2015 Updated Guidelines For The Management of Paracetamol Ingestion

Angela Chiew
Emergency Physician/ Clinical Toxicologist
Prince of Wales Hospital
NSW Poison's Information Centre

Aims of the guidelines

- Guidelines are sets of non-mandatory rules, principles or recommendations.
- Applying guidelines to individual care is always likely to require judgement
- Information needed to achieve best practice
- Guidelines reduce unacceptable or undesirable variations in practice
- Must be up-to-date to be useful

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Area updated

- Decontamination
- Sustained Release Paracetamol ingestion
- “Massive” overdoses
- Paediatric liquid paracetamol ingestion
- Supratherapeutic ingestion
- Hepatotoxicity

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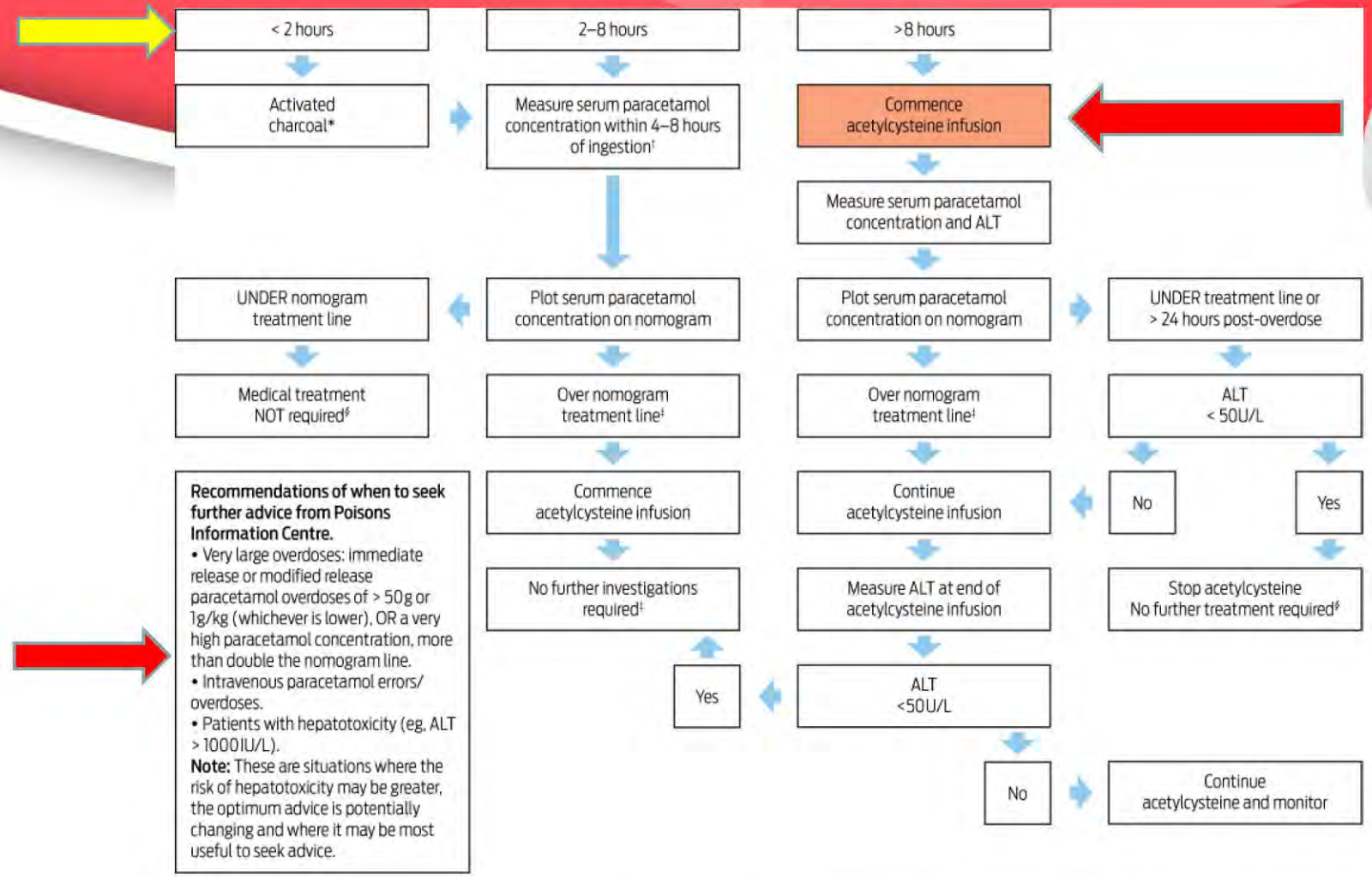
Demographics of paracetamol in Australia

