

**Medical Toxicology**  
**2009 LLSA**  
**San Juan PR**

Tamas R. Peredy, MD, FACEP  
Northern New England Poison Center  
Medical Director



# First Announcement

- 2<sup>nd</sup> Biannual Maine Medical Mushroom Meeting
  - or Shoreside Shroom Symposium
  - or Fungi and other Toxic pick-ups
  - or ain't no bolete, you're just a horny toadstool
- Portland Maine
- September 18-19, 2009



# Amanita phalloides poisoning

Reassessment of prognostic factors and indications  
for emergency liver transplantation

- Escudie L, Francoz C, Vinel J et al
- Clichy, Toulouse France
- 2007 J Hepatol vol 46 p466-473
- Retrospective review, Case series
- 27 pts from 1993-2005
- Inclusion criteria: admission diagnosis of Amanita phalloides poisoning



# 1. Background



# Underlying knowledge

## A) Mushrooms

And other things that cause liver failure

## B) Acute Liver Failure

Mechanisms of liver failure

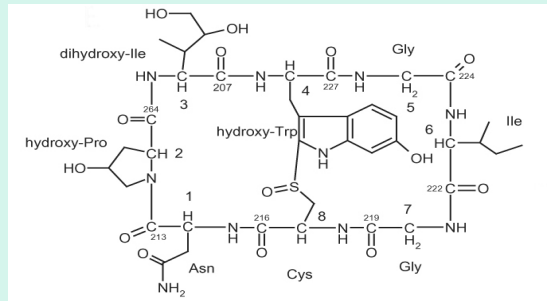
## C) ALF prognosis scoring systems

Other markers of badness



# A) Amatoxin containing mushroom

- *A. virosa*, *bisporigera*, *ocreata* and *verna*
- *Conocybe filaris*
- *G. autumnalis*, *venenata*
- *Lepiota*



# A) Amanita

## ■ Features

- Cap and stem
- White spores
- Free gills
- Bulbous base

## ■ But

- Not all amanita contain Amatoxin
- Non-Amanita may contain Amatoxin



# A) Some other Toxins

## ■ Drugs

- APAP, INH, Valproate, Halothane, Phenytoin, Sulfonamides, PTU, Amiodarone, Disulfiram, Dapsone, Carbamazepine, Ofloxacin, Ketoconazole, Lisinopril, Niacin, Labetalol, Imipramine, Flutamide, Ethanol, Ecstasy

## ■ Herbs

- Borago, Heliotropium, Pulmonaria, Symphytum, Senecio, Crotalaria, Teucrium, Atractylis, Larrea, Cassia, Jin Bu Huan, Sassafras, Kava, Pennyroyal

## ■ Environmental toxins

- CCl<sub>4</sub>, vinyl chloride, toluene, beryllium, phosphorus, DMF

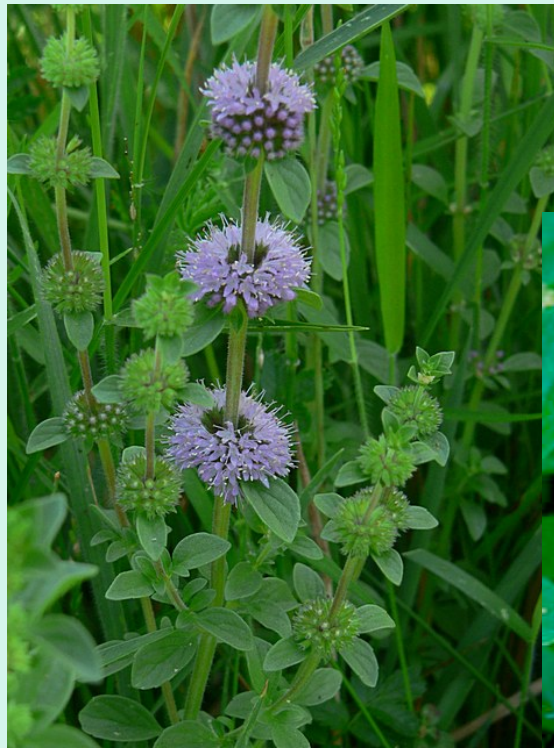


# Some Hepatotoxic Herbs

**Germander**



**Pennyroyal**



**Comfrey**



<http://www.mskcc.org/mskcc/html/11570.cfm>



# B) Acute Liver Failure

## ■ Definition

- Time <26 week duration
- Exclude chronic liver disease (cirrhosis)
- Clinical features
  - ↓coagulation factors
    - Factor 5 < 50%, INR > 1.7
  - Encephalopathy
  - Multisystem organ failure (renal)

