Clinical Biomarkers used to Diagnose and Treat Acute Poisoning in Humans

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Workshop on Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations

DEFINITIONS

Biological Marker (Biomarker) - A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarker Definitions Working Group - 1998

General Poison Management (GPM) ABCDEF (G)

- Airway
- Breathing
- Circulation
- Decontaminate
- Enhance Elimination
- Focused therapy antidotes and or supportive care
- Get tox consult
- Evaluation and assessment is a continuous process throughout these steps

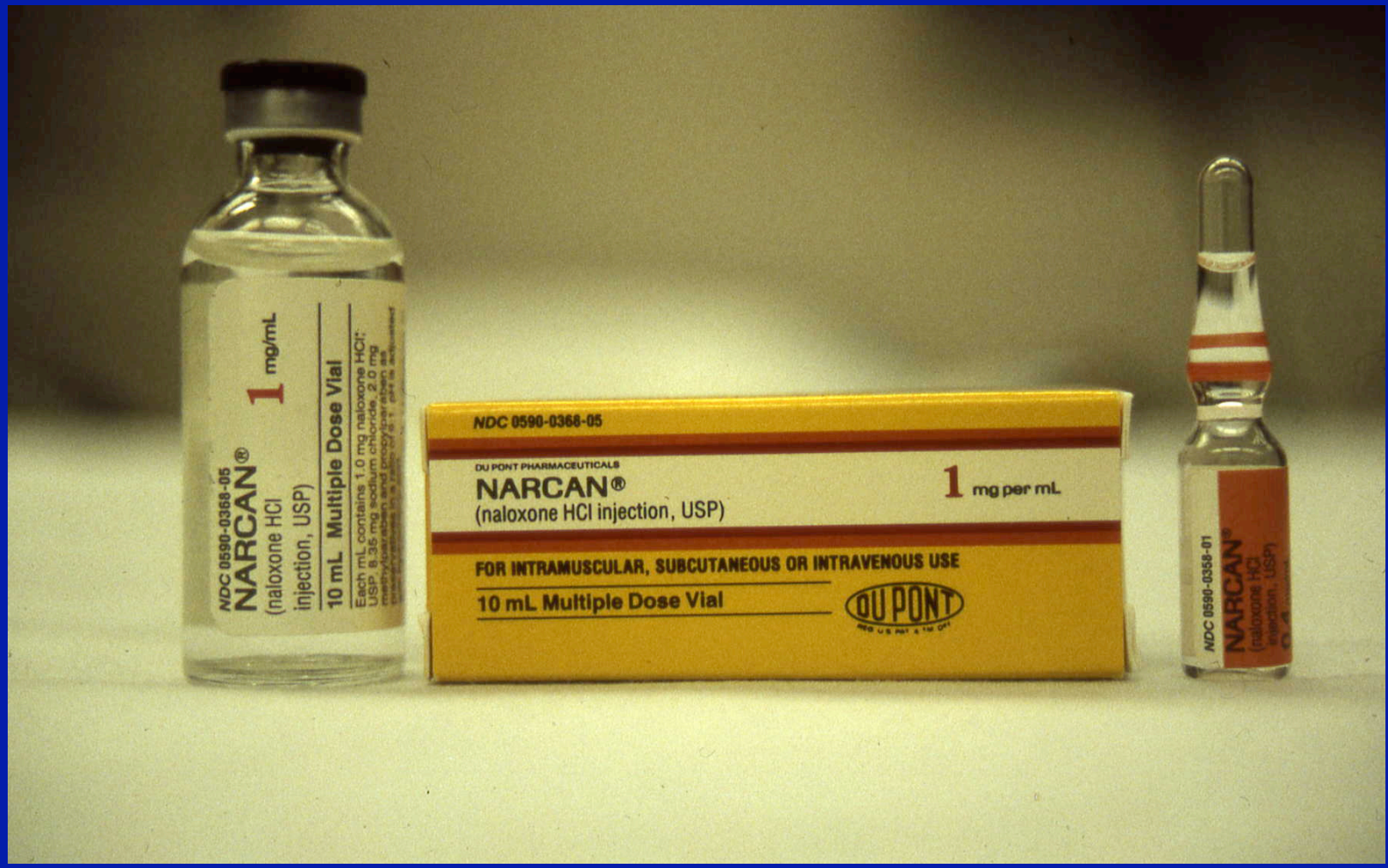
General Approach to Evaluation in GPM

- **Mental Status (comatose, siezures)**
- **Vital Signs (BP, pulse, RR, temp, O_2 sat)**
- **Physical exam (toxidromes)**
- **Objective measures**
  - ABG's, electrolytes (anion gap), electrocardiograms, urine findings, radiologic tests
- **Follow-up diagnostic procedures**
  - serum/urine concentrations
- **Response to interventions**

ABCDEFG

"COMA COCKTAIL"

- *D* extrose
- *O* xygen
- *N* aloxone
- *T* hiamine
- F lumazenil


NDC 0590-0368-05
NARCAN®
(naloxone HCl injection, USP)
1 mg/mL
10 mL Multiple Dose Vial
NDC 0590-0368-05
DU PONT PHARMACEUTICALS
NARCAN®
(naloxone HCl injection, USP)
1 mg per mL
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
10 mL Multiple Dose Vial
DUPONT
NDC 0590-0358-01
NARCAN®

ABCDEFG

"COMA COCKTAIL" - Naloxone

- To reverse opioid and other toxin-induced CNS depression
- Partially effective for benzodiazepines, captopril, clonidine, tramadol, valproic acid
- Consider especially with RR <12, miosis and absent bowel sounds – these are also monitoring parameters
- Evaluate benefit of improved mental status versus risk of agitation or possible withdrawal
- Positive response may lead to avoiding intubation and subsequent risk of aspiration

This is miosis

ABCDEFG

"COMA COCKTAIL"

- *D* extrose
- *O* xygen
- *N* aloxone
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- F lumazenil

ABCDEFG

Flumazenil

- Not to be used routinely in this setting
- Specific benzodiazepine antagonist
- Risk in OD's is unmasking serious complications of concomitant toxins
- Can precipitate benzodiazepine withdrawal reactions, (which are not clearly associated with seizures) especially in short acting agents without active metabolites
- Use in pediatric ingestions and clear sole ingestant adult exposures (iatrogenic)

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ABCDEFG

Circulation: Hyper- or hypotension

- **Fluids and positioning still initial measures**
- **Dopamine is not indicated for all hypotension, often fails with antidepressants**
- **Failure to respond leads to consideration of toxin induced abnormalities**
  - NaHCO3 is initially, followed by norepinephrine suggested for cyclic antidepressants
  - For theophylline consider using beta-blockers
  - Hypertension from sympathomimetic OD or withdrawal states responds well to high dose benzodiazepines

