Alder Hey Children's NHS
NHS Foundation Trust

Guy's and St Thomas' NHS
NHS Foundation Trust

Paediatric Formulations "The Clinical Perspective"

Tony Nunn & Sara Arenas-Lopez

Paediatric Pharmacists
Alder Hey Children's Hospital, Liverpool, U.K.
Evelina Children's Hospital, Guy's & St Thomas NHS Foundation Trust

Introduction

What is an ‘age-appropriate’ formulation?

- Lack of evidence base
- Research underway
- Misinterpretation of ‘reflection paper’

Excipients

Discussed by others

Exposure of neonates of concern

- Developmental toxicokinetics?

Resolution of formulation problems

- Insufficient space for excipients
  - **e.g. oro-dispersibles**
- Additional excipients
  - **e.g. coated granules**

Some common problems

Hyperosmolal solutions

- Especially neonates
  - **Enteral**
    - Associated with NEC
    - N&V
  - **IV**
    - Phlebitis and pain
    - Plasma hyperosmolality
    - Requirement for dilution

      Excess fluid/electrolytes

Some common problems

Measurement of dose volumes

- Accuracy
  - e.g. 0.02 ml with 0.005 ml error = 25%
  - whereas 0.5 ml with 0.005 ml error is 1%
- Potential for error
  - Misinterpretation
  - Dilution
    - 10x errors
- ‘Rinsing’ of syringes (especially for PK studies)

Ensure concentration is appropriate for dose

Ensure amount presented limits risk of overdose if miscalculation occurs

Additional risk factor

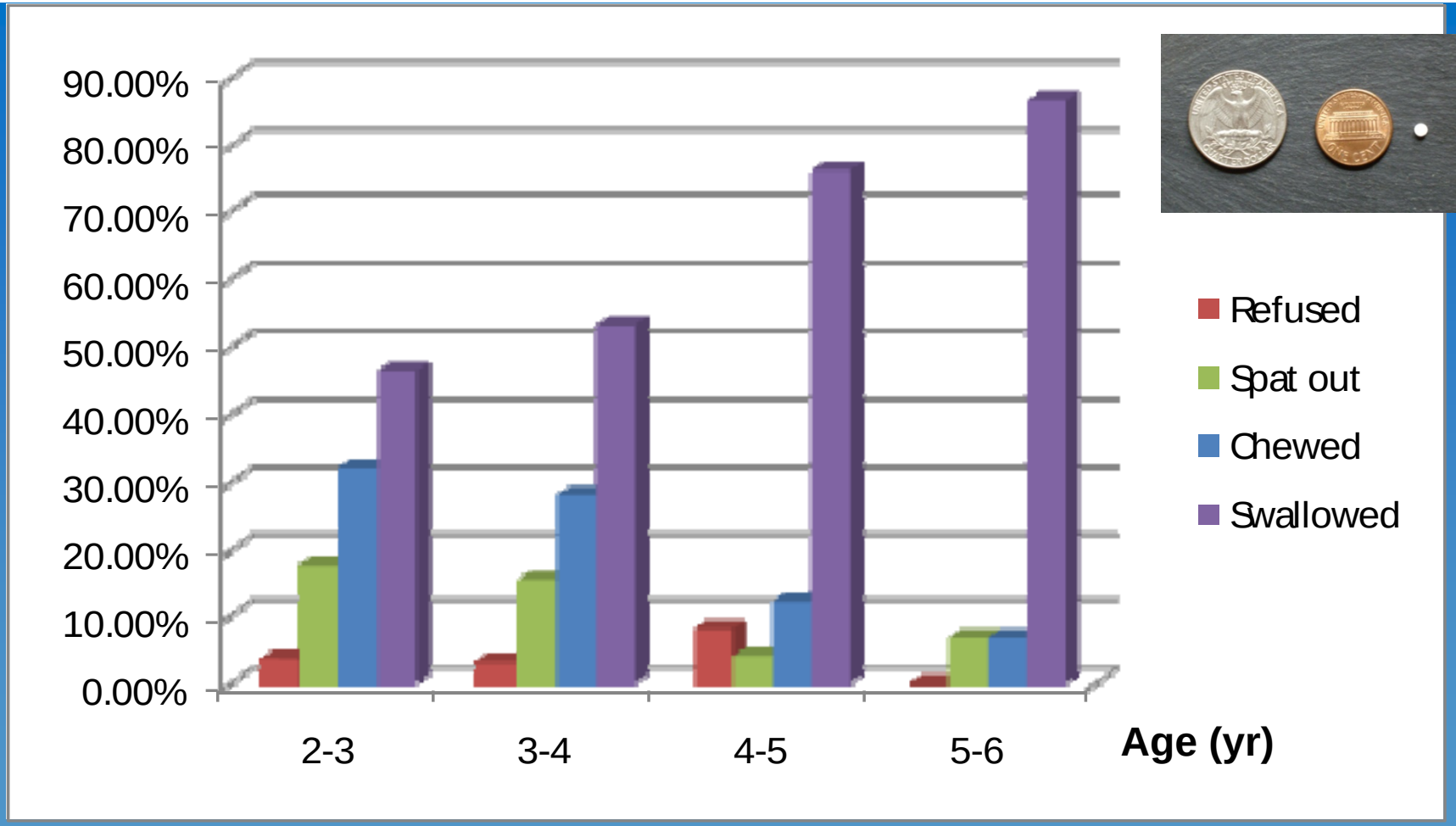
- requiring pharmacy manipulation (if available)

