# DRUG-INDUCED LIVER INJURY (DILI)

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# Pendahuluan

- Hati merup Organ utama yang mempertahankan lingkungan internal tubuh
  - Tempat yg dilalui oleh bbg nutrient
  - Terlibat dlm hampir semua jalur biokimiawi utk pertumbuhan, suplai nutrien, menyimpan energi, melawn penyakit dan reproduksi
  - Mengontrol metab KH, protein dan lemak
- DILI disebabkan oleh :
  - Antibiotik
  - Obat OTC (obat yg dijual bebas)
  - Herbal
  - Suplemen
- Obat = penyebab utama jejas hati
- > 900 obat, toksin, dan herbal yg telah dilaporkan menj adi penyebab jejas hati

# Epidemiologi

- 0,1-3 % MRS (Dig Dis Sci 2007;52:2463-71 )
  - 600 transplantasi hati /tahun di US
- 10% fatal dg *severe ALT elevation and jaundice* (Kaplowitz N. Nat Rev Drug Discov 2005;4:489-499)
- Annual incidence : 10-15 / 10,000 - 100,000 people
- 30% kasus : acute hepatitis
- Penyebab terbanyak *acute liver failure* di US

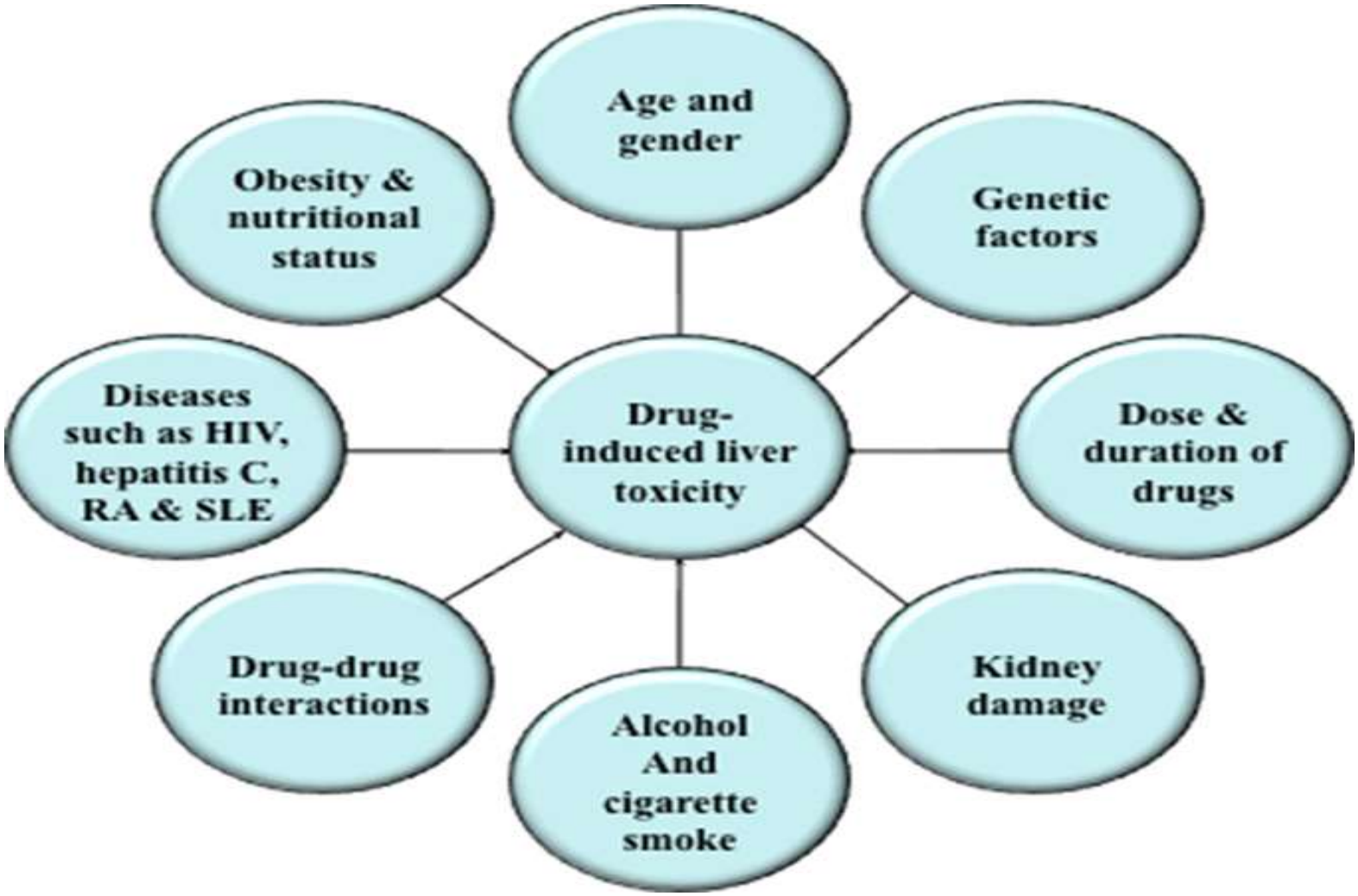
# Metabolisme Obat Di Hati

- Fase 1 – Oksidasi
  - 60 kode gen utk CYP (family-mis CYP2, subfamily- mis CYP2E1)
  - Metab obat di hati- CYP1, 2, 3, and lesser extent 4
  - CYP3A4- 60% dari semua sitokrom hepatik, mempengaruhi 50% obat yg biasa digunakan
  - Aktivitas enzyme tergantung pada bbrp faktor eksogen

# Metabolisme Obat Di Hati

- Fase 2 – konjugasi
  - (UDP)-glucuronyl transferases (UGT1, & UGT2)
  - Sulfotransferases
  - Glutathione S-transferases
  - Menurunkan / menghentikan aktiviatas farmakologis
  - Meningkatkan clearance

# Faktor yg Mempengaruhi DILI



# Faktor yg Mempengaruhi DILI

- Farmakogenetik
  - Polimorfisme enz fase 1, 2, 3 -adanya variasi genetik yang menyebabkan perbedaan aktivitas dan kapasitas suatu enzim dalam menjalankan fungsinya, mis.
    - N-asetiltransferase -INH
      - >>> -asetilator cepat (org Jepang dan eskimo)
      - <<< - asetilator lambat (Amerika dan Eropa) - efek toksik lbh tinggi
- Nutrisi
  - Puasa, malnutrisi, obesitas
    - Ekspresi CYP2E1 ↑ pd obesitas, intake tinggi lemak dan puasa
    - Malnutrisi-resiko DILI asetaminofen ↑