- Graudins (EMA 2015): 2009- 2013:
  - 647 presentations:
  - 272(42%) required NAC:
    - Of those requiring NAC median dose 18g (12-25g),
    - mean first concn 1100µmol/L (950-1225µmol/L) - average time to first 5 hours
- Buckley et al (1999) HATS data : 1987-1996:
  - 981 pts :
    - 748 non toxic,
    - 62 > 150mg/L (1000µmol/L),
    - 51 > 200mg/L (1300µmol/L),
    - **49 high risk (300mg/L/ 2000µmol/L),**
    - 40 presented > 24hrs post

1. Graudins A. **Paracetamol poisoning in adolescents in an Australian setting: not quite adults.** Emerg Med Australas. 2015 Apr;27(2):139-44.
2. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. **Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning?** J Toxicol Clin Toxicol. 1999;37(6):759-67.



NOTE:

*Cooperative adult patients who have potentially ingested greater than 10g or 200mg/kg, whichever is less. For paracetamol ingestions ⩾ 30g activated charcoal should be offered until 4 hours post-ingestion.

† If paracetamol concentration will not be available until > 8 hours post-ingestion, commence acetylcysteine while awaiting paracetamol concentration.

‡ Those patients with initial paracetamol concentrations more than double the nomogram line may benefit from an increase in acetylcysteine dose (see text) and a serum paracetamol and ALT concentrations should be checked at the end of the acetylcysteine infusion.

§ Patients should be advised that if they develop abdominal pain, nausea or vomiting further assessment is required.

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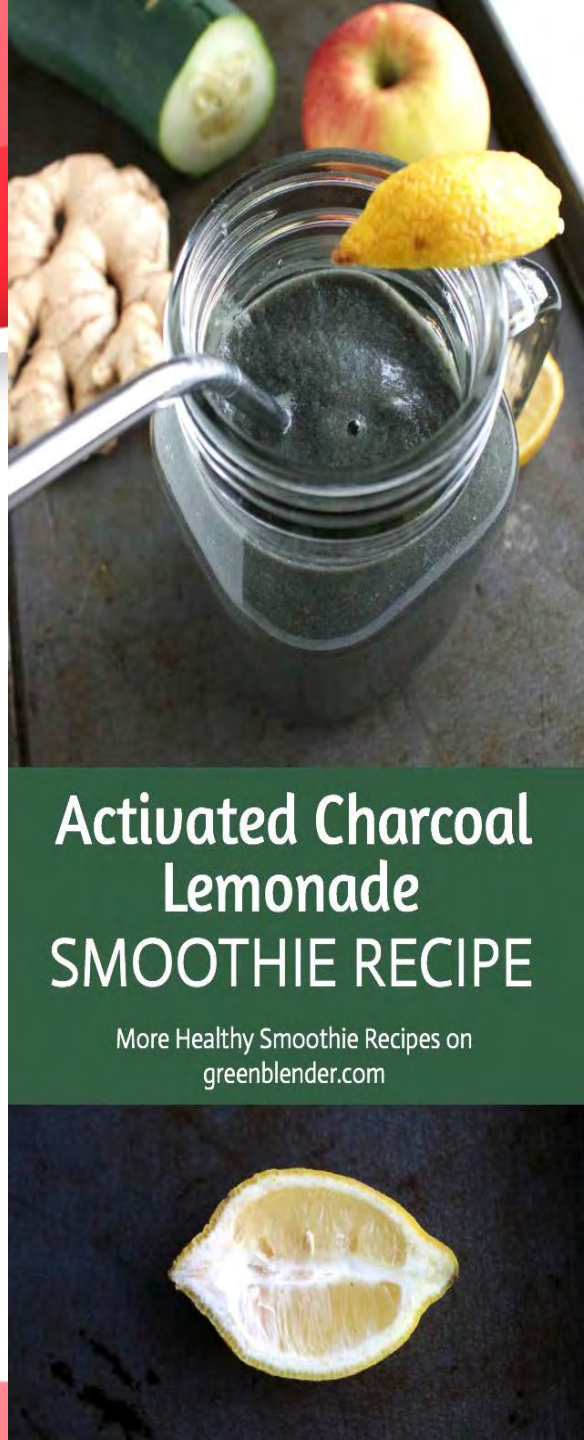
Decontamination