At what age can children take solid oral dosage forms (tablets/capsules)?

Messages

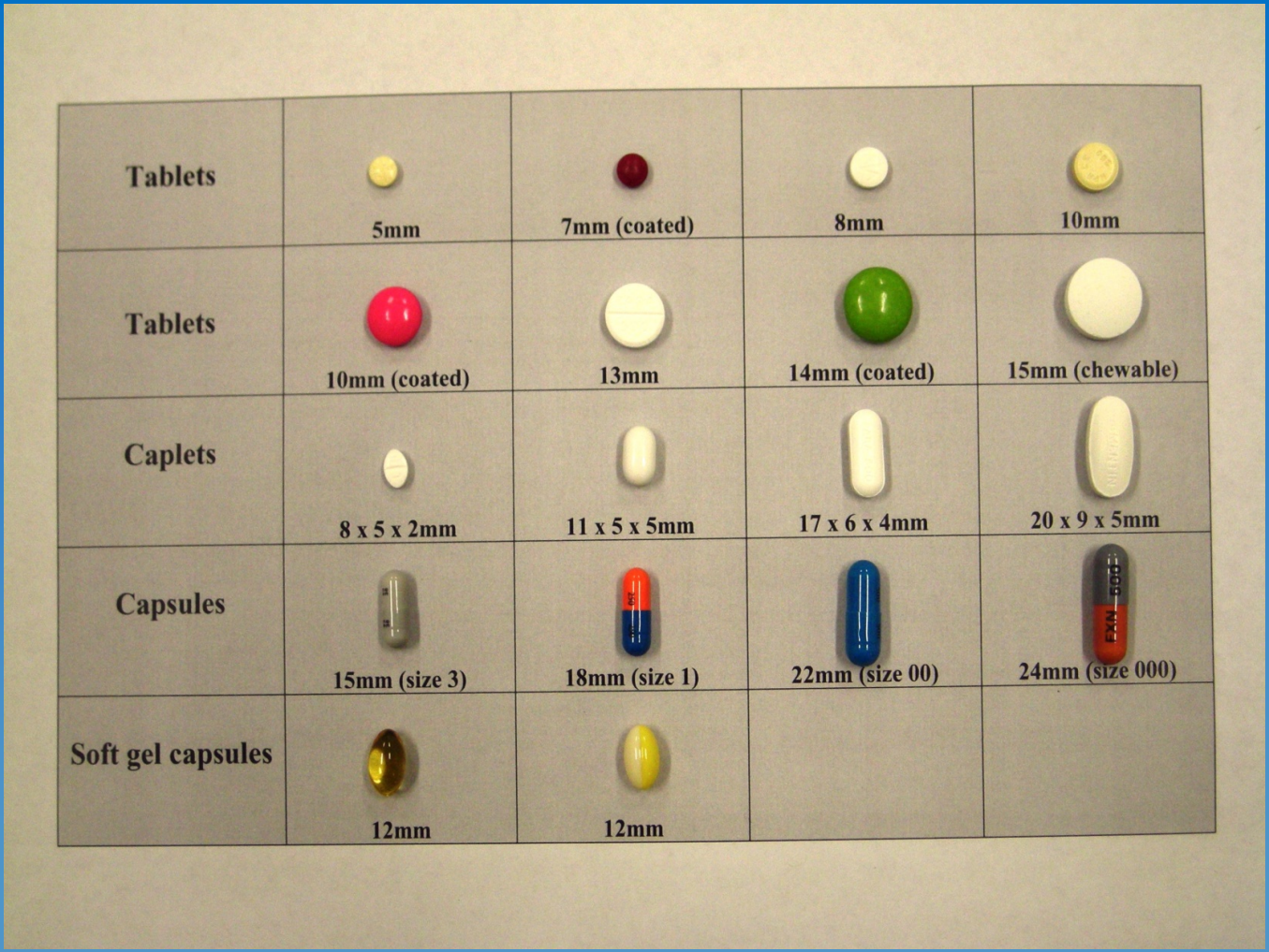
- Not much evidence available
- Wide variety of ages quoted
- Tablets and capsules vary
  - size and shape
  - Method of administration e.g. orodispesible
- Training can help
  - Use of jelly beans etc.
  - Taste of liquid alternative may be an influence
- Demonstrate that dosage form is appropriate for age
  - Ask the children