# Faktor yg Mempengaruhi DILI

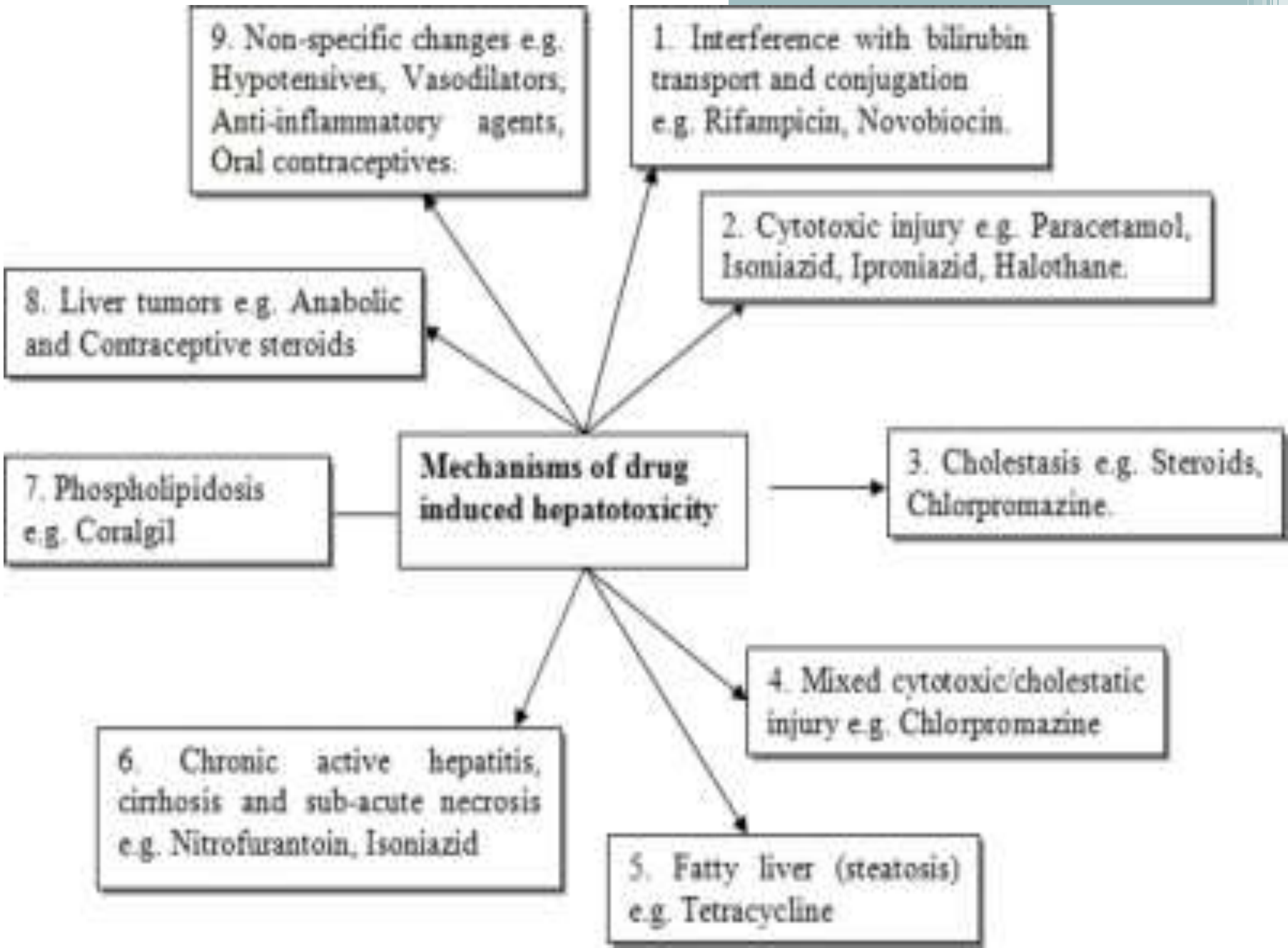
- Multi-drug effect
  - Kompetisi Fase 2 : glukoronidasi dan sulfatasi
    - Fenitoin – me ↓ dosis asetaminofen-induced hepatotoxicity
  - Kompetisi fase 3
    - Atorvastatin, Carvedilol, Sertralin – inhibisi transporter – me ↑ resiko toksik
    - Amiodaron, Diltiazem, Eritromisin, dan St John's wart – induksi transporter
- Usia dan jenis kelamin
  - Dewasa - ekspresi  bbrp CYP ↓ 10% dg pertambahan usia
  - Ekspresi CYP3A4 dan 2E1 pria ≠ wanita
- Dosis dan lama pemakaian

# Faktor yg Mempengaruhi DILI

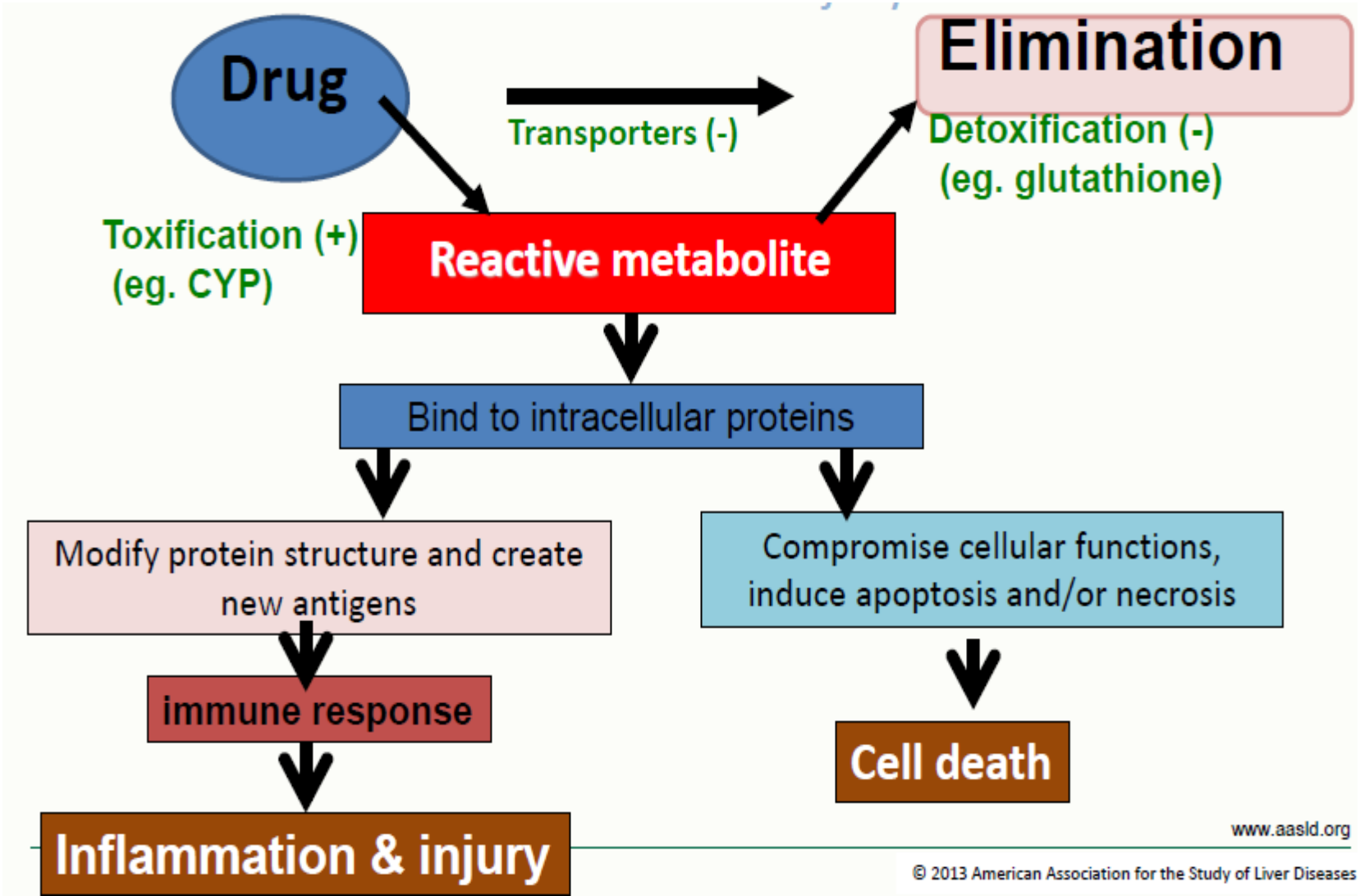
- Penyakit – merubah ekspresi CYP
  - DM – CYP2E1 ↑
  - Hipotiroid – CYP3A4 ↓
- Gangguan fungsi hati (sirosis)
  - Me ↓ jml CYP 450
  - Me↓ klirens hepatik