Activated charcoal should be offered to a cooperative patient:

- **Immediate release paracetamol:**
  - Within 2 hours of paracetamol ingestion in those who have ingested > 10g or 200mg/kg which ever is less
- **Sustained release:**
  - Within 4 hours of ingestion in those who have ingested > 10g or 200mg/kg which ever is less
  - In massive overdoses absorption may continue for up to 24 hours, so patients will likely benefit from activated charcoal even beyond 4 hours
- **> 30g of paracetamol ingested:**
  - Activated charcoal should be offered til 4 hours post ingestion.



Activated Charcoal

- Buckley et al: 15% of those presenting within 2 hours who were given charcoal had a paracetamol concn above the nomogram line compared to 41% of those who did not receive gastrointestinal decontamination.
- Cohort study of more than 4500 overdose patients - 71 (1.6%) developed aspiration pneumonitis. Emesis, seizure and altered mental status were among the independent predictors of aspiration but NOT the administration of AC.
- AC RCT: adults allocated to treatment with AC consumed 83% of their first dose.
- Studies suggest that the incidence of charcoal associated emesis is considerably lower, OF the order of 6–7%.

1. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. **Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose.** J Toxicol Clin Toxicol. 1999;37(6):753-7.
2. Juurlink. **Activated charcoal for acute overdose: a reappraisal.** Br J Clin Pharmacol. 2015 Sep 26. doi: 10.1111/bcp.12793. [Epub ahead of print] Review.

“Massive” Paracetamol Ingestion

- > 30g paracetamol ingested offer activated charcoal til 4 hours post ingestion if co-operative.
- IV acetylcysteine adjustment:
  - Patients who have a paracetamol concentration **more than double the nomogram line**
  - Consider increasing the dose of acetylcysteine in the 100mg/kg over 16 hours infusion (3rd bag) -that is double dose to 200mg/kg IV NAC over 16 hours
- Near the completion of IV acetylcysteine:
  - check ALT and paracetamol concn
  - Acetylcysteine should be continued if they have an ALT >50U/L or a paracetamol greater than 10mg/L (66µmol/L).