Mini-tablets



Thomson et al. 2009 Pediatrics ;123(2): e235-e238

Tablet and capsule sizes



Children's preferences

Liverpool YPG	GOSH School Children
11-16yrs (n=8)	**11-16yrs (n=9)**
Variable solid dosage form preference	Round tabs<10mm diameter preferred
Soft gel caps not preferred to larger tablets except by one (youngest 8 & 9 yr old's 1st choice)	Soft gel caps not preferred to larger tablets
More optimistic about ability to swallow solids	Much less likely to be able to swallow solids
Flavour: strawberry>orange>banana	Flavour: orange>cherry=apple
Dislikes about taking medicines: palatability rated highest (smell, flavour taste)	
Dislikes about taking medicines: side effects such as nausea and drowsiness	

Does my medicine taste nice?

Taste, smell and texture of liquid medicines

- Taste testing
  - Adult/paediatric taste panels
  - In use testing
  - Electronic methods
- Volume
  - Concentrated drops and accuracy

Taste masking with food or liquids

- Paradigm
  - Whole dose will not be consumed
  - Food/drink aversion
  - Common practice and provides ‘masking’ at point of administration
- Granules/particles
  - Intended to be added to food

Liquid oral medicines

Messages

- Not much evidence available
  - Cultural differences?
- Children are concerned about palatability
- Large volumes of unpalatable liquids will be rejected
- Small volumes preferred (if dosed accurately)
- Food and drink frequently used to mask poor taste

Manipulating dosage forms

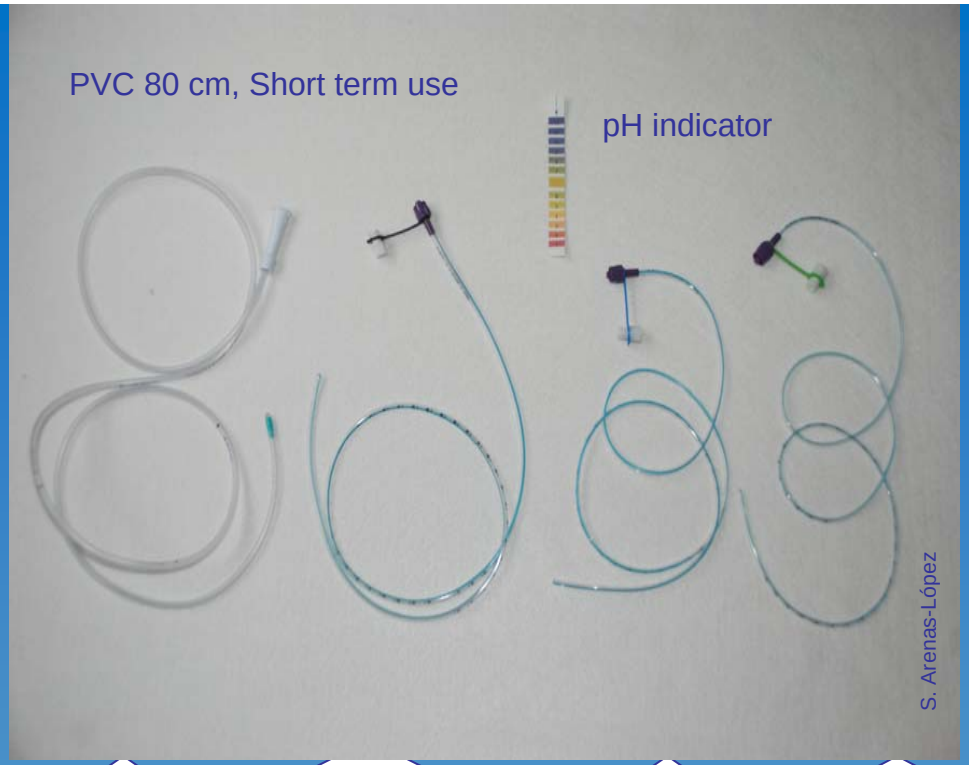
Convenience (crush tablets/open capsules)