# Mekanisme DILI

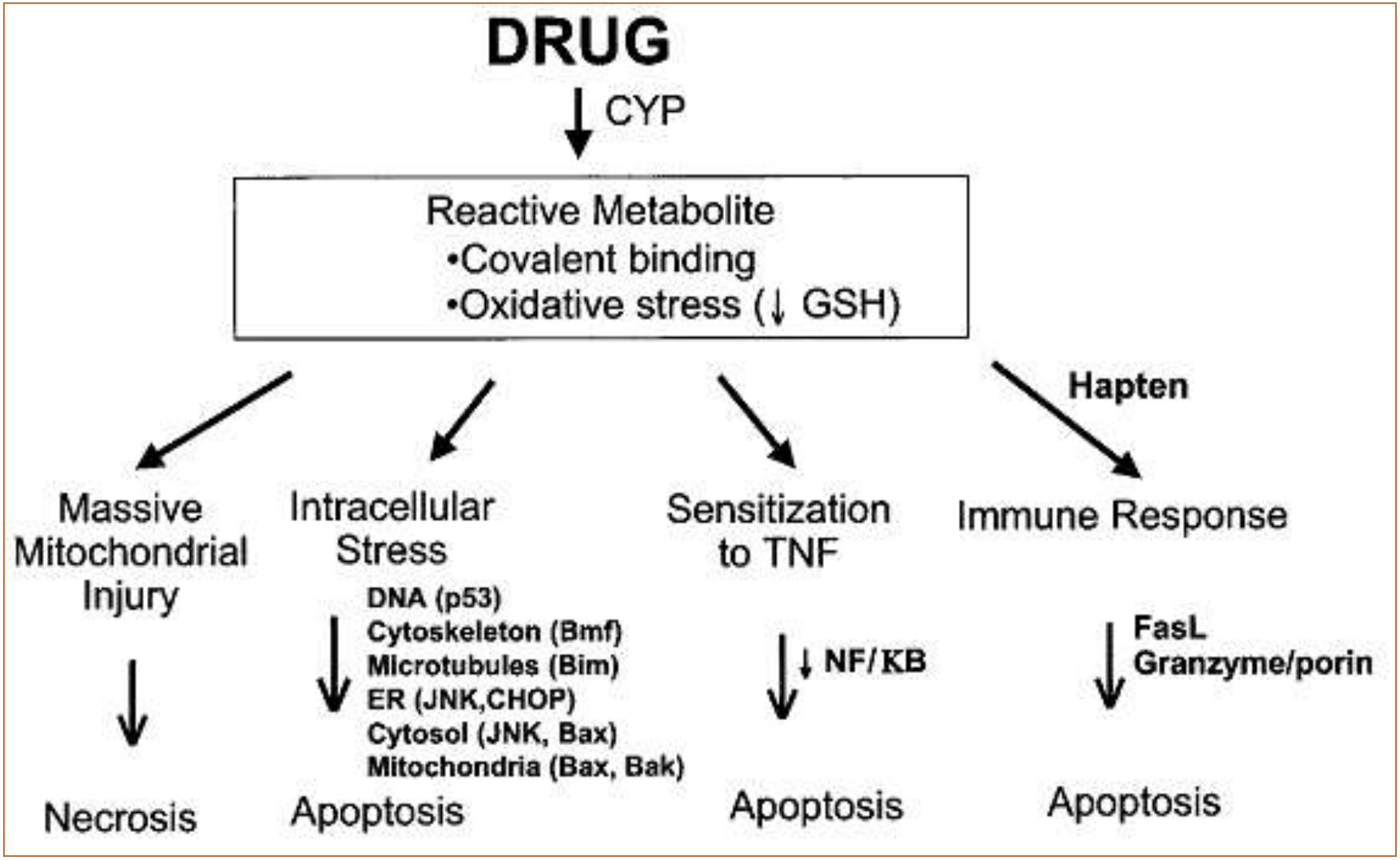
- Jejas intrinsik (jejas langsung atau tdk langsung pd hepatosit) - Hepatocellular (cytotoxic) injury
  - Jejas langsung – terjadi ikatan kovalen dg makromolekul seluler- mis Tylenol, $CCl_4$, Chloroform, Phosphorus
  - Modulasi (induksi/inhibisi) transporter obat atau enzim yg memetabolisme - me ↑ konsentrasi metabolit reaktif dlm hepatosit
  - Toksisitas pd mitokondria - deplesi cadangan ATP – kematian sel
- Hambatan Bile Acid Export Pump (BSEP) – cholestatic injury
- Asetilasi histon – hambat transkripsi DNA – hambat regenerasi sel
- Mixed injury


9. Non-specific changes e.g. Hypotensives, Vasodilators, Anti-inflammatory agents, Oral contraceptives.
1. Interference with bilirubin transport and conjugation e.g. Rifampicin, Novobiocin.
2. Cytotoxic injury e.g. Paracetamol, Isoniazid, Iproniazid, Halothane.
8. Liver tumors e.g. Anabolic and Contraceptive steroids
7. Phospholipidosis e.g. Coralgil
Mechanisms of drug induced hepatotoxicity
3. Cholestasis e.g. Steroids, Chlorpromazine.
4. Mixed cytotoxic/cholestatic injury e.g. Chlorpromazine
6. Chronic active hepatitis, cirrhosis and sub-acute necrosis e.g. Nitrofurantoin, Isoniazid
5. Fatty liver (steatosis) e.g. Tetracycline

