Hepatotoxicity

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Overview

- INH, Rifampin, and PZA all are associated with DILI (drug-induced liver injury)
- Only one case of DILI has been reported for Ethambutol
- Fluoroquinolones are rare causes of DILI
- Risk of DILI in active TB treatment studies ranges from 5 to 33%

INH

- Probably the most common cause of TB DILI
- Age related, ?pregnancy related, daily ETOH may increase risk 4 fold
- Concomitant use of Rifampin increases the risk

Rifampin

- Occasionally causes interference with bilirubin uptake resulting in sub-clinical or overt jaundice. This may be transient.
- Rarely causes hepatocellular injury when used alone
- Meta-analysis of INH + Rifampin estimated a risk of DILI of 2.55%
- Rifapentine is similar, but rifabutin has < risk

PZA

- When used with rifampin, EMB, or a fluoroquinolone for treatment of LTBI, DILI has been reported in 18-58% of cases
- When used as part of RIPE, incidence much lower
- Dose and duration dependent
- Can induce DRESS syndrome or granulomatous hepatitis

Approach to patient with DILI

- Stop meds! if AST/ALT > 5X normal if asymptomatic, and >3X normal if symptomatic
- For fulminant disease, consider N-acetyl cysteine
- Consider other causes of hepatotoxicity
- Follow AST/ALT weekly and when < 2X normal, rechallenge

Rechallenge after DILI

- Begin Ethambutol + INH *or* Rifampin
  - Pattern and timing of LFT abnormalities can help
  - In most cases it will be EMB + Rif
- Allow 3-5 days before adding in next drug
- PZA should generally be added last and you may decide not to rechallenge.

High Risk for DILI

- Chronic ETOH, chronic hep B/C, hx. of abn. LFTs, taking other hepatotoxic meds, +/- pregnant/ 3 mos. postpartum
- Initiate standard RIPE, but follow closely (q 2-4 weeks) with ALT/AST

Pre-existing liver dysfunction

- Caveat: Abnormal LFTs in disseminated TB can be related to the TB and will improve with standard RIPE
- Baseline LFTs > 3X upper limit of normal (ULN)
  - strongly consider use of regimen with 2, not 3 hepatotoxic drugs: INH/Rif/EMB, PZA/RIF/EMB
- Presence of cirrhosis
  - strongly consider use of only one hepatotoxic drug: Rif/EMG/and +/- levo, moxi, or cycloserine

Pre-existing liver dysfunction

- Presence of active, acute hepatitis (ETOH or viral) or hepatic encephalopathy
  - Initiate treatment with EMB, fluoroquinolone, and injectable (usually Strep but can use Amikacin or Capreomycin) +/- cycloserine
  - If and when LFTs normalize to < 2 ULN, add in standard drugs as tolerated