Hypotension (CRASH)

- C Clonidine
- R Reserpine (antihypertensives)
- A Antidepressants
- S Sedative hypnotics
- H Heroin (opiate withdrawal)

Bradycardia (PACED)

- P Propranolol (beta blockers)
  Phenobarbital (barbiturates)
- A Anticholinesterase drugs
- C Clonidine, CCB
- E Ethanol (alcohols)
- D Digoxin, Darvon

Tachycardia (FAST)

- F Free base (cocaine)
- A Anticholinergics
- S Sympathomimetics
- T Theophylline/Thyroid hormones

Hyperthermia (NASA)

- N NMS, nicotine
- A Antihistamines
- S Salicylates, sympathomimetics
- A Anticholinergics, antidepressants

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A TASTE FOR POISON

TOXIDROMES - Bradycardia & Hypotension

- 1A and 1C antiarrhythmics, beta-/calcium-channel blockers, clonidine, antidepressants, digoxin
- Also organophosphates and cyanide
- Very difficult situation; few diagnostic lab tests and therapeutic measures vary widely.
- Try fluids/position/atropine first. Then calcium, glucagon, naloxone, Digibind

A TASTE FOR POISON

TOXIDROMES - Opioid

- Altered mental status, coma, shallow/slow respirations, bradycardia, hypothermia, miosis
- Opiates, dextromethorphan, pentazocine, propoxyphene
- Diagnosis should have been made with naloxone use at presentation but consider inadequate dosing

A TASTE FOR POISON

TOXIDROMES - Sedative/hypnotic

- Sedation, coma, apnea, delirium, hallucinatiosn
- Classically; barbiturates, benzodiazepines, ethanol, opiates, sedatives
- Consider anticholinergics, antihistamines, anticonvulsants (look for nystagmus)
- AVOID stimulant use

A TASTE FOR POISON

TOXIDROMES - Stimulant

- Restlessness, hyper- /hypo- tension, tachycardia, tremor, seizures, coma, euphoria, mydriasis, insomnia
- Amphetamines, caffeine, cocaine, nicotine, PCP, sympathomimetics
- Also OTC diet aids and sleep deterrents
- Again, withdrawal syndromes can present in this fashion
- HIGH doses of benzodiazepines may be required

A TASTE FOR POISON

TOXIDROMES - Anticholinergic

- **Fever, ileus, SVT, dehydrated, mydriasis, myoclonus, delirium, hallucinations, seizures, coma**
  - (Can't see Can't spit; Can't pee Cant sh*t)
- **Consider: Antihistamines, tricyclic antidepressants, phenothiazines, anticholinergics, carbamazepine**
- **Differential includes NMS, serotonin syndrome, malignant hyperthermia, heat stroke, lethal catatonia**

A TASTE FOR POISON

TOXIDROMES - Cholinergic

- Salivation, lacrimation, urination, defecation, gastrointestinal upset, emesis (SLUDGE)
- Also bradycarcia, bronchoconstriction miosis
- Consider: pesticides, ophthalmic cholinergics, myasthenia medications
- Watch infant/toddler with diarrhea and dehydration - ask for recent household/daycare
- BIG doses of atropine may be necessary

Anticholinesterases-cholinergic (DUMB BELLS or SLUDGE)

- D Defecation
- U Urination
- M Miosis
- B Bronchorrhea/spasm

- B Bradycardia
- E Emesis
- L Lacrimation
- S Salivation

- S Salivation
- L Lacrimation
- U Urination
- D Defecation
- G GI distress
- E Emesis

Anticholinergics- helpful hints

- **Hot as a hare, red as a beet, dry as a bone, blind as a bat, mad as a hatter**
  - (Or Can't See, Can't Spit; Can't Pee, Can't Sh*T)
- **Anti-SLUDGE**
  - Lack of:
    - Salivation
    - Lacrimation
    - Urination
    - Defecation
    - GI distress (diarrhea)
    - Emesis

A TASTE FOR POISON

TOXIDROMES - Seizures

- **O**rganophosphates, **T**ricyclics, INH (insulin, iron) and **S**alicylates
- **C**ocaine, **A**mphetamines, **M**ethylxanthines, **P**CP **B**eta-Blockers, **E**thanol, **L**ead, **L**ithium
- Enormous list, fortunately most are self-limited

acronym - Otis Campbell

ABCDEFG

Seizures

- Always use benzodiazepines or barbiturates
- Two important exceptions are cyclic antidepressant and INH OD's
- For cyclic antidepressant-induced seizure use $NaHCO_3$
- For INH-induced seizures use pyridoxine (1 gm:1 gm)
- Avoid phenytoin - contraindicated in theophylline OD

ABCDEFG

Evaluation Tips

- **Reliance on physical exam or lab data alone to determine a specific ingestant very unreliable**
- **Most common co-ingestant is alcohol, what should you expect in terms of affecting the physical exam?**
- **Alert the lab to what you suspect**
  - You don’t always get a lot of blood or urine

ABCDEFG
TOXIC GAPS

- **Anion gap acidosis: "A Cat Piles Mud"**
- **Alcoholic ketosis. CO/cyanide, ASA, Toluene. Paraldehyde, INH (Iron,NSAID's), Lactic acidosis, Ethylene glycol, Sepsis, Methanol, Uremia, DKA.**
  - AG = Na – (CL + HCO3)= (nl) 10-15
    - **A Must Do Calculation!!**
- **Osmolar gap: toxic alcohols, mannitol, glycerol**
  - OG = (2xNa)+(BUN/2.8)+ (Glu/18)+(EtoH/4.6)

Anion and Osmolal Gap!

- **One of the most specific "biomarkers" in clinical toxicology**
- **Mnemonic is ME DIE**
  - » M Methanol
  - » E Ethylene Glycol
  - » D Diuretics
  - » I Isopropyl Alcohol (acetone)
  - » E Ethanol