# Hepatocellular injury



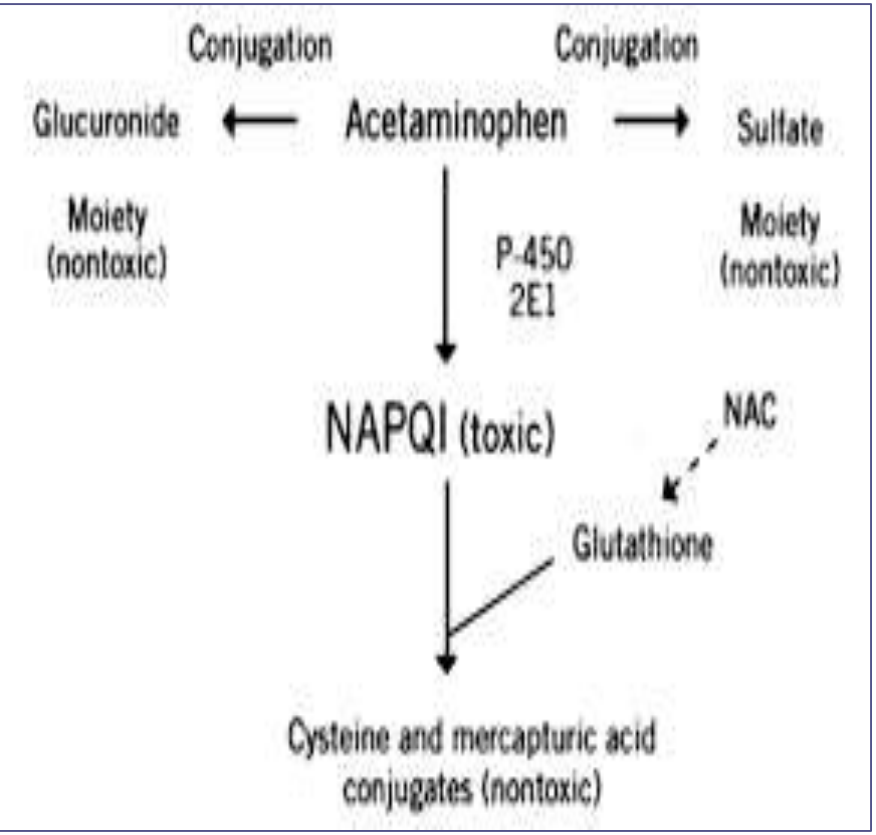
# Drug-induced Hepatic Necrosis/Apoptosis

