

Epidemiology

- 2k cases/yr
- 50% spontaneously survive vs 25% transplanted (represent 5% of LT, of these 15% still die) vs 25% die
- ALF Study Group in 2007 was a big study looking at ALF

Definition

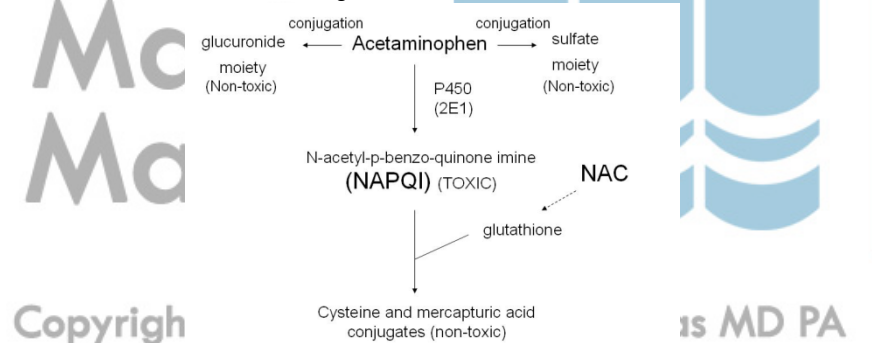
- Definition: **Acute Hepatitis (<26wks) + Hepatic Encephalopathy + Coagulopathy (INR ≥ 1.5) + No Prior Chronic Liver Dz (except Wilson's, AIH, vertically acquired HBV, HAB/HBV/HCV/HDV superinfection, HBV reactivation therefore if a chronic dz is present otherwise consider decompensation rather than ALF)**
 - NB terms based on onset of Sx (1) Fulminant (<2wks) vs Sub-Fulminant (2-12wks) (2) Hyperacute (<7d) vs Acute (7-21d) vs Subacute (>21d but <26wks, less edema, more ascites/renal failure, poorer survival) are not used anymore b/c not prognostically helpful, usually these terms are based on the onset of jaundice rather than non-specific Sx
 - NB survival is inversely related to the rapidity of onset of encephalopathy, TB, etiology (Drugs, Idiopathic, AIH, HBV, Wilsons)
 - NB if you don't meet criteria for ALF then call it ALI
 - NB alcohol can never cause ALF even if encephalopathy/coagulopathy rather it is always called acute alcoholic hepatitis, pathophysiology is different from other causes of ALF in that these pts never actually develop cerebral edema

Mechanism

- ALF triggers unregulated inflammation aka "cytokine storm"

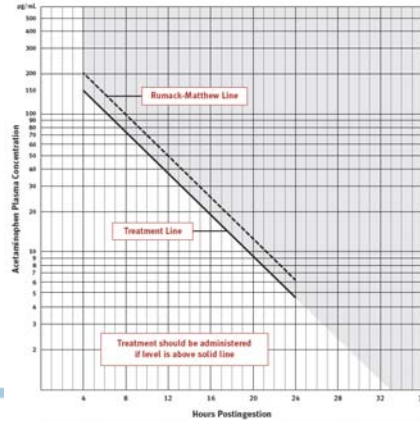
Etiology

- **Acetaminophen aka Acetyl-Para-Amino-Phenol (APAP) aka Tylenol (45%)**
 - Very common in UK
 - Dose: >125mg/kg/d however severe liver injury can occur w/ >50mg/kg/d
 - Mech: 90% of Tylenol is conjugated (good) vs 10% of Tylenol is oxidized (bad) by P450-2E1 producing a toxic intermediate metabolite NAPQ1 which is removed by glutathione but with overdose levels of glutathione are rapidly depleted resulting in accumulation of NAPQ1 which damages liver