ABCDEFG

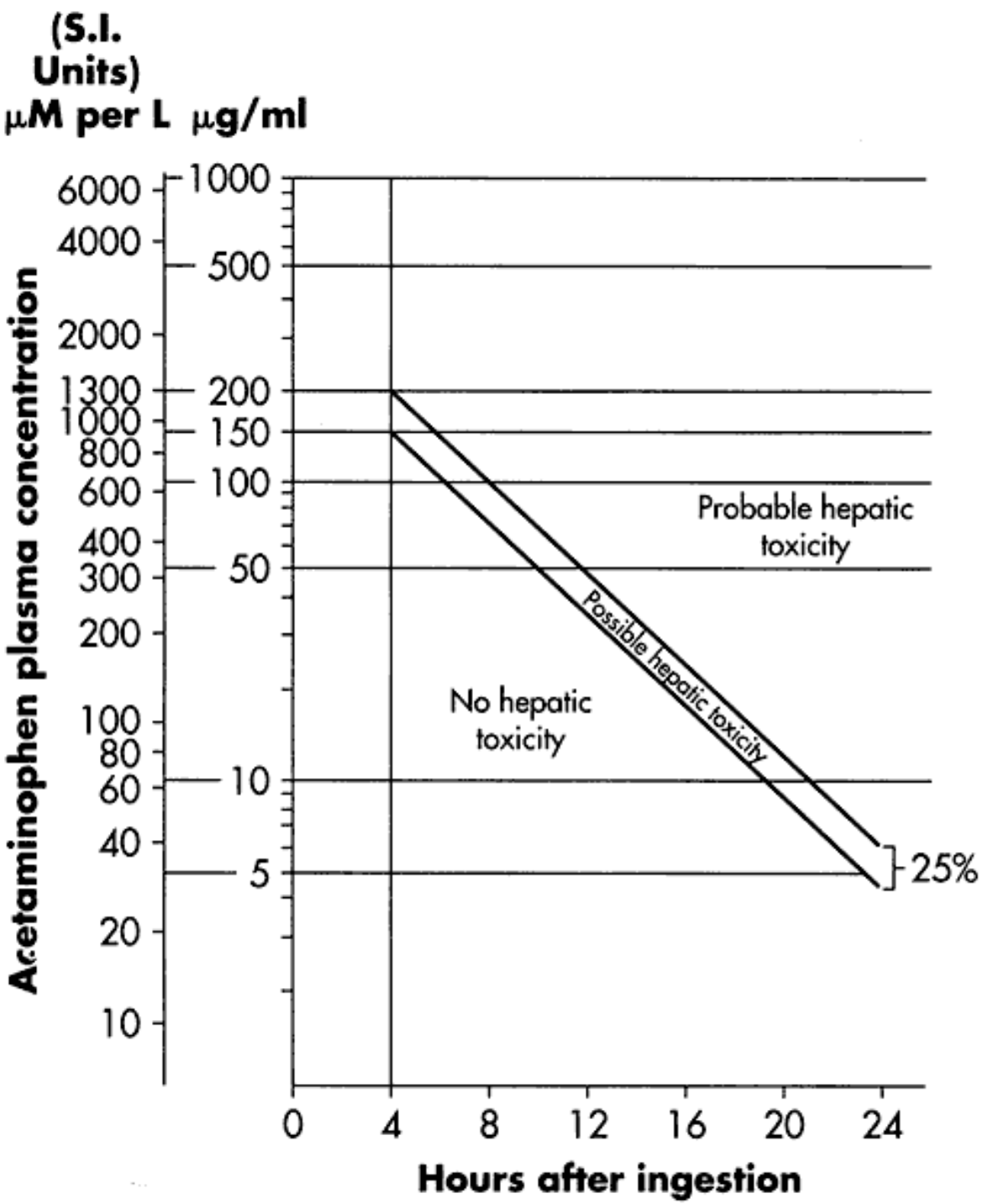
SERUM DRUG CONCENTRATIONS

- Useful: acetaminophen, carboxy or met-Hgb, digoxin, alcohols, iron, lithium, theophylline, asa
- Chronicity of exposure is important in evaluation and treatment; acute ingestions require higher Cp's for toxicity usually
- Timing: repeat every 2-4 hours until clearly descending
- Repeating concentrations most important with SR products

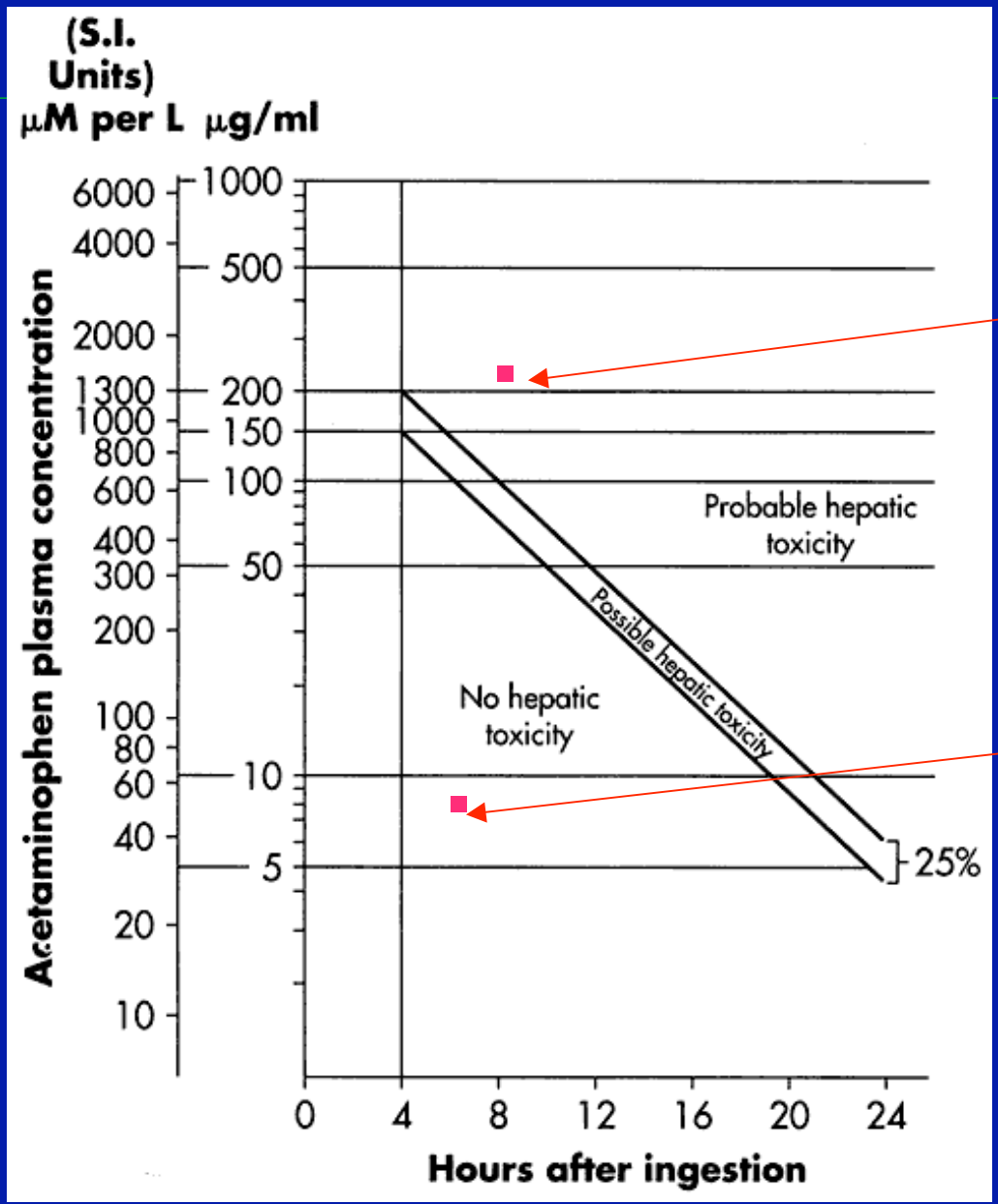
ABCDEFG

SERUM DRUG CONCENTRATIONS -tips

- Always order an acetaminophen in deliberate OD's or in analgesic exposures
- Nomogram for acute single overdoses of acetaminophen
- Acetaminophen serum concentration is best example of clinical biomarker in clinical toxicology
- Remember metabolites can give an indication of the timing of the ingestion