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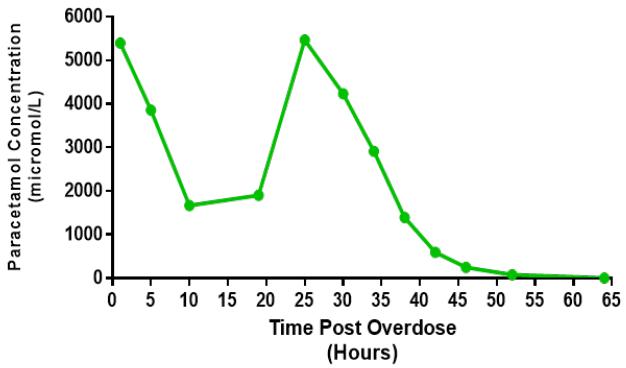
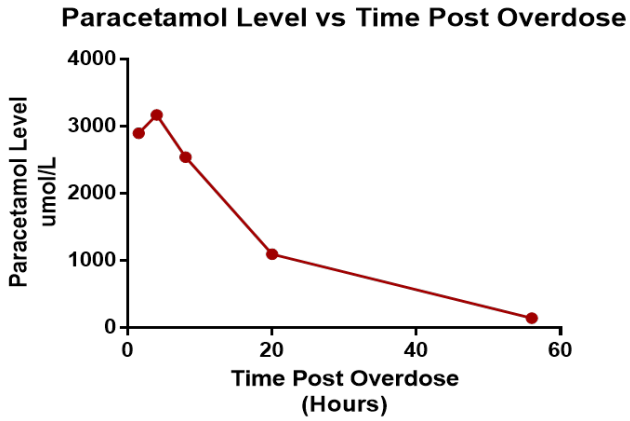
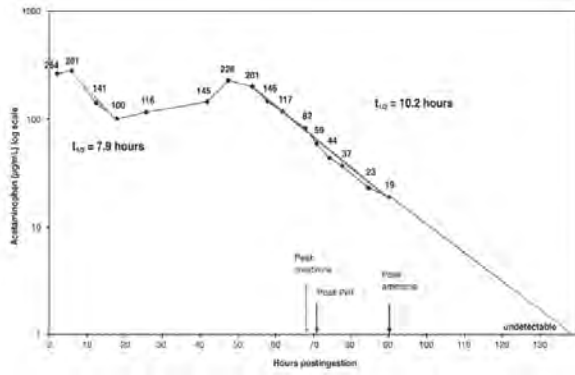
Massive Paracetamol Overdose

- Delayed and erratic absorption may be seen in massive overdose
- Can have elevated paracetamol levels at 24 hours post overdose







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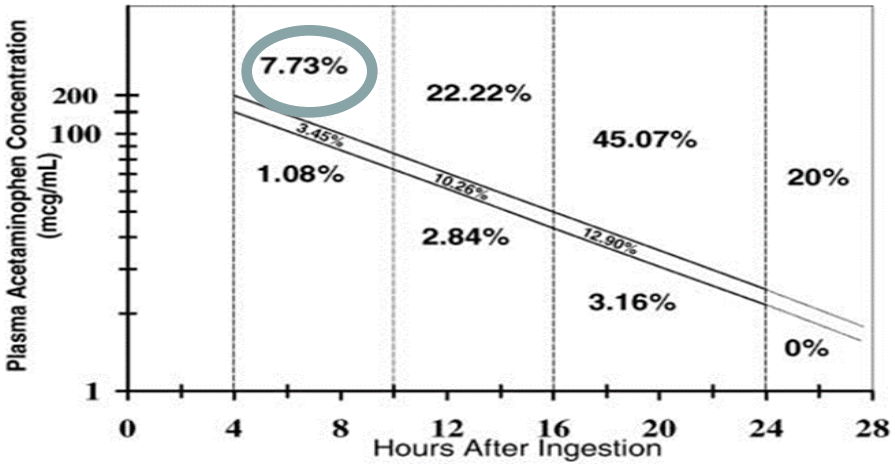
Hepatotoxicity despite early treatment



Graph: % hepatotoxicity, after Rx with oral NAC. Study of 2540 people

Australian Data:

- Australian Paracetamol Project/ HATS and POWH.
- 145 massive paracetamol overdoses ingestion > 40g
- 5 patients treated within 8h developed hepatotoxicity – 1 required a transplant.
- Those receiving activated charcoal had significantly lower levels.

Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. Clinical Toxicology 2002;40(1):3-20.

Acetylcysteine Dose in "massive" overdose

- The original acetylcysteine dosing was conceived to detoxify the paracetamol toxic metabolite NAPQI, based on a 4% conversion rate.
- "Standard" dosing might be insufficient in the setting of massive ingestion.
- Severely poisoned patients a higher proportion of the dose undergoes conversion to NAPQI
- Suggest a dual approach:
  - Prolonged IV acetylcysteine
  - Increase in dose of IV acetylcysteine
- **Doubling the third dose of IV NAC international survey**: 164 responses, 19 countries - most would increase NAC dose, 33% choose 3000umol/L as the cut of

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Modified release paracetamol

- In those who have ingested > 10g or 200mg/kg whichever is less – commence acetylcysteine
- Acetylcysteine may be discontinued:
  - if serial levels, taken **4 hours apart are below the nomogram line and are decreasing.**
- Near the completion of *N*-acetylcysteine the patient should have a **repeat** ALT and paracetamol concentration.
- *A*cetylcysteine should be continued if the ALT is increasing or paracetamol concentration is greater than 10mg/L (66µmol/L).

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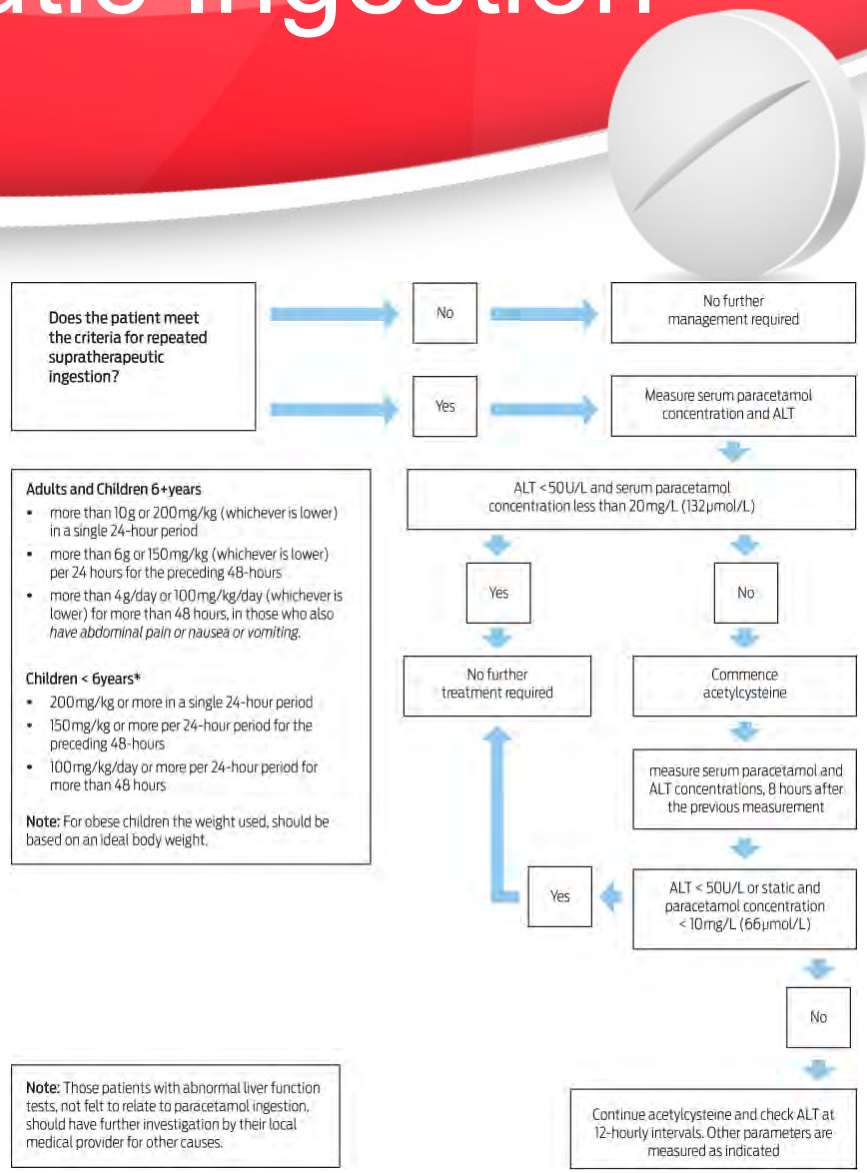
Supra-therapeutic Ingestion

