TB drug-induced Hepatotoxicity: Rechallenge regimen

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- This rechallenge regimen is based on the regimen designed by Prof G Maartens and used by the adult ID service at GSH
- The GSH regimen is based on the regimen of the American Thoracic Society, which rechallenges anti-TB drugs at full doses (Reference: Am J Crit Care Med 2006;174:935-52)
- TB drug-induced hepatitis is over-diagnosed. The case definition is “Transaminases more than 5-fold elevated or more than 3-fold elevated with symptoms / jaundice”
- If TB drug-induced hepatitis is present anti-tuberculosis therapy should be discontinued.
- The basis for the TB diagnosis should be reviewed. If there are reasonable grounds for diagnosing TB then (1) in patients with extensive or severe TB disease or those in whom resolution of the hepatotoxicity is slow, a full background regimen (3 drugs) should be initiated using drugs with low / no hepatotoxic potential (refer below); (2) alternatively if TB disease is mild and there is rapid resolution of the hepatotoxicity, background therapy of ethambutol and levofloxacin / moxifloxacin can be initiated prior to “Day 1” of the rechallenge.
- Patients should only be rechallenged only once the symptoms of hepatitis have resolved, bilirubin levels have returned to normal and transaminases have decreased to <100.
- Rechallenge with pyrazinamide was previously not recommended. A recent trial has shown that most patients do tolerate pyrazinamide. Hence PZA rechallenge should be considered in patients with severe TB (e.g. military TB, TBM, or drug-resistant TB).
- Rechallenge is not recommended for those who have had fulminant hepatitis (defined as hepatic encephalopathy with coagulopathy)
- Transaminase concentrations, especially ALT should be monitored frequently (e.g. 3 times per week) during rechallenge, and every 2 weeks for a month following successful rechallenge.
- If possible all patients with drug-induced liver injury should have their TB isolates sent for drug susceptibility testing. Do not rechallenge with an agent to which the isolate is resistant

**Background therapy:** Ethambutol, levofloxacin or moxifloxacin ± amikacin

**Day 1:** Add rifampicin at full dose*

**Day 3 or 4:** Check ALT

**Day 5:** If ALT still within acceptable limits add isoniazid at full dose*

**Day 8 or 9:** Check ALT:

**Day 10:** Consider adding pyrazinamide (refer above for indications)

**Duration of TB therapy:** Should be individualised after rechallenge – consult with ID service for advice.

The following are guidelines

- Pyrazinamide not rechallenged / not tolerated: stop levofloxacin or moxifloxacin ± amikacin*, continue isoniazid, rifampicin and ethambutol for total duration 9 months
- Rifampicin not tolerated: stop ± amikacin, continue levofloxacin/moxifloxacin, ethionimide, isoniazid, and ethambutol for total duration of 18 months
- Isoniazid not tolerated: stop levofloxacin or moxifloxacin ± amikacin, add ethionamide to rifampicin and ethambutol for total duration 12 months

**Notes**

* Amikacin only initiated if the child required a full liver-sparing regimen prior to the rechallenge
*If rifampicin or isoniazid not tolerated, ethionimide at full dose should be added to the rechallenge