(S.I. Units)
μM per L μg/ml
Acetaminophen plasma concentration
6000
4000
2000
1300
1000
800
600
400
300
200
100
80
60
40
20
10
1000
500
200
150
100
50
10
5
Probable hepatic toxicity
Possible hepatic toxicity
No hepatic toxicity
25%
0
4
8
12
16
20
24
Hours after ingestion

Acetaminophen nomogram



220 mg/l at 8 hr

13 mg/l at 6 hr

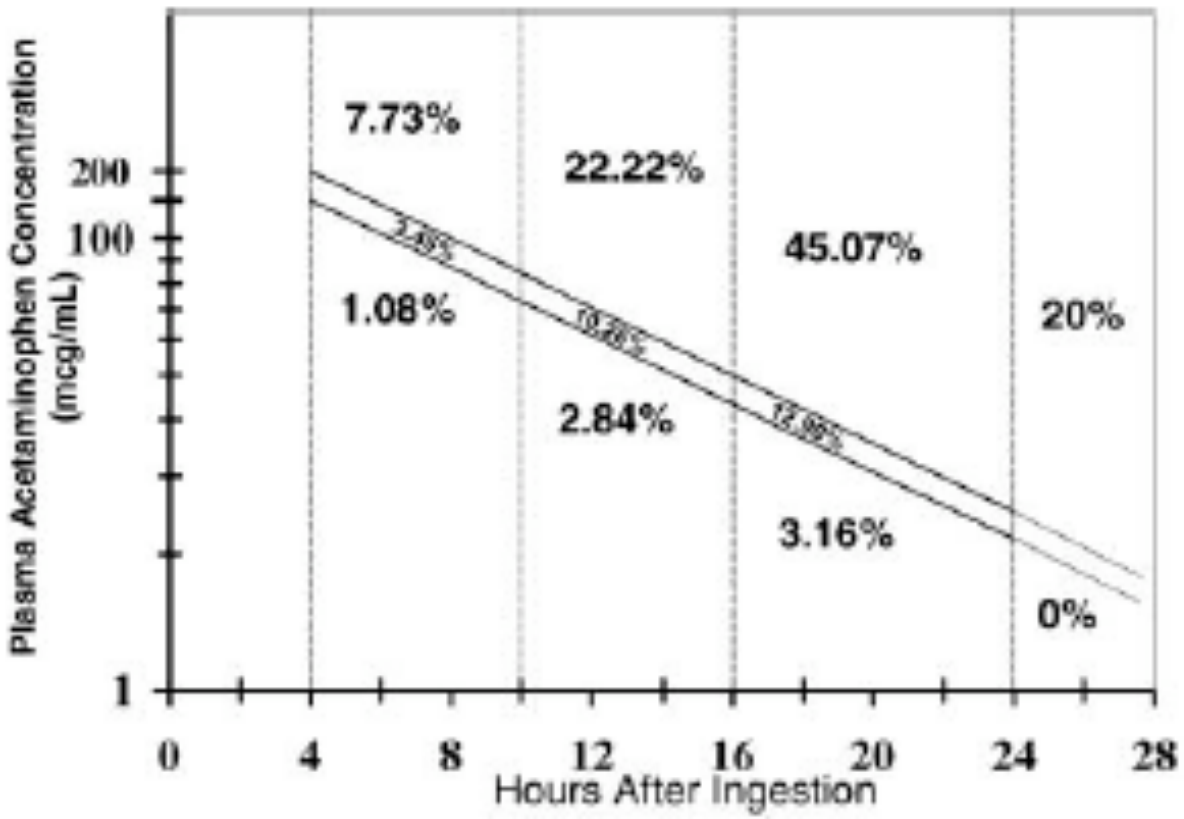
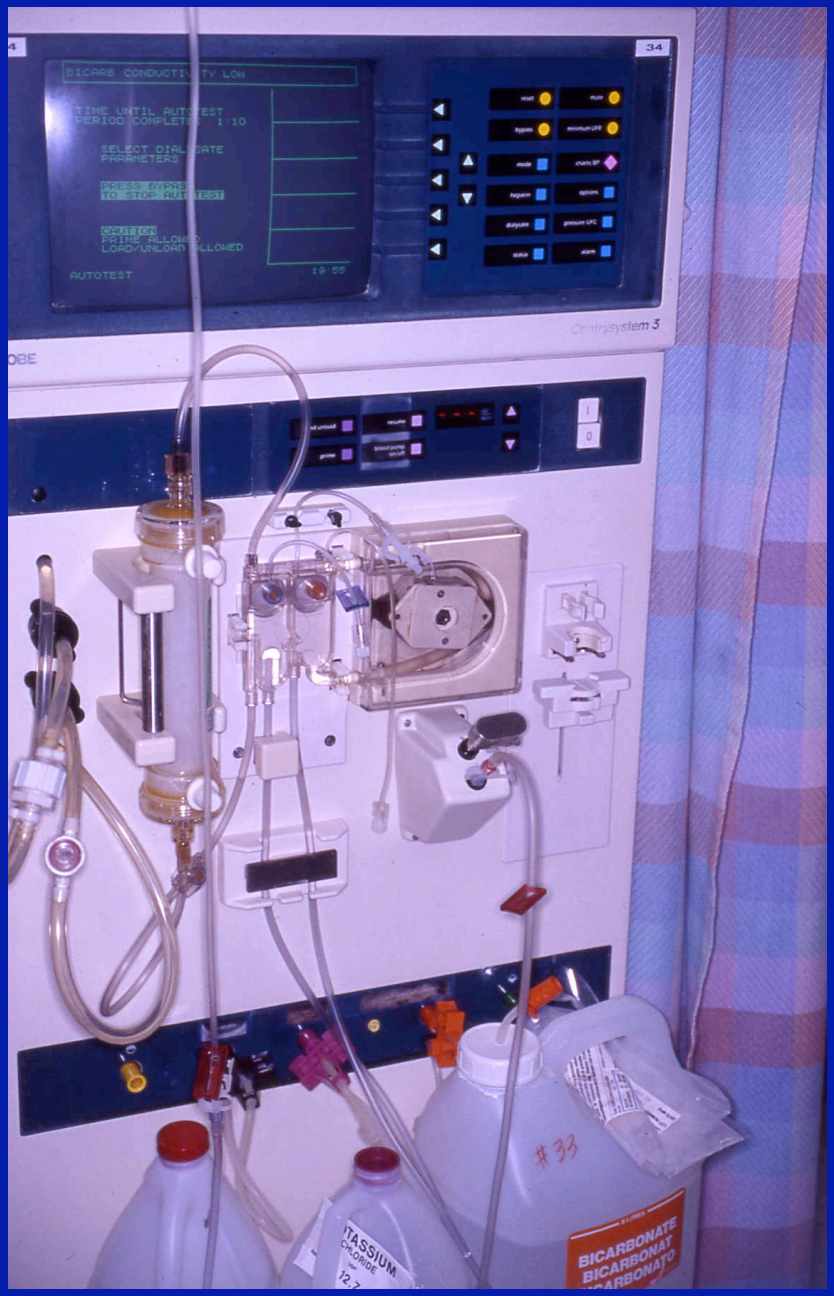