- Enteral tubes
  - Naso-enteric
  - Gastrostomy/jejunostomy
  - Interaction with feeds/materials

Accuracy

- Splitting tablets
- Many other manipulation types

Naso-gastric tubes



12 Fr
>10 year

10 Fr
>1 year
<10 years

8 Fr
<1 year

6 Fr
Neonates
< 4-5 months

12 Fr
>10 years

6 Fr
Neonates
> 4 months

Extemporaneous preparation

Variations in captopril formulations used to treat children with heart failure: a survey in the United kingdom

Hussain Mulla, Magdi Tofeig, Frances Bu'Lock, Nilesh Samani, Hitesh C Pandya

Arch Dis Child 2007;**92**:409–411

Table 1 Composition and stability of liquid captopril formulations used to treat children with heart disease in the UK

	Strengths	Expiry (days)	Stability data*	Excipients
"Specials" manufacturer				
Cardinal Health Martindale Products	Various	90		Fractionated oconut oil, Cab-o-sil
The Specials Laboratory	Various	28	No	Xanthan gum 1%, ascorbic acid
Nova Laboratories (flavoured)	Various	28	No	Flavoured suspension Diluent A in a 1:1 ratio with water, ascorbic acid
Nova Laboratories (unflavoured)	Various	8	No	Suspension diluent A in a 1:1 ratio with water
NHS manufacturing unit (St Mary's Pharmaceutical Unit)	1, 5 and 12.5 mg/ml	35	No	Xanthan gum 0.4%, methyl hydroxyl-benzoate, propyl-hydroxy benzoate
Imported (Bristol–Myers Squibb, Australia)	5 mg/ml	28	Yes	Citric acid, sodium citrate, disodium edetate, sodium benzoate
Extemporaneous formulations				
Southampton General Hospital	1 mg/ml	14	No	Ascorbic acid, water
Bradford Royal Infirmary, Royal Hospitals, Belfast, and St George's, London	Various	14	No	Suspension diluent A
St George's, London	Various	14	No	OraPlus/OraSweet (1:1 ratio)
Queen's Medical Centre, Nottingham, and Gloucester Royal Infirmary	Various	14	No	Suspension diluent A in a 1:1 ratio with water

Suspension diluent A contains xanthan gum 1%, methyl hydroxybenzoate and propylhydroxy benzoate. St George's Hospital, London, provided two extemporaneous methodologies.
*Evidence of comprehensive in-house stability data on the final finished product.

- industry-verified?

Manipulation/extemporaneous dispensing

Dosage forms will be manipulated

- By carers
- By pharmacists
- Not much evidence
  - Mainly on splitting tablets
  - Issues
    - Accuracy
    - Bioavailability
    - Health and safety

Industry verification?

Other routes of particular interest

Buccal
- e.g. midazolam for prolonged fits; preferred to rectal

Nasal
- e.g. diamorphine and other opioids for pain
  - delivery devices and accuracy of dose delivery
  - preferred to oral morphine

Transdermal
- Continuous delivery without IV infusion
- Skin permeability and age
  - Bioavailability

Rectal
- Acceptability
  - cultural differences
  - convenience (e.g. schools; emergencies)
- Ability to vary dose with age/weight