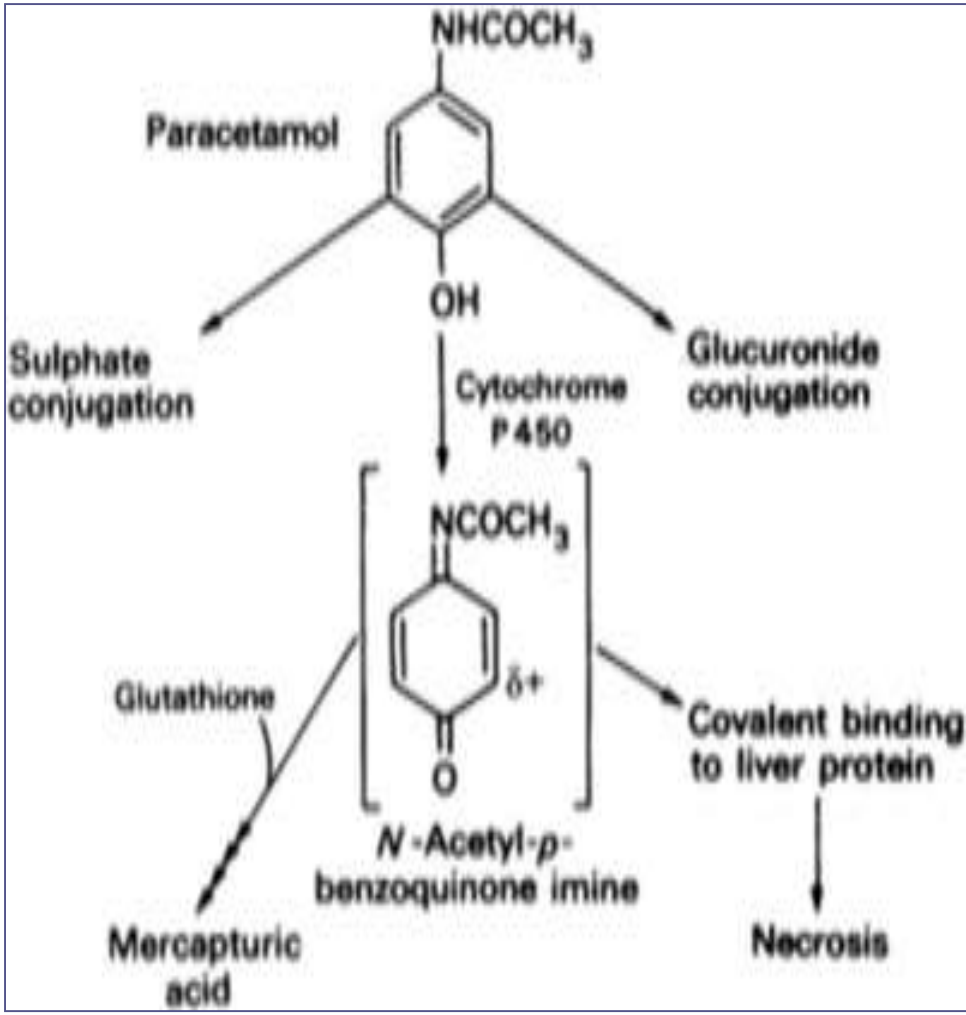


# Drug-induced cytotoxic liver injury

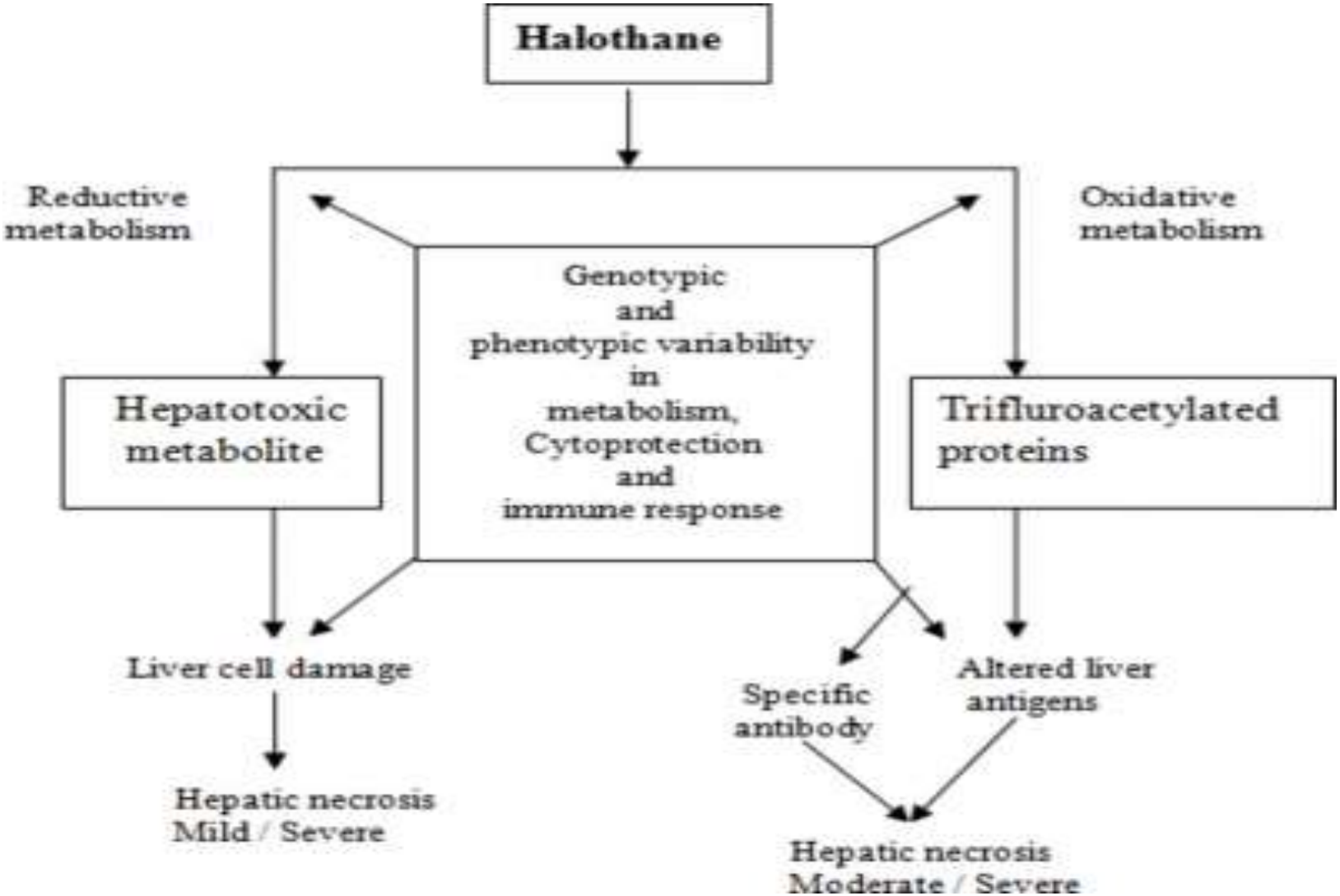
- Paracetamol - dimetabolisme melalui 3 jalur : 2 reaksi konjugasi dan 1 reaksi enzimatik dg CYP450 (5%) . Reaksi enzimatik tsb menghslkan metabolit reaktif : N-acetyl-p-benzoquinone (NABQI) . Bila didetoxifikasi oleh GSH akan berubah menj derivat N-asetilsistein
- Isoniazid dan Iproniazid – dimetabolisme menghasilkan hidrazin – kerusakan tipe sitotoksik pd hepatoselular