Figure 4. Outcome nomogram—additional data from the National Multicenter Study.


AUTOTEST
Centrysystem 3
#33
BICARBONATE
BICARBONAT

ABCDEFG

HEMO-DIALYSIS, -PERFUSION

Specific Concentrations with an indication

- Toxic alcohols
  (ethylene glycol, methanol at 50 mg%)
- Salicylate (60, 100 mg%)
- Lithium (> 4.0 mEq/l (if post-distribution)
- Theophylline (60, 100 mg/l)

(chronic , acute overdose [ ]'s indications)

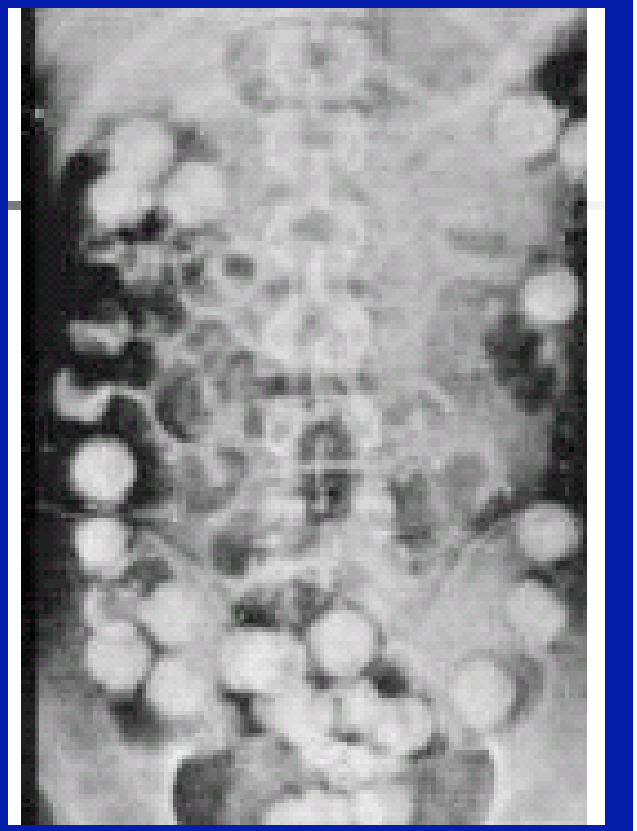
ABCDEFG
Drug/Toxin concentrations

- Always check the units (especially with nomograms)
  - **Watch out for ASA and alcohols – often reported in mg%**
- Consider the known pharmaceutical and pharmacokinetic properties.
  Is it absorption, distribution or elimination phase?
- Concentrations should follow known pharmaco-kinetic behaviors
  - **Think how bezoars/ concretions or SR products might affect concentrations**