Desirable features of paediatric formulations

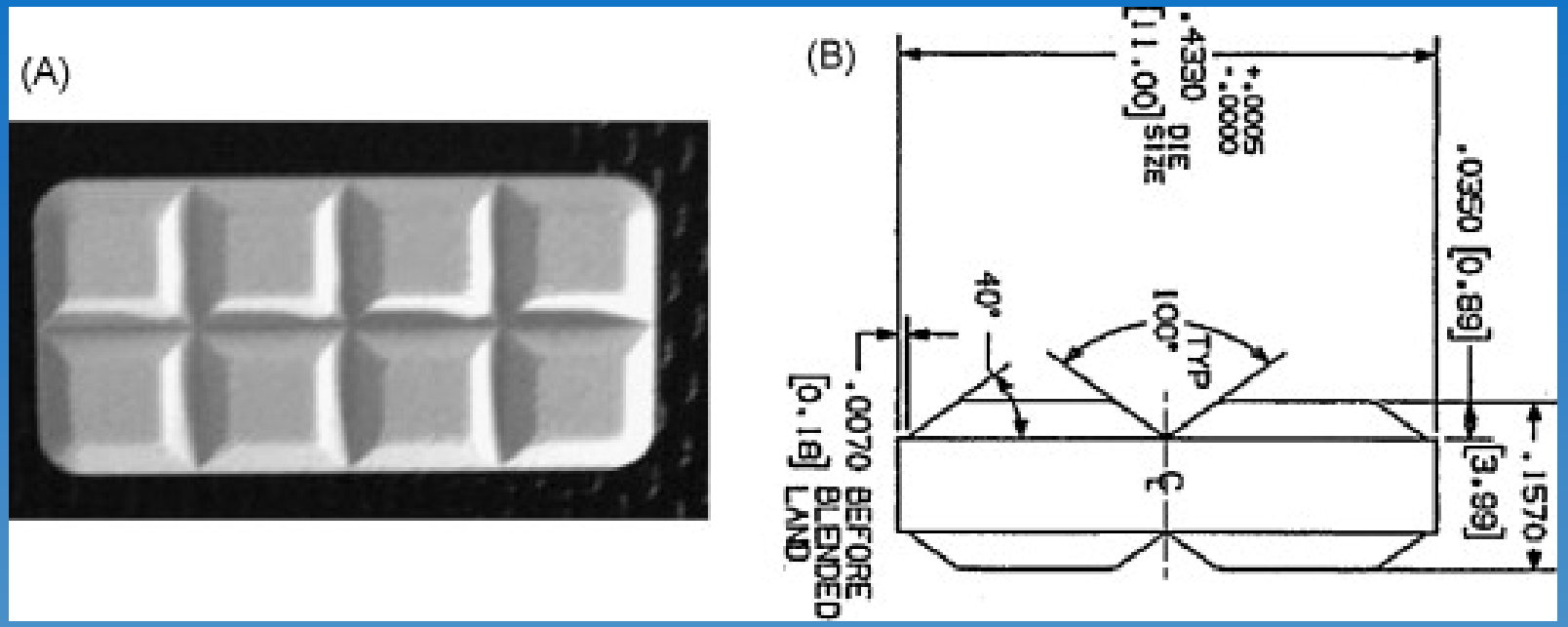
Affordable
Commercially viable
Transportable and low bulk/weight
Minimal administration frequency
- Simple regimen

One dosage form fits all or full range/choice
Minimal impact on life style
Minimum, non-toxic excipients
Convenient, easy, reliable administration
- Palatable
- Minimal manipulation

Easily produced, elegant, stable
- Heat stable

Achievable?

Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications



- dispersible
- accurate

Kayitare E, Vervaet C, Ntawukulilyayo JD, Seminega B, Bortel V, Remon JP. Int J Pharm 2009 Mar 31; 370(1-2): 41-6

Parenteral Route: General Considerations

- Required if drugs not effectively absorbed by the enteral route or if quick/high/or constant blood and tissue Cp required
- Injections not generally liked by children
- Attention to needle size and method of injection
- Transcutaneous needle free administration using air pressure to fire dose sprayed through skin (i.e growth Hormones)
- If only adult sizes are provided the potential for medication errors increases considerably (i.e furosemide injection 1000 times the neonatal dose, LMWH)
- Freeze-dried powders require reconstitution & a proportion of the volume measured to provide the dose (Displacement Volume to be considered)
- Other parenteral routes include intrathecal, epidural, SC infusion, intraosseous injection or techniques such as PCA, NCA

IV Route

- In some cases IV administration the only appropriate route

Used for: Medicinal products, blood derivatives, nutrition and fluid therapy

- Accessing small veins in neonates & children may be difficult as fragile vasculature system & peripheral venous access may need to be reassessed often
- Formulation of the injection & instructions for dilution & administration important to prevent damage to the veins. Important to research both peripheral & central routes & provide information in SmPC