## ■ Causes (partial list)

- Toxins
- Infectious HAV, HBV, HSV
- Other: Shock, Autoimmune, Budd-Chiari, Wilson's, Reye's, Heat stroke, Malignancy, Pregnancy
- Epidemiology
  - Less than few thousand/yr US, Survival 65-90%



## B) Mechanisms

- Hepatocellular – APAP, amatoxin
- Steatosis
  - Macrovesicular
    - Ethanol, amiodarone
  - Microvesicular
    - Valproate, nucleoside analogs, DMF
- Cholestasis – estrogens, cyclosporine
- Immunogenic -halothane
- Vascular - pyrrolizidine
- Fibrosis – Vit A, MTX
- Oncogenic – vinyl chloride, arsenic, aflatoxin



# B) Amatoxin

## ■ Drug transport

### ■ Influx OATP

#### ■ OATP1B3

- Rifampin 1200 mg/day, Silymarin

### ■ Efflux BSEP/P-GP

## ■ Enterohepatic recirculation

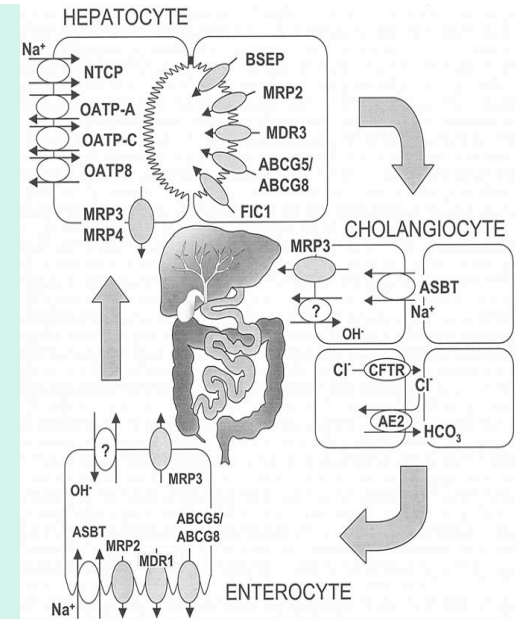
### ■ AC, Biliary diversion

## ■ DNA dependent eukaryotic RNA polymerase inhibition

### ■ 140 kDa subunit

### ■ Impaired protein synthesis (transcription)

### ■ Apoptosis



# C) Predicting need for orthotopic liver transplantation (LT)

## ■ King's College criteria

### ■ APAP

- Arterial pH <7.3 (lactate >3 mmol/L) or
- Encephalopathy (grade III or IV) and
  - PT >100 seconds (INR >6.5)
  - serum creatinine >300  $\mu\text{mol/L}$  (>3.4 mg/dL)

### ■ Non-APAP

- PT >100 seconds (INR >7) or 3/5
  1. Patient age of <10 or >40
  2. Serum bilirubin >308  $\mu\text{mol/L}$  (18 mg/dL)
  3. Jaundice duration >7 days before encephalopathy
  4. PT >50 seconds (INR >3.5)
  5. Non-A, non-B hepatitis, halothane or other drug toxicity



# C) King's College

## Paracetamol related

- pH <7.30 despite adequate fluid resuscitation (regardless of grade of encephalopathy)

or

- Prothrombin time >100 sec **and** creatinine >300 µmol/l **and** grade III or IV coma

## Non-paracetamol related

- Prothrombin time >100 sec (regardless of grade of encephalopathy)

or

- Any three of the following (regardless of grade of encephalopathy)
  - (a) aetiology: non-A non-B hepatitis, idiosyncratic drug reactions
  - (b) age <10 or >40 years
  - (c) jaundice to encephalopathy of >7 days
  - (d) prothrombin time of >50 sec
  - (e) serum bilirubin >300 µmol/l