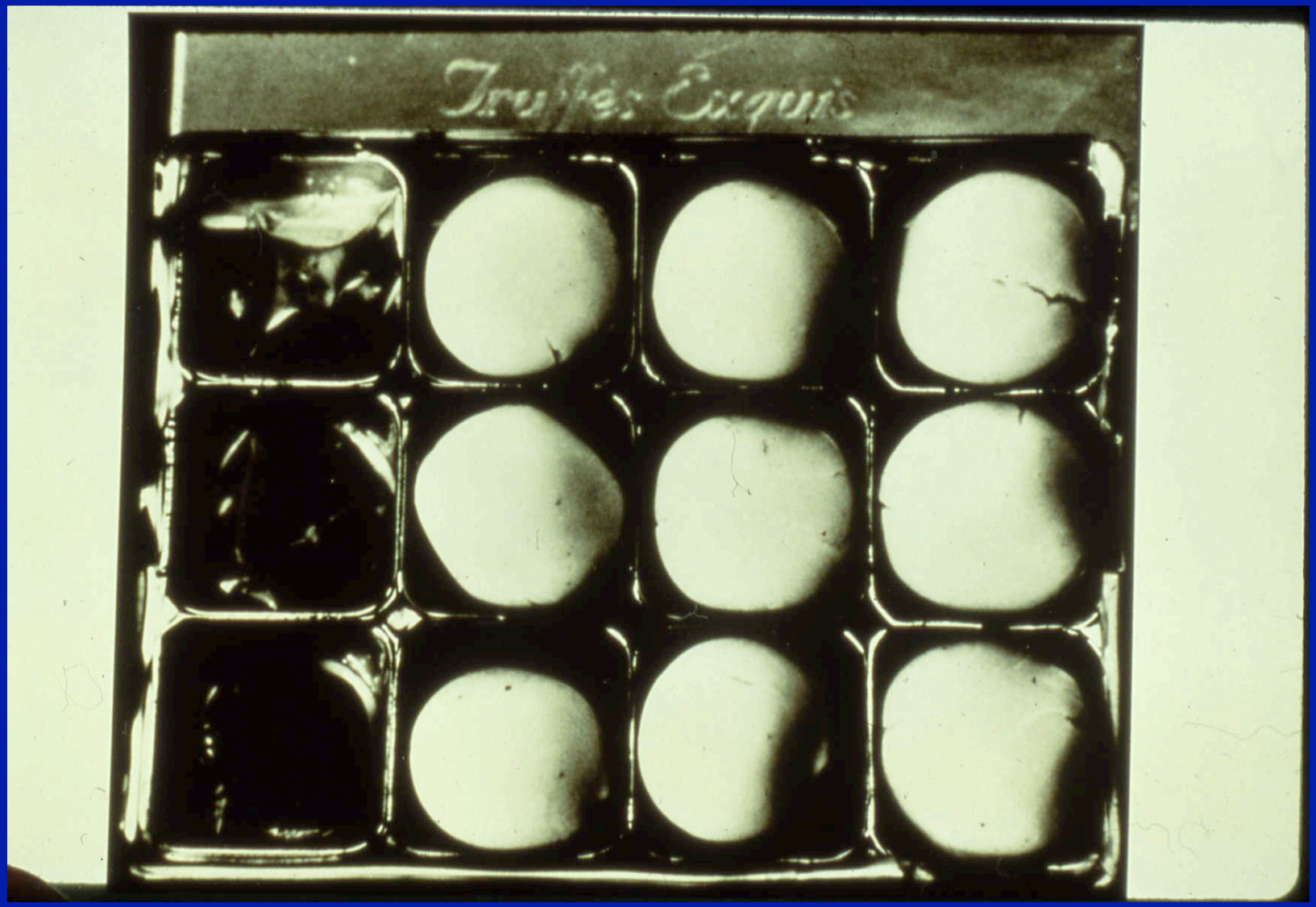
ABCDEFG

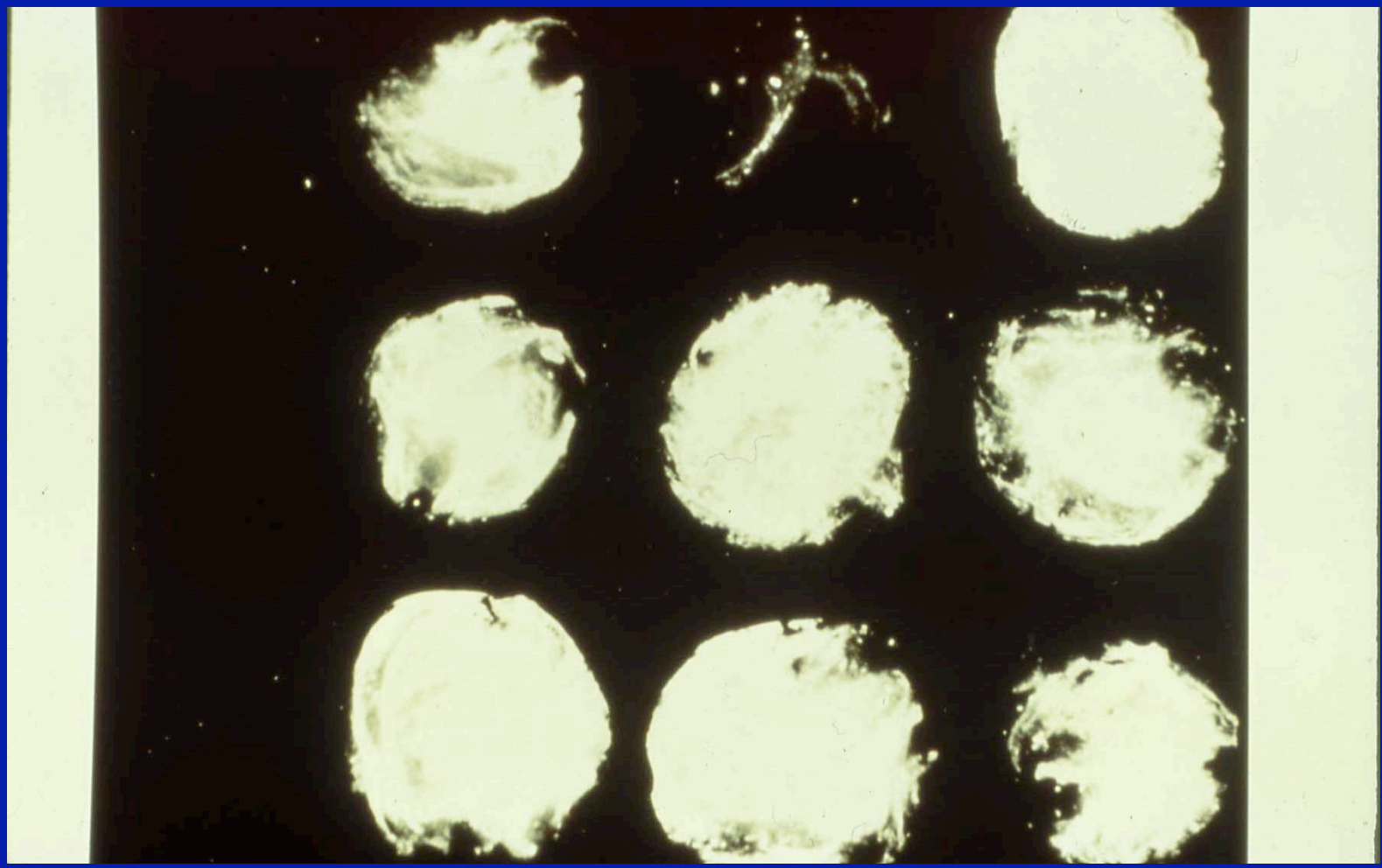
RADIOGRAPHY - KUB

- Heavy metals, Iron, Packets (drugs), SR's
- Specifically; street drug vials/packets, iron, lead, lithium, zinc, coins, batteries.
- Facilitates diagnosis and serially useful in assessing decontamination
- Contrast may be necessary for visualization.



acronym - HIPS


Truffes Exquis



ABCDEFG

Urine tox screens

- Usually not helpful, lack appropriate temporal correlation to presentation
- What does the "tox screen" screen for ?
- Often only common drug of abuse screens, positives results often do not change empiric therapy
- Results are usually independent of the acuity of the exposure
- More important from a legal standpoint