- RFs (causing toxicity at lower doses)
 - Anything that activates the P450 system: chronic alcohol/malnutrition, INH/Phenytoin/Rifampin, et al (NB cirrhosis has lower levels of P450 hence one's risk of Tylenol toxicity is actually lower!!!)
 - Anything that decreases glutathione levels: chronic alcohol/malnutrition, older age, Zidovudine et al
- S/S
 - Phase I: begins 1-2hrs after ingestion and lasts up to 12hrs, pain/N/V, subside spontaneously
 - Phase II: lasts 12-48hrs, NO Sx, AT begin to rise
 - Phase III: lasts 2-5d, Sx of ALF/RF
- Prognosis: 20% mortality
- Dx
 - 4hrs after (b/c if you measure before some Tylenol is still in the stomach and not absorbed yet therefore levels will be falsely low) ingestion you should start monitoring levels Q4hrs and they should decrease by ½ Q4hrs, Prescott nomogram only helpful if ingestion time is known AND not chronic AND not sustained release form
 - NB low or absent levels does not rule out since the time of ingestion may be unknown or occur over several days and thus may have already cleared
 - NB if PT is > # of hrs after ingestion then proceed w/ transplant otherwise Tx below
 - Other poor prognostic factors: high CR, encephalopathy
 - NB bili is surprisingly low (~4) and ALT is surprisingly high (~4000)
- Tx
 - gastric lavage if <2hrs of ingestion and activated charcoal if <4hrs of ingestion and keep NGT in place to give NAC
 - N-Acetylcysteine aka NAC (Mucumyst) 5% solution

- Mech: increases glutathione levels
- NB some just give NAC b/c it has protective properties even if Tylenol is not considered the cause
- if <36hrs (though earlier is better w/ best effect if <16hrs) after ingestion and above Tx line (line is 25% below the Rumack-Matthew Line) on nomogram
- PO: 140mg/kg load then 70mg/kg Q4hrs x17doses (much better b/c mild SEs: N/V, urticaria, bronchospasm)
- IV: 150mg/kg load over 15min then 50mg/kg over 4hrs then 100mg/kg over 16hrs (not as good b/c severe SEs: anaphylaxis but done if GIB)



Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion (adapted from reference 100, with permission). The nomogram has been developed to estimate the probability of whether a given acetaminophen concentration in relation to the interval post-ingestion will result in hepatotoxicity, and, therefore, whether an antidote therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. This nomogram only relates to acute ingestion.
2. Single values only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for possible errors in plasma acetaminophen assays and estimated time from ingestion of an overdose.

For additional antidote information, call your regional poison control center. For special consultation, call the Rocky Mountain Poison and Drug Center, toll-free number, 1-800-525-8900, available 24 hours a day.

- **Idiopathic (20/50% adult/children)**
 - Possibly unidentified mitochondrial toxins
- **DILI (10%) esp Antimicrobials, AEDs, Stimulants, Herbals/Supplements**
 - Ex: Isoniazid, Valproic Acid, Halothane, Phenytoin, Sulfonamide, PPU, Amiodarone, Dapsone, Disulfiram
 - Idiosyncratic reaction usually w/in 6mo of drug initiation, always get history the last 1yr, no antidote, always a DOE, stop any suspected medication immediately
 - recent epidemiologic studies are suggesting that prior cases of "DILI" were actually acute HEV infection
- **Infection esp HAV (5%), Reactivated or HDV Superinfected HBV (5%), HCV, HEV, HSV/VZV**
 - NB single (HAV/HEV/HSV/VZV/CMV) or dual coinfections/superinfections (eg. chronic HCV/HBV + acute HAV/HEV/HDV/HIV) is the most common in non-US
 - NB often the classic Ag and Ab are lost during ALF so called "occult infection" hence check PCR
 - HAV: elderly, no Tx just supportive
 - HBV: HDV **coinfection/superinfection or reactivation** when pt becomes immunocompromised for whatever reason (NB some advocate Px of any HBV sAg+ pt who is starting an immunosuppressive med or BMTx and to continue this Px until 6mo after stopping the immunosuppressive med or after BMTx) consider Tx w/ Lamivudine, rarely de novo infection causes ALF
 - HCV: rarely de novo infection causes ALF
 - HEV: pregnant women, esp in endemic areas, no Tx just supportive
 - HSV/VZV/CMV: Acyclovir & Gancyclovir, liver Bx is helpful
 - Peliosis Hepatis
 - Amebic Abscess
- **Vascular esp Ischemia (5%), BCS/HVT**
 - Ischemia: sometimes hypotension is not documented
 - BCS/HVT: significant ab pain/ascites/HM, confirm w/ imaging, r/o cancer as cause before you transplant
- **Autoimmune esp AIH (5%)**
 - Very high globulins (>20) but antibodies may be absent hence liver bx is important
 - Tx w/ steroids but controversial
- **Diet**
 - Foods
 - Mushrooms
 - 100/5000 species are poisonous w/ 90% 2/2 *Amanita phalloides* and *Amanita verna* which produce one of the most lethal toxin (amatoxin) in nature
 - can grow anywhere in the US
 - Stages: GI Sx including N/V, cramps, diarrhea (<1d post ingestion) then clinical improvement (1-2d post ingestion) then ALF (>2d post ingestion)
 - Dx: no blood test, clinical history w/ stages of S/S