# Paracetamol-induced cytotoxic liver injury

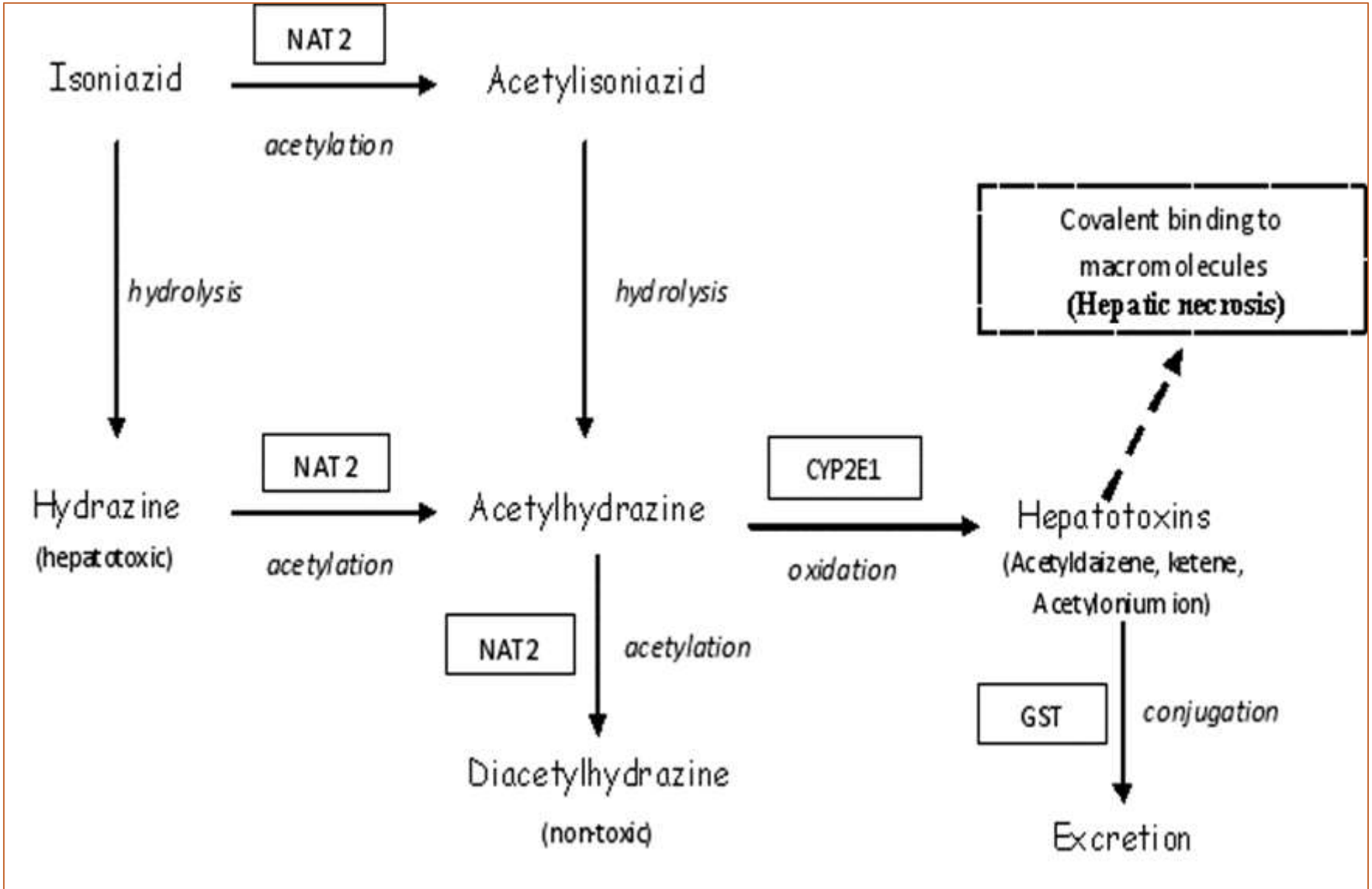


# Halothane induced cytotoxic liver injury



# INH-induced Hepatic Necrosis



# OBAT ANTI TB

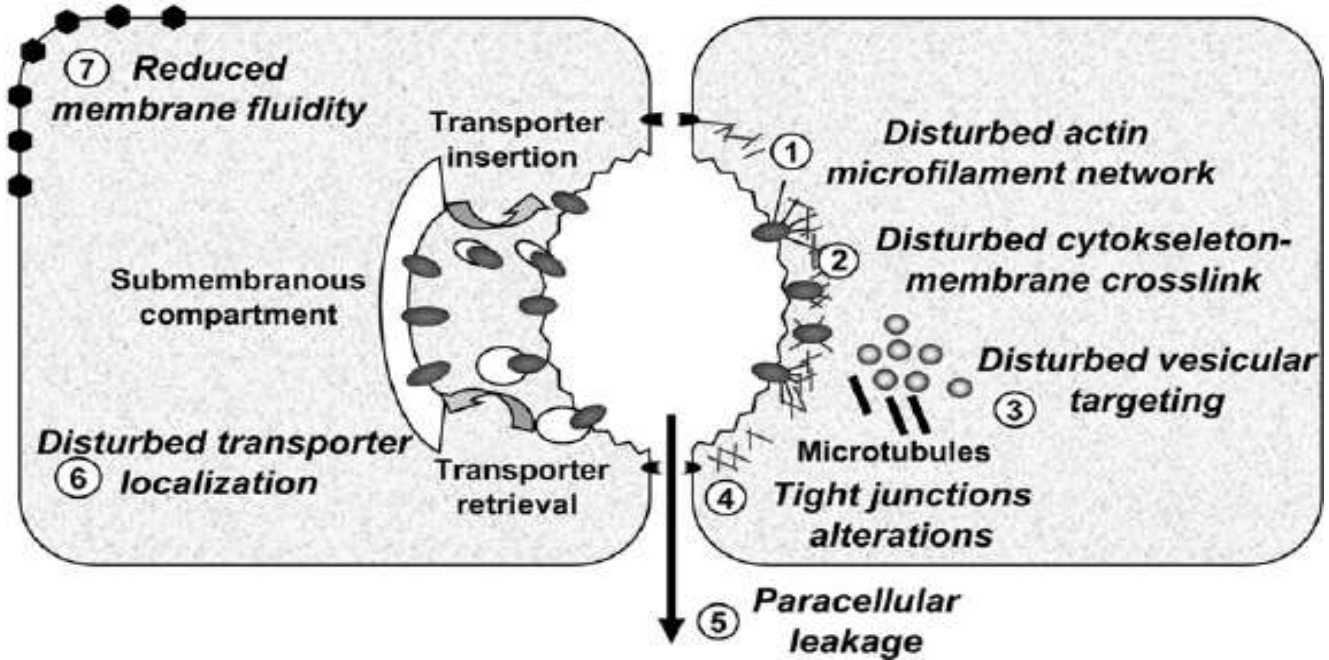
- Insiden anti-TB menyebabkan hepatotoksisitas = 2-28%
- Potensial hepatotoksik : Pirazinamid (PZA), INH, Rifampisin
- Pemakaian bersama → potensiasi efek toksik
- RIF (induktor) →CYP450 (enz metab) → asetilhidrazin (AcHz)(metab toksik)
- RIF →induksi metab INH→ isonicotinic acid + hydrazin (metab toksik dari INH) → potensiasi efek toksik
- INH (induktor)→CYP2EI→ hydrazin (metab toksik)
- INH(inhibitor) → CYP1A2 (enz yg mendetoksifikasi hydrazine)→INH menginduksi toksisitas dirinya sendiri
- Mekanisme heptotoksistas PZA blm jelas
- PZA →pyrazinoic acid→oksidasi oleh xantine oxidase → 5-hydroxypyrazinoic acid (metab toksik)

# NSAID

- Paracetamol, Nimesulid, Diklofenak, Ibuprofen
- Insiden rendah (1-8 kasus / 100.000 pasien/th), tp jika terjadi , ES serius
- Difenilamin (struktur NSAID ) → uncouple oxidative phosphorylation di mitokondria→mitokondria swelling→ATP hepatik ↓↓→ jejas hepatosit

# CHOLESTATIC INJURY

- Ketidakmampuan hepatosit mensekresi bilirubin disebabkan gangg sekresi garam bilirubin.
- Kolestasis ada 2 tipe :
  - Steroid induced cholestatic : C-17 substitited testosteron, kontrasepsi oral
  - Sensitivity type of cholesatatic : fenotiazin(CPZ, trifluoperazin, promazin, pecazine) - not dose-related-terj stl periode awal sensitisasi 1-4 mgg



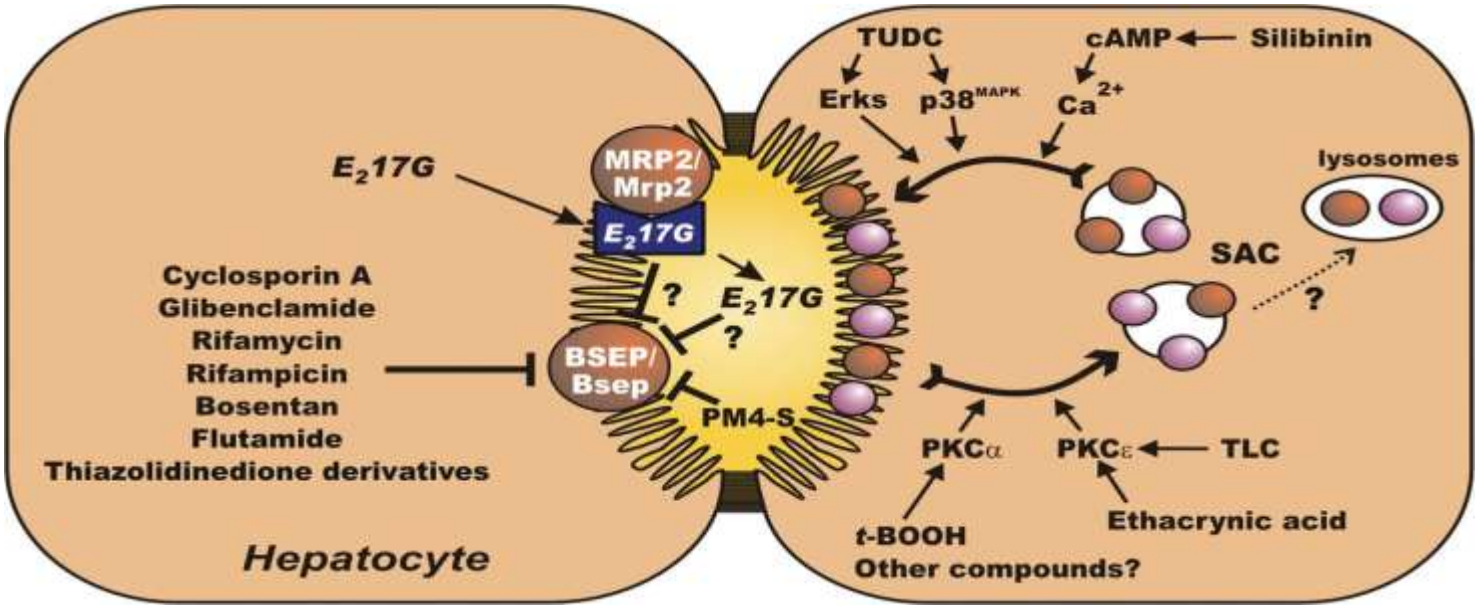
- This **inhibition** of the **hepatobiliary export** of bile salts by **troglitazone** and troglitazone sulfate may lead to a drug-induced intrahepatic **cholestasis** possibly contributing to their **hepatotoxicity**