## C) Predicting need for orthotopic liver transplantation (LT)

- Clichy criteria

- Grade III/IV encephalopathy and

- Factor V

- < 30% older than 30; < 20% younger than 30



# C) Predicting need for orthotopic liver transplantation (LT)

## ■ Ganzert criteria

■ between day 3-10

■ Prothrombin index  $< 25\%$  and

■ Creatinine ~~X~~  $> 106$   $\mu\text{mol/L}$



## C) Predicting need for orthotopic liver transplantation (LT)

### ■ Other scoring systems

- APACHE II >15
- MELD/PELD >30

### ■ Other markers

- Low serum phosphate
- High arterial ammonia
- Factor VIII/V ratio
- Serum Gc-globulin <100 mg/L
- Alpha fetoprotein  $\uparrow$ 4  $\mu$ g/L



# 2. Methods



# French referral hospitals

- Retrospective review, Case series
- 27 pts from 1993-2005
- Inclusion: admission diagnosis of Amanita phalloides poisoning
- Retrospectively applied scoring systems
- Outcomes
  - Survival, Transplantation
  - Also looked at hepatic resection, other symptoms
- Limitations
  - Small numbers
  - Referral bias



# 3. Results



# Outcomes of 27 pts

- Mortality rate 6/27 or 22%
- Died or transplanted 8/27 or 30%
  - All death PT index <50%
  - All but 1 death encephalopathy
  - Liver transplantation (LT)
    - 1 age contraindication to LT died
    - 2 wait list LT died
    - 2 of 4 died after LT



# Fatality risk factors

- Gender male 0 of 14 died, female 8 of 13 died
- Shorter ingestion to diarrhea interval (8 hrs)
- Factor V <10% after day 3
- Others
  - Higher blood lactate
  - Lower PT index (higher INR), factor V activity
  - Prolonged interval ingestion to PT index nadir
  - Biphasic transaminase pattern



# Scoring systems

B I N G O				
7	25	44	57	62
15	22	40	50	70
11	30	FREE SPACE	46	74
2	28	37	55	68
10	27	39	59	75

## ■ King's criteria

### ■ Time to fulfill LT criteria

■ 48 hr APAP

■ 60 hr non-APAP

■ Age, bilirubin, onset to encephalopathy unhelpful

■ Encephalopathy, creatinine unhelpful

## ■ Clichy criteria

■ 3 death before encephalopathy (multisystem organ failure)

■ 1 survivor with Clichy criteria

## ■ Ganzert

■ 2 survivors with Ganzert criteria



# 4. Conclusions



# In summary

- Short interval ( 8 hr) ingestion to diarrhea
  - ‘critical early alarm’
- Neither encephalopathy nor abnormal creatinine may occur prior to need for LT
- Non-APAP King’s College performed the best
  - PT index <10% (INR >6.5) day 4 or after
- Consider auxiliary (partial) transplant



# Key Concepts

1. Liver transplant necessity prediction (scoring) is challenging in *Amanita* poisoned patients because they deteriorate rapidly often without multi-organ involvement.



# Key Concepts

2. Non-APAP King's College criteria were 'most efficacious' compared with APAP King's College, Clichy and Ganzert scores because encephalopathy and renal insufficiency did not always occur prior to death or transplantation.



# Key Concepts

3. A 'critical early alarm' predictive of poor outcome is an interval  $< 8$  hours from Amanita ingestion to onset of diarrhea.



# Key Concepts

4. The best single predictor of fatality for Amanita intoxication was an INR  $\geq 6$  on post-ingestion Day 4 or afterward.



# Key Concepts

5. Given the rapid, single organ failure pattern of Amanita poisoning, auxiliary (partial) liver transplantation should be considered.



# References

1. Bailey B Meta-analysis of prognostic criteria, Crit Care Med 2003.
2. Polson J, Lee WM, AASLD Position Paper: Mgmt of ALF, Hepatol 2005.
3. Yantorno SE, Kremers WK, Meld is superior, Liver transplant 2007.