- Tx: Gastric Lavage w/ Activated Charcoal + Fluid Resuscitation (very important) + Penicillin-G + Silymarin (not formally available in US therefore have to use commercial herbal preparation of milk thistle) + NAC (often given but no clear evidence it works)
 - Some pts can recover w/o transplant but most need it to survive
 - unripened fruit of the ackee tree in Jamaica creates a hepatotoxin (hypoglycin A)
 - fruit of the cycad tree in Japan creates a hepatotoxin (cycasin)
- Contaminated Food
 - Spanish Toxic Oil Syndrome 2/2 rapeseed oil contaminated w/ anilines in Spain in 1981
 - Epping Jaundice 2/2 flour contaminated w/ methylenedianiline in England in 1965
 - Yusho Oil Disease 2/2 rice contaminated w/ dioxins in Japan in 1968
 - Porphyria Cutaneaou Tarda Epidemic 2/2 grain contaminated w/ a fungicide in Turkey in 1950
- **Metabolic esp Wilson's**
- **Cancer esp metastatic malignant infiltration (lymphoma, lung, breast, melanoma)**
- **Steatotic esp Reye's Syndrome, HELLP/AFLP, Nucleoside Analogue Use**

S/S

- Non-Specific S/S of anorexia, fever, jaundice, AMS, RUQ pain, fatigue, N/V
- NB always check UTox to r/o other ingestants, HIV, et al

Important Points

- **Early Recognition**
 - Referral to Transplant Center esp if INR >2, HE >2, <10yo or >45yo, etiologies w/ poor prognosis, Tylenol w/ pH <7.3
- **Early Determination of Etiology**
 - TJ (not TC b/c of profound coagulopathy) Liver Bx very helpful for HSV, lymphoma, et al and when etiology is idiopathic
- **Give NAC for any cause and it is especially effective in early encephalopathy!!!**

MOF (Cause of Death: MOF 50%, Infection 25%, Cerebral Edema 20%, Bleeding 5%)

- **Liver = ALF**
 - Liver Transplant Evaluation (LTE)
 - Only definitive therapy for pts who are unable to achieve regeneration of sufficient hepatocyte mass to sustain life
 - Criteria (none are standardized, used widely in the US or able to adequately predict outcome and candidacy for liver transplant)
 - King's College Hospital Criteria
 - If Tylenol etiology then proceed w/ LTE if pH <7.3 despite normal HD OR PTT >100s + Cr >200 + Grade $\geq$ III HE
 - If non-Tylenol etiology then proceed w/ LTE if PTT >100s OR any three of the following (cryptogenic/halothane/DILI cause, age <10yo >40yo, jaundice-to-encephalopathy interval >7d, PTT >50s, Bilirubin >300)
 - French Criteria, Clinchy Score, APACHE Score, AFP <3.9 day one after ALT peak, MELD >30
 - NB ALF 2/2 Wilsons and Budd-Chiari uniformly need a transplant to survive
 - NB these pts get the highest priority and usually receive a transplant w/in 1wk
 - NB it is all about whether the liver can regenerate
 - NB ALF transplants have worse survival the FIRST 3mo after transplant when compared to cirrhotic transplants but AFTER 3mo survival is the same
 - NB viral reactivation after transplant is an important issue
 - Liver Support Systems
 - Why? donor grafts are not always available, not all pts are transplant candidates, the decision to transplant is not straightforward since spontaneous recovery has is possible but hard to predict, after Tx pts will have to be on immunosuppresants
 - Goal is to provide time for natural liver regeneration to occur
 - Two Main Types: (1) Non-Cell Based: Molecular Absorbent Recirculation System (MARS) (pt's plasma is exposed to an albumin concentration gradient allowing bilirubin and other albumin bound toxins to move across, ultra-filtrate then undergoes renal dialysis), plasmapheresis, charcoal based hemoabsorption, hemodialysis, albumin based extracorporeal adsorption (2) Hepatic Cell-Based: Extracorporeal Liver Assist Device (ELAD) uses human hepatocytes, Bioartificial Extracorporeal Liver Support System (BELS) uses porcine hepatocytes
 - Hepatic function required for life is unknown nevertheless the most common approach is to remove toxins
 - Trials show no benefit in mortality and there are no statistically powered randomized clinical trials with defined efficacy endpoints
- **CNS = AMS & Cerebral Edema**
 - AMS 2/2 accumulation of unmetabolized NH₃, disturbance of central glutamatergic/serotonergic pathways, production of false NTs, activation of GABA receptors, altered cerebral energy metabolism

