8-13

Reintroduction of ATT

Cirrhosis patient

- Hepatotoxic ATT is contraindicated in those with life-threatening hepatotoxic effects (ALF, ACLF, underlying decompensated disease)
- In other cases, restart once AST/ALT < 2 times ULN
- Add RIF before INH (less hepatotoxic)

Summary

- ATT hepatotoxicity is reported ranging from 2-28%
- ATT induced ALF has very high mortality
- Screen & diagnose hepatotoxicity early to prevent transition to ALF
- Sequential reintroduction of R fb H (avoid Z if severe hepatitis)
- No PZA in patients with cirrhosis
- Use R or RH (+E & Levoflox) depending on severity of liver disease

Thank you