- Patients should have a paracetamol level and ALT measured if they meet the criteria for supratherapeutic ingestion.
- Criteria for supratherapeutic ingestion:
  - more than 10 g or 200 mg/kg (whichever is less) in a single 24-hour period
  - more than 6 g or 150 mg/kg (whichever is less) per 24 hours for the preceding 48-hours
  - more than 4g/day or 100 mg/kg/day (whichever is less) for more than 48 hours, in those who also have abdominal pain, nausea and vomiting



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Acetylcysteine

- Calculation based on actual body weight to the nearest 10kg
- **Ceiling weight of 110kg**

Table 4: Volume of acetylcysteine to be charted for each infusion, based on actual bodyweight and rounded up to the nearest 10 kg

Patient's body weight (kg)	Initial acetylcysteine infusion Dose: 150 mg/kg over 60 min to be added to 200 mL of 5% glucose	Second acetylcysteine infusion Dose: 50 mg/kg over 4 hours to be added to 500 mL of 5% glucose	Third acetylcysteine infusion Dose: 100 mg/kg over 16 hours to be added to 1000 mL of 5% glucose
	Dose acetylcysteine (g) = volume (mL)* = *(0.75 x wt [kg])*	Dose acetylcysteine (g) = volume (mL)* = *(0.25 x wt [kg])*	Dose acetylcysteine (g) = volume (mL)* = *(0.5 x wt [kg])*
50	7.5 g = 37.5 mL	2.5 g = 12.5 mL	5 g = 25 mL
60	9 g = 45 mL	3 g = 15 mL	6 g = 30 mL
70	10.5 g = 52.5 mL	3.5 g = 17.5 mL	7 g = 35 mL
80	12 g = 60 mL	4 g = 20 mL	8 g = 40 mL
90	13.5 g= 67.5 mL	4.5 g = 22.5 mL	9 g = 45 mL
100	15 g= 75 mL	5 g = 25 mL	10 g = 50 mL
110†	16.5 g= 82.5 mL	5.5 g = 27.5 mL	11 g = 55 mL

* Assuming concentration of acetylcysteine is 200 mg/ml.

† **Note:** All patients weighing greater than 110 kg should be dosed according to a bodyweight of 110 kg.

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Acute Liver Injury and Hepatotoxicity

- Acetylcysteine should be continued until:
  - The patient is clinically improving,
  - ALT levels are decreasing,
  - The international normalised ratio (INR) is improving < 2
  - Paracetamol concentration is less than 10 mg/L (66 µmol/L).
- Regular clinical review and 12-hourly (or more frequent) blood tests are recommended if there is clinical deterioration.
- A markedly prolonged **INR is common** in patients with severe hepatotoxicity and correction **is not** required, unless there is evidence of bleeding.
- **Avoid** correction of INR until discussion with a Liver Transplant Unit

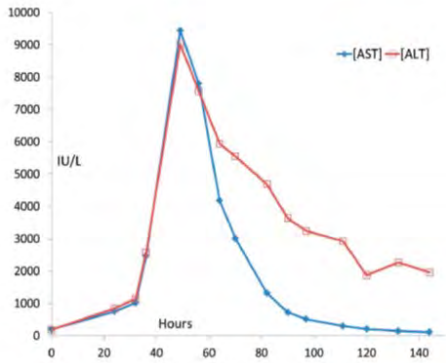

Fig. 1. Time course of AST and ALT concentrations in an actual patient treated for acetaminophen overdose. After the peak AST concentration, the AST concentrations decline more rapidly than the AST concentrations.