- Tx: RRT (refer below), Tx of infection, dx of subclinical epileptiform activity and Tx, no clear data on the chronic Tx for HE (eg. lactulose/rifaximin, there is the concern for gaseous distension prior to transplant w/ the use of lactulose)
 - NB any AMS warrants ICU care as the condition can deteriorate quickly
 - NB better to check arterial ammonia levels therefore place Art Line
 - NB anxiety should be managed w/ small dose short acting benzo
 - NB prophylactic AEDs is controversial
- o Cerebral Edema w/ ICH 2/2 loss of autoregulation and accumulation of non-osmo active NH_3 in astrocytes which is converted to osmo active glutamine leading to intracellular edema
 - Overview: brain only has a limited amount of room (cranium) to swell into and once filled it has nowhere else to go but herniate
 - S/S: bilateral dilated/fixed pupils, N/V, HA, AMS, papilloedema, Parinaud's Sign aka Sunset Eyes, splitting sutures, bulging fontanel, decreased HR and increased BP (opposite of shock called Cushing Effect)
 - Two types of edema
 - Vasogenic
 - o Definition: due to disruption of the integrity of the blood-brain barrier; allowing fluid to escape into the interstitial tissue (the brain has no lymphatics)
 - o Causes: neoplasms, abscesses
 - Cytotoxic
 - o Definition: increase in intracellular fluid because of cellular injury
 - o Causes: generalized ischemic injury
 - Complications: Herniations, Hypoxia, Cushing's, Apnea (most common cause of death, you can transplant the liver BUT you can't the brain hence the brain is the most important organ to follow)
 - Supratentorial Edema
 - o Uncus: uncus on the parahippocampal gyrus herniates under the tentorium pushing on the PCA causing an ipsilateral lateral occipital infarction, cerebral peduncle causing contralateral hemiparesis, CN III causing palsy and ipsilateral pupil dilation from compression of parasympathetic nerve, on basilar artery causing Duret hemorrhages in brainstem, brainstem affecting the RAS, etc
 - Infratentorial Edema
 - o Cerebellar Tonsil: tonsils herniate down the foramen magnum pushing on the brainstem causing autonomic dysfunction and coma
 - o Cingulate: cingulate gyrus herniates under the falx pushing on the ACA causing an ipsilateral medial frontal/parietal infarction
 - o Subfalcine: cerebrum herniates under falx pushing on various structures causing various S/S
 - Dx
 - ICP Monitoring using a Subarachnoid Bolt placed by NS
 - o based on Monro-Kellie Doctrine (there are 3 compartments in the cranium: brain + blood + CSF)
 - o calculate CPP ($\text{CPP} = \text{MAP} - \text{ICP}$) w/ goals of MAP >65 and ICP <20-25 w/ CPP >50-60
 - o often not placed b/c of coagulopathy (goal INR <2 and plt >50)
 - o evidence is unclear that it provides substantial survival benefit
 - o r/o infection when placed for >5d and hemorrhage
 - o used in about 1/2 of transplant centers
 - o w/o monitoring the Dx of ICH/CE cannot reliably be made based on S/S
 - o monitoring is particularly important during transplant surgery b/c of the swings in HD
 - CT Head
 - o not that sensitive for edema
 - Tx (risk of Cerebral Edema and ICH is based on grade of HE (similar Grade used for cirrhosis) hence a stepwise approach is advocated)
 - Grade I-II
 - o Medicine Ward for Grade I and Medical ICU for Grade II
 - o Neuro checks Q1hr
 - o Quiet environment, avoid turning pt, reverse Trendelenburg, minimize ET suction, minimize tactile stimulation, et al to prevent ICP surges
 - o Avoid over transfusion and hydration and generally keep pts dry by following CVP hence place upper chest central line, consider RRT to remove volume
 - o Check CT head to r/o other cause for MS deterioration eg. hemorrhage
 - o Avoid sedatives
 - Grade III-IV
 - o " " +
 - o Intubate for airway protection
 - NB if sedation is needed it is preferred to use Propofol b/c rapidly reversible to check for neuro checks, PK not affected by liver, reduces cerebral blood flow