- **Cholestasis** induced by some **drugs** is mediated, at least in part, by **inhibition** of **BSEP**, resulting in intracellular accumulation of cytotoxic bile salts. For examples: **cyclosporine**, **rifampicin, glibenclamide** & the cholestatic **estrogen** metabolite

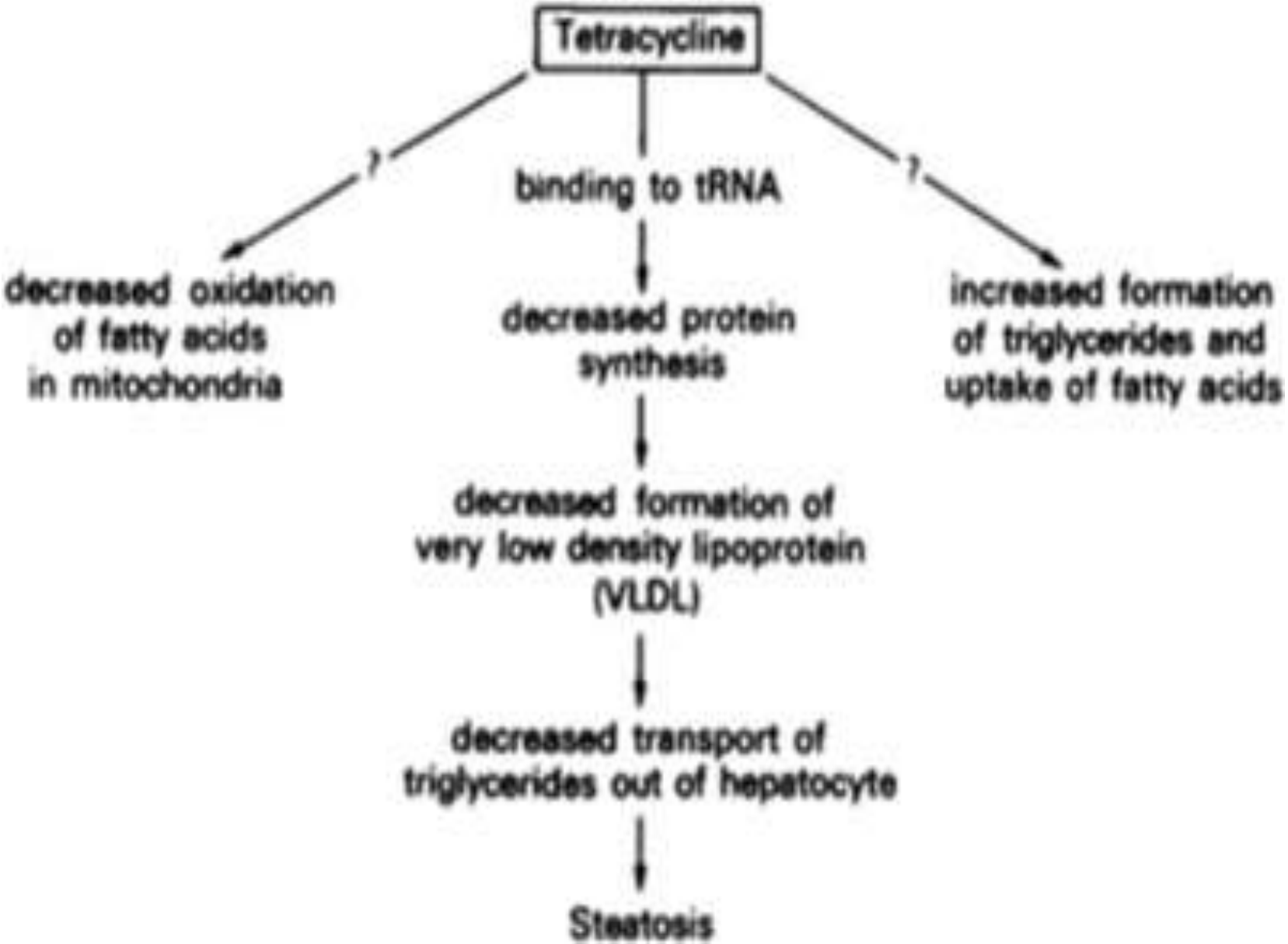
- One should consider the possibility that drugs which **inhibit BSEP** may cause **cholestasis**
- The evaluation of BSEP inhibition will play an important role in the **identification** of compounds that could be a **potential** cause of cholestasis.

# Mempengaruhi up-take, transport dan konjugasi bilirubin

- Rifampicin – dose dependent- menghambat uptake dan ekskresi bilirubin → blirubin conjugated dan unconjugated ↑ (hiperbilirubinemia) → jaundice, tanpa kerusakan hepatosit
- Novobiocin – menghambat UDP glukoroniltransferase → unconjugated ↑