Risk of IV therapy

Infection

Phlebitis

Infiltration

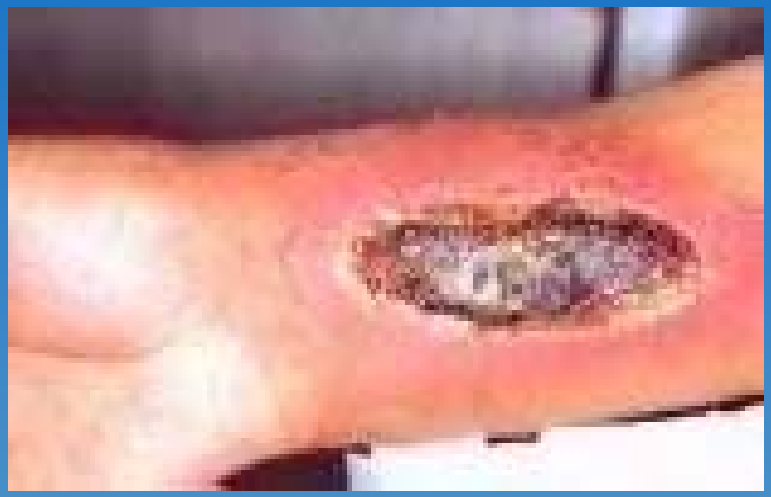
Fluid Overload

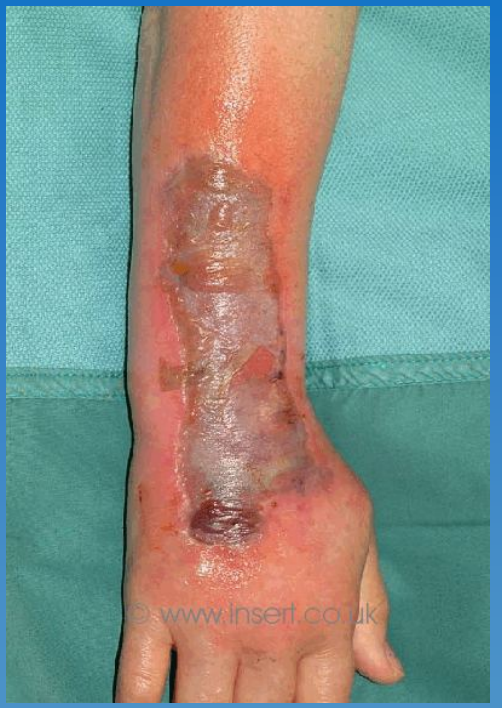
Electrolyte Imbalance

Embolism

Extravasation

Extravasation Injuries





Lines

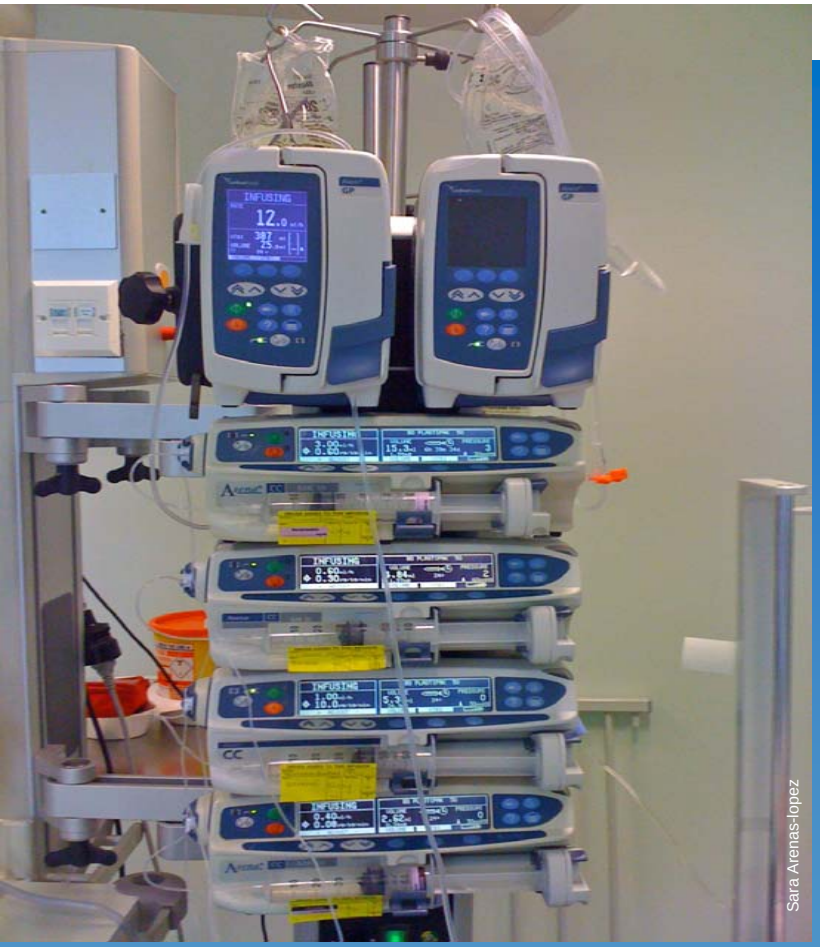
- Peripheral (Single lumen, Y Site connections)