- NB if paralysis is needed it is preferred to use atracurium
 - Reverse Trendelenburg
 - Avoid stimulation that may increase ICP (Valsalva, etc)
 - If ventricular catheter in place for monitoring ICP consider CSF drainage
 - NAC has been shown to increase CBF
 - If ICP >20-25mmHg then (none of Tx below have been shown to be helpful in a prophylactic manner)
 - 1st: Osmotic Diuresis w/ Mannitol 20% (0.5-1g/kg IV x1 and ICP not <20-25 and if serum osm is not >320 then you can repeat bolus x1 6hrs after last dose) + RRT to remove volume b/c volume overload
 - 2nd: Hypertonic Saline 30% (30mL IV boluses Q2hrs w/ target Na 145-155)
 - 3rd: Hyperventilation with goal PaCO₂ b/t 25-30mmHg (low CO₂ prevents cerebral vasodilation but this effect is short lived and potential reflex vasoconstriction can occur resulting in hypoxia)
 - NB Hypothermia w/ cooling blankets w/ target 32-34°C (significant r/o infection, arrhythmia, etc limits its use)
 - NB Barbiturate Coma (significant hypotension limits its use)
 - NB even though steroids are used for Tx of cerebral edema 2/2 cancer steroids have no role in Tx of cerebral edema 2/2 ALF
 - Seizure: may increase ICP therefore Tx w/ phenytoin however prophylaxis is controversial
- **ID = Septic Shock**
 - Etiology: liver is instrumental in immune fxn and with liver failure there is impaired neutrophil and Kupffer cell phagocytic fxn, reduced hepatic complement production, increased gut bacterial translocation
 - Types: sepsis, SBP, pneumonia, UTI (NB multiple infections are common)
 - Tx: prophylactic BS antimicrobials (antibiotics/antifungals) is very controversial but mainly done if > Stage III HE, hypotensive or on transplant list otherwise just check CXR, UA, panCx bacterial/fungal Qd
 - NB bowel decontamination has not been shown to impact survival
 - NB often S/S are subtle with change in mental status being the most common S/S
 - NB when Cx negative but still S/S or decompensation then consider fungal infections with Candida
 - NB SIRS promotes hepatocellular necrosis and inhibits hepatocyte regeneration and progression into deeper stages of HE
 - NB importantly infection may preclude transplant or complicate post-op course hence aggressively searched for and Tx
- **CV = Hemodynamic Instability**
 - Etiology: splanchnic/systemic vasodilation, adrenal insufficiency, microcirculatory plugging/damage
 - Tx: NAC has been shown to improve hemodynamics, pressors to keep MAP >60mmHg (best one is controversial, NorEpi is often advocated, generally avoid dopamine/vasopressin), colloids are better than crystalloids (regardless all solutions should contain dextrose to maintain euglycemia)
- **Renal = Acute Kidney Injury**
 - Etiology: hemodynamic instability resulting in pre-renal state to outright HRS, Tylenol induced papillary necrosis, et al
 - Tx: CVVHD is better than IHD b/c the hypotension that occurs w/ IHD results in a fall in CPP that may exacerbate cerebral edema
 - NB RRT is instrumental in decreasing toxins that lead to AMS
- **GI = Malnutrition & Ulcer Px**
 - Etiology: energy requirements are increased in ALF w/ impaired gluconeogenesis resulting in aggressive breakdown of protein/fat and difficulty in liver regeneration
 - TX: enteral TFs (severe protein restriction is not recommended) and H2B/PPI
- **Heme = Coagulopathy & Pancytopenia**
 - Etiology: liver cannot make factors, there is consumption of factors and platelets in SIRS, BM suppression can occur (esp w/ viral ALF), et al
 - Tx: don't correct unless actively bleeding or undergoing a procedure or severe (Plt <10K or INR >7)
 - Why? b/c (1) when you give VitK/FFP you are also giving them fluid which increased ICP, (2) only 10% of pts spontaneously bleed, (3) there are also decrease levels of AC like Protein C/S
 - If you do correct for a procedure then goal Plt > 50k and INR <1.5
 - NB use of recombinant activated factor VII (rFVIIa) is being looked at but expensive
- **Metabolic = Electrolyte Abnormalities**
 - Hypoglycemia (2/2 impaired hepatic gluconeogenesis): check DFS Q1-2hrs and use D₅W gtt
 - Hypokalemia
 - Hypophosphatemia (2/2 liver regeneration therefore a good sign)
 - Lactic Acidosis (2/2 impaired liver clearance): follow ABGs
 - Hyper-A/L (2/2 concurrent pancreatitis)
 - Adrenal Insufficiency (2/2 ?): stress dose steroids if infection ruled out and there is persistent hypotension
 - NB no need to check LFTs more frequently than Qd