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When to call the liver unit

A liver transplant unit should be consulted if any of the following criteria are met:

- INR >3.0 at 48 hours or >4.5 at any time;
- oliguria or creatinine >200 µmol/L;
- persistent acidosis (pH < 7.3) or arterial lactate >3 mmol/L;
- systolic hypotension with blood pressure less than 80 mmHg, despite resuscitation;
- hypoglycaemia;
- severe thrombocytopenia;
- encephalopathy of any degree, or any alteration of consciousness (Glasgow coma scale <15) not associated with co-ingestion of sedatives.

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Paediatric accidental liquid paracetamol ingestion

- **Children 6 years and under**
- If they have ingested **greater than** 200mg/kg measure a paracetamol concentration any time after 2 hours.
- Management:
  - 2 (to 4) hour concentration is below 150mg/L (1000µmol/L), acetylcysteine **is not** required.
  - If the paracetamol level at 2 hours is greater than 150mg/L (1000µmol/L) level repeated at 4 hours
  - 4 hour level is > 150mg/L commence acetylcysteine

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Predicting concentrations in children presenting with acetaminophen overdose

B. J. Anderson, FFICANZCA, N. H. G. Holford, FRACP, J. C. Armishaw, MBChB, and R. Aicken, FRACP

- Children between 1-5 years are thought to be less susceptible to toxicity then older children and adults.
- It is estimated <5% of children with paracetamol level above the nomogram line will have transiently abnormal LFT
- **Earlier peak levels because of short absorption half life and shorter elimination half life**
- Elimination half life increases with size

- Modelled 1000 children - in the simulation maximum concentration was reached **before 2 hrs in 95% of children**.
- Compared to 121 children (NO children had a level > 200mg/L at 4 hours)
- Adults in the model 4x as many individuals with T1/2 > 4 hrs compared with 1 yr olds
- Anderson's paper recommends a 2 hour level of 225 mg/L(1500µmol/L) but **to increase the safety threshold in children a consensus was reached to lower this level at 2 hours to150mg/L (1000µmol/L) and to furthermore repeat a level at 4 hours.**

J Pediatr. 1999 Sep;135(3):290-5.

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Paediatric (<6yrs) liquid paracetamol ingestion

- A 2 hour level should only be utilised in a well-child with an isolated paracetamol ingestion, in all other cases a 4 hour level should be performed.
- Furthermore for those children who present later than 4 hours post ingestion or in children older than 6 years of age then treat as per adult acute paracetamol exposure.

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When to call PIC or a Toxicologist

- Very large overdoses:
  - Immediate release or modified release paracetamol overdoses of > 50 g or 1 g/kg (whichever is lower).
  - A very high paracetamol concentration, more than double the nomogram line.
- Intravenous paracetamol errors/ overdoses.
- Patients with hepatotoxicity (e.g. ALT > 1000 IU/L).

Note: These are situations where the risk of hepatotoxicity may be greater, the optimum advice is potentially changing and where it may be most useful to seek advice.

Australian Toxicology Monitoring Study(ATOM) – Australian Paracetamol Project (APP)

- Prospective Observational Study
- Recruit patients through calls to the NSW and QLD PIC
- Inclusion:
  - > 14yrs
  - Ingestion of > 35g of paracetamol
  - Paracetamol level > 2000umol/L (300mg/L) at anytime
  - Ingestion of > 10g of sustained release paracetamol
  - Any patients with deranged LFT: AST > 500IU/L, ALT > 500IU/L (that is 10X the upper limit of normal)

COMMENTS or QUESTIONS

"As it's your first day we're going to start you on something easy."

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