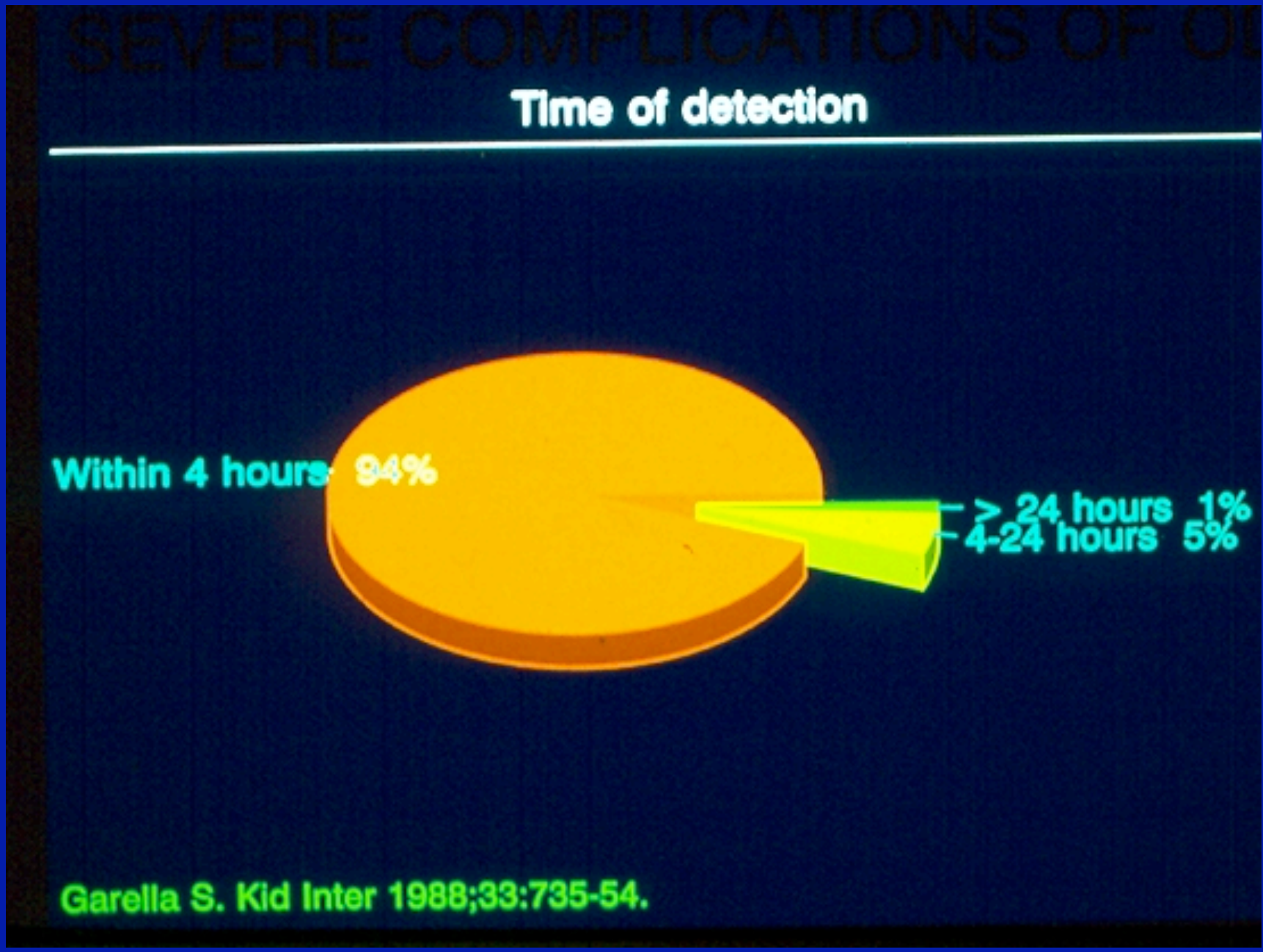
ABCDEFG

Miscellaneous evaluation measures

- **Fingerstick glucose**
  - A very fast result
- **Blood gases**
  - Most often arterial but if you are only assessing acid:base and not oxygenation, then venous is just as good and much less painful and difficult
- **Pregnancy testing**
  - Always in women of child bearing age
- **Measures to assess pH**
  - Useful with unknown liquids as a fast screen for corrosiveness

ABCDEFG Focused Therapy

- **Toxidromes**
  - generate a differential diagnosis
  - Thus, a prioritized list of empiric therapies
- **Laboratory determinations**
  - add or refine the list of potential toxins
  - Thus add or refine empiric therapies
- **Therapeutic Interventions and response**
  - Refine or finalize the diagnosis
- **Why aren't there more markers?**


SEVERE COMPLICATIONS OF
Time of detection
Within 4 hours 94%
> 24 hours 1%
4-24 hours 5%
Garella S. Kid Inter 1988;33:735-54.

SEVERE COMPLICATIONS OF OD

Time of resolution

Garella S. Kid Inter 1988;33:735-54.

ABCDEFG Focused Therapy

- **Why aren't there more markers?**
  - Isn't enough time
  - Incidence is insufficient to be prepared for all possibilities
  - Money