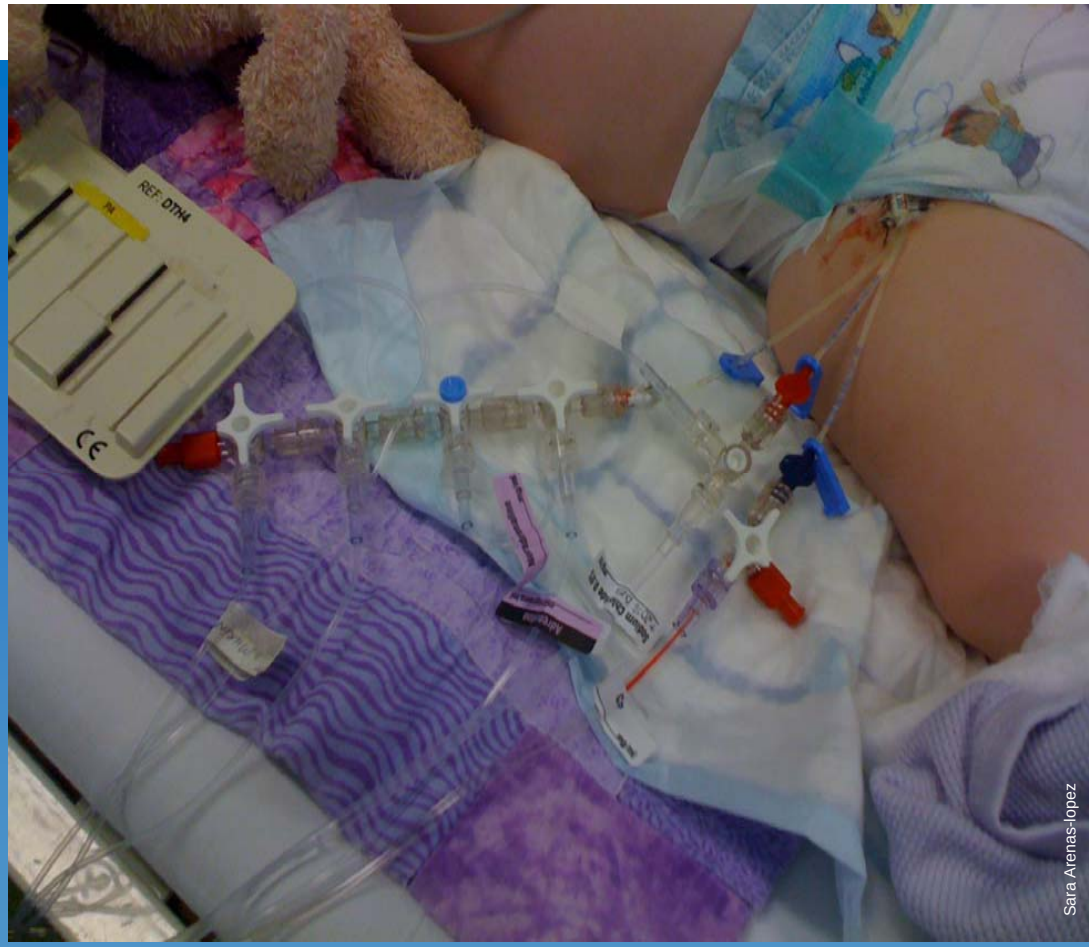
pH, Osmolarity, concentration and infusion rate critical