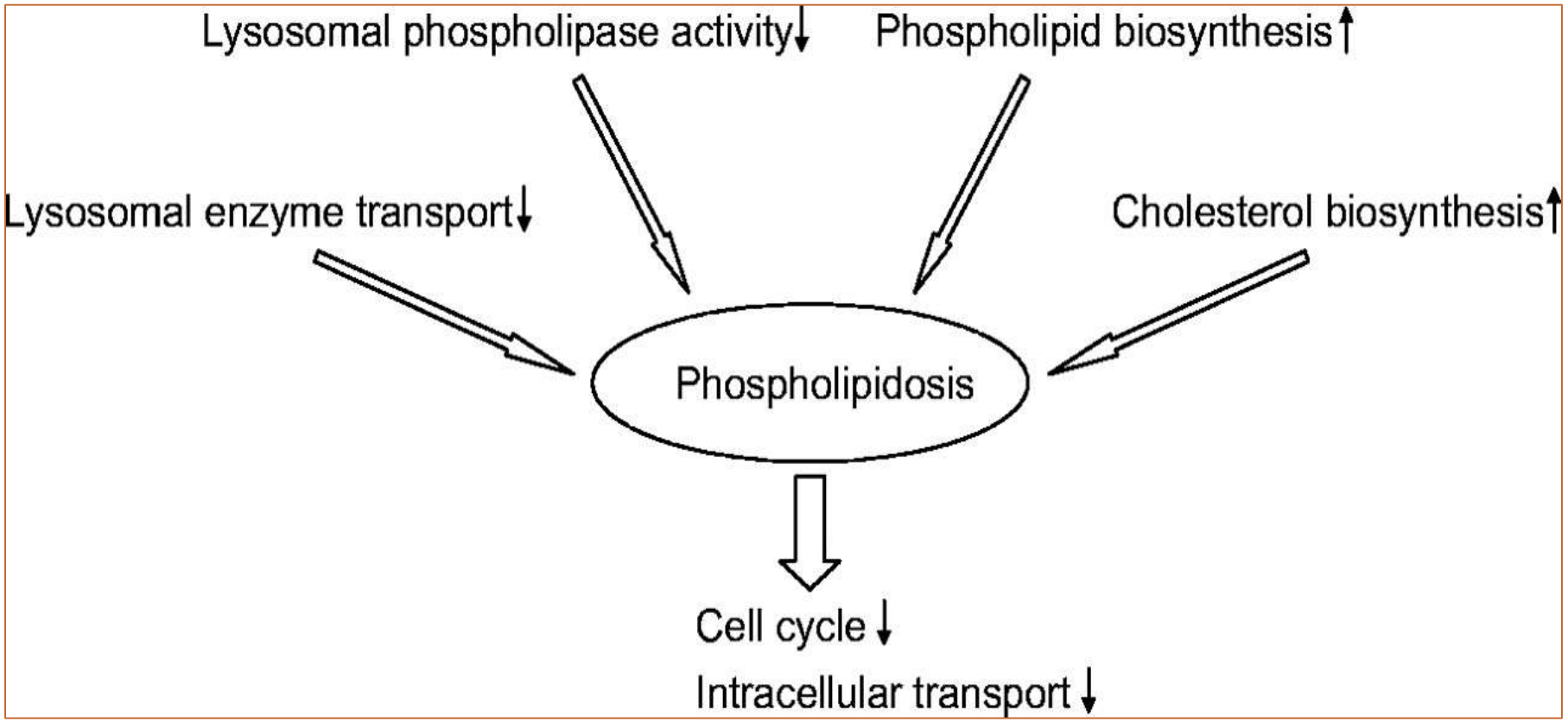


# Tetracyclin-induced Fatty liver



# Drug - induced Phospholipidosis

Mis. Coralgil (coronary dilator), Oxysterol



# Manifestasi Klinis

- Hepatocellular
  - ALT (alanine aminotransferase )/ALP (alkaline phosphatase) ratio >5
  - ~50% of DILI is hepatocellular
  - AST>>ALT- think muscle injury or alcoholic hepatitis
    - Neither > 400
- Cholestatic
  - ALP> 2x ULN (upper limit of normal)
  - ALT/ALP ratio < 2
- Mixed
  - 5> ALT/ALP ratio > 2
- **Hy's law (Hyman Zimmerman)-** serum bilirubin >2x ULN, aminotransferases >3x ULN
  - Associated with **worse prognosis**
  - Mortality as high as 14 %

| Drug | Liver injury |
| --- | --- |
| Acetaminophen, isoniazid, nevirapine, ritonavir, valproate | Acute hepatocellular injury with ALT elevations (+/- bilirubin)[2] |
| Amoxicillin: clavulanate*, chlorpromazine, erythromycin, ACE inhibitors | Cholestatic hepatitis with alk phos elevations (+/- bilirubin)[2] |
| Sulfonamides, phenytoin | Mixed hepatitis with ALT and/or alk phos elevations (+/- bilirubin)[2] |
| Nitrofurantoin, minocycline | Chronic hepatitis |
| Methotrexate | Fibrosis/cirrhosis |

[1]Kaplowitz N Clin Infect Dis. 2004;38:S44-S48 (modified). [2]Aithal GP. Clin Pharm Ther 2011;89(6):806–815.
*Amoxicillin:clavulanate may also cause hepatocellular injury

# Manifestasi Klinis

- Symptoms
  - Acute DILI
    - Malaise
    - Low-grade fever
    - Anorexia
    - Nausea and Vomiting
    - Jaundice
    - Acholic stools
    - Dark urine
- Chronic DILI
  - may present with signs of cirrhosis or decompensation
    - Jaundice
    - Palmer erythema
    - Ascites
    - Hepatic Encephalopathy

# Herbal & Supplements

- 9-14% of cases of DILI in Western countries
- Longer exposure before DILI
- 42% in US use some form of alternative therapy
  - 69% do not disclose supplement use to health care providers
  - 52% use herbal/sup concurrently with prescription meds
- Common- Herbalife, Hydroxycut, Chinese herbal, LipoKinetix, Androstenedione, Black cohosh, Green tea extract, Mistletoe, Licorice

# Diagnosis DILI

- Anamnesis teliti dan  menyeluruh
- Lakukan tes darah untuk mencari penyebab lain dari injuri hati
- Imaging  Cholestasis- untuk menyingkirkan obstruksi bilier
- Cari paparan  obat  sebelum onset injuri hati
- Singkirkan penyebab penyakit hati yang lain
- Menghentikan obat  yg diyakini menjadi penyebab injuri- utk proses perbaikan
- Rechallenge tidak disarankan – injuri  ulang – lbh cepat dan berat

# Diagnosis DILI

- PAPARAN OBAT
  - Hentikan obat yg sdh sdh diketahui sering menyebabkan DILI
  - Selalu tanyakan ttg OTC, herbal dan atau supplements yg dikonsumsi
  - Cek obat di **http://livertox.nih.gov/**
    - Presentasi kasus
    - Karakteristik Drug-specific liver injury
    - Direct link to references and other online recources
    - New cases of DILI welcome

# Hepatocellular injury – RUCAM score

| RUCAM Assessment | Time | Score |
|---|---|---|
| Time to onset of ALT>2xULN after drug start | 5-90 days<br>≤15d after stopping | +2<br>+1 |
| ≥50% decrease in ALT after stopping drug | < 8 days<br>< 30 days | +3<br>+2 |
| Negative hepatitis screens and ultrasound | | +2 |
| Hepatotoxicity in product characteristics/label | | +2 |
| No concomitant medications<br>Concomitant medications | | 0<br>-1 to -3 |
| Positive rechallenge | | +3 |
| Alcohol or pregnancy | | +1 |
| Age > 55 | | +1 |

**Scoring**:
Highly probable >8
Probable 6-8
Possible 3-5
Unlikely 1-2
Excluded ≤0

Toxicologic Pathology 2005; 33: 155-164

# Penatalaksanaan DILI

- Hentikan pemakaian obat yg diduga penyebab DILI- sebagian besar kasus, perbaikan hati spontan terjadi setelah obat dihentikan
- Berikan antidotum
  - N-Acetylcysteine for acetaminophen liver injury
- Liver transplantation
- Pembatasan penggunaan obat atau hanya dipakai utk eksperimen
  - IV carnitine for valproate liver injury
  - Ursodeoxycholic acid for cholestasis
  - Corticosteroids for hypersensitivity cases

# Terima kasih....