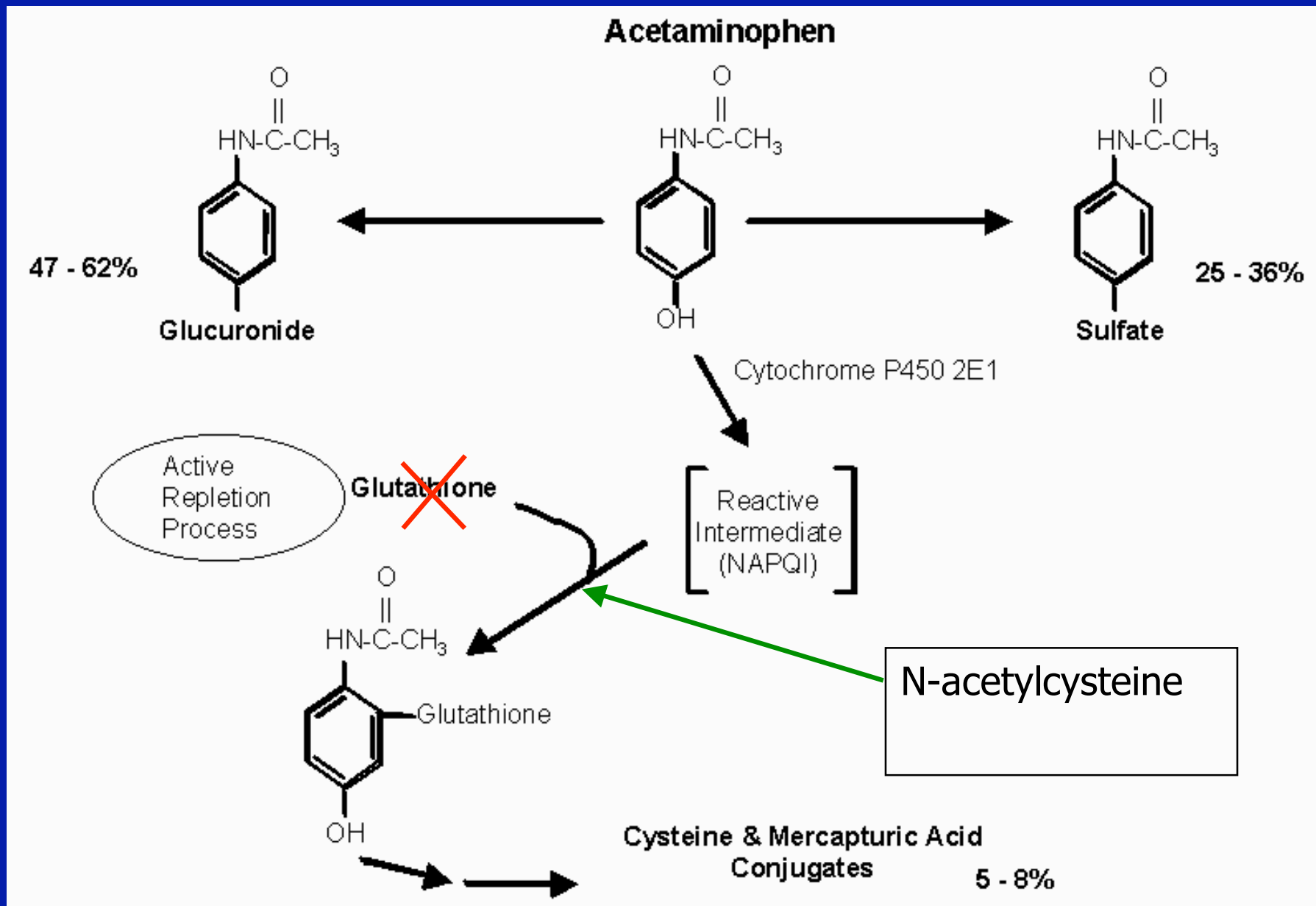
ABCDEFG

Clinical pearls for poisoned patients

- What is the turn around time for the test ? Is it a send-out ?
- Non-STAT labs should be run STAT for poisonings
- Consider dilution errors if symptoms don't match values or values change too rapidly

Where do we need more help?

- **Acetaminophen**
  - Isnt it perfect already?
    - Increasing number of deaths
    - Inability to predict need for liver transplant
    - Assessing the chronic exposure
- **Psychiatric medications**
  - Serotonin vs Neuroleptic vs Anticholinerig vs just sleeping
  - Massively elevated ammonia
  - Should everyone get a Li, CBZ, VPA done?
- **Serum concentrations**
  - What is a “bad” number before it causes badness?
- **Bradycardia/Hypotension**
  - Cause?
  - And a focus on who needs hyperinsulinemic therapy


Acetaminophen
47 - 62%
Glucuronide
25 - 36%
Sulfate
Cytochrome P450 2E1
Active Repletion Process
Glutathione
Reactive Intermediate (NAPQI)
Glutathione
N-acetylcysteine
Cysteine & Mercapturic Acid Conjugates
5 - 8%

Where don't we know we need help?

- **Drug interactions involving oxidative metabolism**
- **Understanding transporters and assessing function clinically in an acute care setting**
- **Idiosyncratic metabolic hypersensitivity reactions (ie, with aryl amines)**
  - How do we recognize them? How do we avoid them?

Changes in Deaths

- Since 1983, analgesics and antidepressants have ranked 1st and 2nd in absolute number of deaths reported to Poison Control Centers.
- In the first 16 available reports (through 1998); sedative/ hypnotics, cardiovasculars and asthma therapies were the next 3 most common drug causes although the first 2 did alternate rank several times.
- In 1999, anticonvulsants (predominantly through valproic acid) entered the top five (in fact top 10 of drugs) WHY?

Changes in Deaths

- Prior to 1994, antidepressants barely ranked 1st , since 1997 analgesics have ranked 1st and have doubled the number of deaths. Drug interactions potentially account for a significant # of antidepressants cases
- Cardiovasculars have become predominantly SR calcium channel blockers.
- Starting with clozapine, new antipsychotics have supplemented old "sleepers" in helping to maintain the ranking of sedative/hypnotics and represent 33% of deaths in this category.

Common factors?

- Sustained-release formulations can add prolonged absorption, (often referred to as “long elimination half-life”) or active metabolites. Mortality with these agent clearly increased over immediate release. Is it PK or PD? Peak concentrations or AUC?
- Agents with cardiac and vasculature or CNS effects.
- Oxidative metabolism, especially through CYP3A4
- Large volume prescribing
- Elderly and or psychiatric patients
- **QT prolongation**
- **Absent laboratory tests or antidotal therapy**

SRI Antidepressants

SSRI'S

- Paroxetine*
- Fluoxetine*
- Citalopram
- Fluvoxamine
- Sertraline

SRI's

- Bupropion
- Venlafaxine
- Nefazodone
- Mirtazapine

Red face type represents CYP 3A4 metabolsim effects. * indicates 2D6 effects. Both affect TCA's

Atypical Antipsychotics

- Prior to 1998 data, atypicals not listed in TESS data separate from older phenothiazines. 1983-1997 data averaged < 10 deaths due to phenothiazines annually, most mixed ingestions.
- Since then death to antipsycotics increased 100-150%, all due to atypical antipsychotics.
- All have been multidrug ingestions and most have been suicides
- Rare, agranulocytosis with clozapine (includes one “1 will kill kid”)

Atypical Antipsychotics

- Clozapine, Risperidone, Olanzapine, Quetiapine
- Also, potent 5HT2 antagonists
- Present with sedation in acute ingestion. Chronic presentation is NMS vs Serotonin syndrome
- Differential toxin diagnosis long.
- No specific lab test, usually rely on urine drug screen (if available)

Calcium Channel Blockers

- Represent >60% cardiovascular deaths past five years. (several “1 will kill kids” cases)
- 5-10 NDA’s expected next 18 months.
- Common presentation: altered mental status, hypotension, bradycardia. No common readily available lab test. Differential includes beta blockers, digoxin, clonidine, Type IA and IC antiarrhythmics.
- Conventional, well published antidotal therapy absent. Recent promise with hyperinsulinemia- But who needs this therapy? Does hyperglycemia need to be present?

Calcium Channel Blockers

- Cardiovascular agents fatality rate rose 200% since 1983 - due predominantly to CCBs. In that same interval, no ACE inhibitor, ARB's, diuretics, or peripheral alpha1 blockers deaths were reported.
- Following a suicide attempt, serious consideration should be given to warning against continued access to CCBs, or is reasonable using the more peripheral vasculature selective agents, shorter acting agents and or immediate release dosage forms

Anticonvulsants

- Several new agents on market
  - **Gabapentin (Neurontin)**
  - **Topiramate (Topamax)**
  - **Lamotrigine (Lamictal)**
  - **Levetiracetam (Keppra)**

- All seem relatively benign from acute toxicity.
- Lamotrigine associated with Anticonvulsant Hypersensitivity syndrome (especially with VPA)

VALPROIC ACID

- Incidence of overdose deaths annually prior to 1997 was < 5.
- Currently averaging >10 per annum.
- Commonly presents with CNS depression and GI symptoms.
- Marked inhibitor of CYP metabolism, epoxide hydrolase and other hepatocellular free radical scavenging systems
- Enjoying widespread use in multiple psychiatric diagnoses and now in SR form
- Interferes in fatty acid metabolism, concommitant hyperammonemia, is this a biomarker?