- Central (Single, double or triple lumen + Y-Site):
  - PICC
  - Tunnelled lines (i.e Hickman Lines)
  - Implantable Ports

Dilution of injections less critical due to rapid dilution & permits higher concentrations in fluid restricted children. Rate of infusion slowly may still apply to avoid cardio-respiratory collapse

IV Infusion rack & Y-Site connections





IV Fluid Therapy & Electrolytes

- Given as maintenance and/or replacement therapy and/or line patency

Risk: Dilutional hyponatraemia with hypotonic solutions

- This may be co-administered with medicines.

Check for: for total fluid & electrolyte balance & Compatibility

- Sometimes used to further dilute IV medicinal products (i.e Sodium Chloride, Glucose, Bicarbonate or lactate contaning solutions)

Risk: Clinical effect

IV Route: Critical Care Neonates & children

- Neonates: Small number of lines to administer all the medicines + nutrition + blood products and Fluid maintenance (i.e Y site) → RISK PHYSICAL & CHEMICAL INCOMPATIBILITIES!!

- Devices for IV administration to be specified. Adsorption of the drug to the giving sets, filters → UNDERDOSING in neonates
- The need for additional dilution or flushing may be important for effective administration and avoiding local & systemic unwanted effects BUT:

    - Take into account fluid & electrolyte balance
    - 10 ml of sodium chloride 0.9% flush provides 1.53mMol of sodium. This may be the total daily sodium requirement of a preterm baby 3mMol/kg and a 0.5kg → RISK HYPERNATRAEMIA

IV Route: Critical Care Neonates & children

- Manipulations:
  - Risk of infections (these children can be immunosuppressed)
  - Calculation errors
  - Precipitation of the solution (i.e phenytoin in neonates)
- Use of standard concentrations preferred than amount/kg
- Safe concentration and administration in a critically ill children required In PIP
- Total parenteral nutrition, information on potential interactions (Chemical and clinical) to be provided
  - Avoid concomitant administration of TPN and study drug via same line

IV Fluid Therapy Case: E.M 10 kg

Total Daily Fluid Allowance: 2ml/kg/hr= 48ml/kg/day

IV Continuous Infusions in 0.9% Sodium Chloride running at:

- Morphine 1ml/hr (20 µ/kg/hr)
- Clonidine 1ml/hr (1 µ/kg/hr)
- Dopamine 2ml/hr (20 µ /kg/hr)
- Adrenaline 2ml/hr (0.2 µ /kg/hr)
- Noradrenaline 2ml/hr (0.2 µ /kg/hr)
- Milrinone 1ml/hr (0.5 µ /kg/min)
- CVP + Arterial Line: 2ml/hr

Total fluid from IV Infusions:

11ml/hr= 26.4ml/kg/day= 4mMol/kg/day of sodium

Safety of IV injectables

•Incidence of errors in prescribing, preparing and administering injectable medicines > than for other forms of medicine.

In one study, at least

-one error occurred in 49% of IV medicine doses prepared & administered on hospital wards

-1 % were judged to be potentially severe errors

-and 29% potentially moderate error

National Patient Safety Agency (NPSA)

Risk factors Description

1. **Therapeutic risk**
2. **Use of a concentrate** →PIP
3. **Complex calculation** →PIP
4. **Complex method** →PIP
5. **Reconstitution of powder in a vial** →PIP
6. **Use of a part vial or ampoule, or use of more than one vial or ampoule** →PIP
7. **Use of a pump or syringe driver (accuracy)** →PIP
8. **Use of non-standard giving set/device required** →PIP

Total number of product risk factors

>6 factors = high-risk product **(Red).**

3-5 = moderate-risk product **(Amber).**

1-2= lower-risk product **(Green).**

Clinical “wish list” when assessing PIP’s

- Compatibility issues→ PIP
- Contribution to daily fluid and electrolyte allowance →PIP
- Information on devices for IV administration and use implications → PIP
- Safe Concentration for peripheral and central access & infusion rate→ PIP
- Complex method (calculations, avoid decimal points, multiple manipulations, part vials (volume< 0.5ml difficult to measure as it is dead space of syringe & needle) or several vials per dose→ Exploring ready-to-use preparations/ standard concentrations & dose banding → PIP
- Technical information to take into account practice → PIP

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