Hypodermoclysis:
Subcutaneous Infusion in the Prehospital Setting

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Dehydration in Children:
Definition and Etiology

Loss of fluids and electrolytes due to:
• Increased fluid output
  • Gastroenteritis (#1 cause)
  • Fever
  • Heat/exertion
  • Trauma (bleeding/burns)
• Decreased fluid intake
  • Anorexia
  • Sore throat
  • Respiratory distress

Dehydration in Children:
Epidemiology of Gastroenteritis

Diarrhea is one of the leading causes of illness and death in young children
• 1950-70s: ~4.6 million children died/year
• 1980s: 3.3 million children died/year
• 1990s: 2.5 million deaths/year in children under 5 years
• 2003: ~1.87 million children died

In the United States, acute gastroenteritis in children annually accounts for
• More than 1.5 million outpatient visits
• 200,000 hospitalizations
• ~300 deaths/year

Current Approach

Globally
• Prevention
  • Clean water supply
  • Vaccines, when available
  • Oral Rehydration Therapy (ORT)
  • Intravenous Fluids (IVF) rarely available

Developed Countries
• Prevention
  • Vaccines prevalent
  • Water supply very safe, stable infrastructure
  • ORT vs. IVF debate ongoing

Practice Guidelines

AAP Practice Parameter 1996: The Management of Acute Gastroenteritis in Young Children
• Management of acute diarrhea in children aged 1 month – 5 years

CDC 2003: Managing Acute Gastroenteritis Among Children: Oral Rehydration, Maintenance and Nutritional Therapy
• AAP Statement of Endorsement 2004
  • Endorsed the CDC 2003 guidelines
  • 5-year expiration date

Current Treatment Options:
Oral Rehydration Therapy

Recommended for mild-to-moderate dehydration
• All age groups
• Dehydration of any etiology
• No routine laboratory studies needed
• Decreased need for venipuncture
• Physiologically-based
• Facilitated co-transport
• Functions even during diarrhea
• Simple intervention
• Promotes absorption even in excess of losses
• Effective restoration of circulating volume
• Not simply electrolyte replacement
ORS – A Specific Formulation

- Best co-transport with 1:1 glucose-sodium ratio
- Maximizes fluid absorption
- AAP/CDC allow 2:1
- Pedialyte is 3:1
- Gatorade is 12:1
- Two WHO solutions currently
  - Original
  - Reduced osmolarity
- Minimizes osmotic fluid losses

Current Treatment Options: Intravenous Fluid Therapy (IVFT)

- Preferred treatment for severely dehydrated children or children who can not tolerate ORT
- Fast onset; may be followed with ORT
- Challenges:
  - Intravenous access can be difficult and time-consuming
  - Small, fragile veins
  - Collapsed vein due to hypovolemia
  - Agitation or inability to cooperate
  - Multiple attempts are often needed
  - Average >2 attempts per child
  - Painful and distressing to child
  - Upsetting to parents and clinicians
  - Requires extra staff time and resources
  - May delay treatment and raise the risk of complications

IVs in the ED
Difficult Intravenous Access (DVA)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>See the Vein</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel the Vein</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt;3 yrs</td>
<td>1-2 yrs</td>
<td>&lt;1 yr</td>
<td></td>
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<tr>
<td>Premature</td>
<td>No</td>
<td>Yes</td>
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Need for Alternative Approach?

- Globally
  - If ORT fails, children die
  - Access to health services (IVF) extremely limited
- Developed Countries
  - ORT
    - Considered “slow”
    - Some children refuse ORT
  - IVF
    - Difficult venous access (DVA) patients
    - Children
    - Dehydration
    - Painful/invasive

Hypodermoclysis: Subcutaneous Rehydration

- Predates intravenous fluids
- Common in veterinary medicine
- Not just “an IV infiltrate”

Skin Anatomy

- Epidermis
- Dermis
- Hypodermis
Subcutaneous (SC) Fluids: An Alternative Route for Mild to Moderate Dehydration

- Isotonic fluids can be given subcutaneously instead of intravenously
- SC lines can be inserted quickly and easily: no need for advanced training or skills to start or maintain
- May avoid some complications of IV therapy, such as discomfort, thrombophlebitis, or sepsis
- Can be interrupted and resumed without clotting
- Many sites are suitable, including relatively pain-insensitive, out-of-sight, or out-of-reach areas

May offer economic advantages over IV
- No need for skilled infusion nurses or multiple staff members
- Isotonic fluids can be given subcutaneously instead of intravenously
- Tissue permeability returns to baseline within 24-48 hr
- Permits flow rates approaching 500 mL/hr in adults
- Permits flow rates 4-fold over SC alone in adults

Potential risks for animal pathogen
- Some animal products preserved with thimerosal, a safety issue
- Extracted from bull or sheep testes
- Extracted from bull or sheep testes
- Only available hyaluronidase product removed from the market

First human recombinant hyaluronidase (rHuPH20) 2005
- Identification of human hyaluronidase gene family allowed development
- Enhanced dispersion/absorption
- Permits flow rates approaching 500 mL/hr in adults
- Tissue permeability returns to baseline within 24-48 hr
- Absorption of fluids into bloodstream is rapid
- In pre-IV era, animal-derived forms were safely used to augment SC hydration in children, using isotonic fluids

Hyaluronan (HA)
- Integral viscoelastic component of the interstitial matrix
- Forms barrier to movement of molecules in interstitial space
- Large, (Mega Dalton) repeating sugar polymer found in interstitial tissue

NORMAL STRUCTURE/FUNCTION
- Large, (Mega Dalton) repeating sugar polymer found in interstitial tissue
- Forms barrier to movement of molecules in interstitial space
- Integral viscoelastic component of the interstitial matrix

Augmentation of SC Hydration with Hyaluronidase
- Enhanced dispersion/absorption
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Evolution of Hyaluronidases

1928 Duran Reynolds discovers the first “spreading factor” in extracts of rabbit testis
1939 Spreading factor shown by Chain and Duthie to degrade mucopolysaccharids
1947 Hector treats first patient by hypodermoclysis using bovine hyaluronidase preparation
1949 Aktinson reports increased onset of akinesia and decreased tissue distortion with the use of hyaluronidase in ophthalmic anesthesia
1999 Only available hyaluronidase product removed from the market
2004 Bovine and ovine extracted hyaluronidases reintroduced to market
2005 First human recombinant hyaluronidase (rHuPH20)

Recombinant Human Hyaluronidase
- Until recently, only animal-derived hyaluronidase was available
- Identification of human hyaluronidase gene family allowed development of soluble human recombinant form (rHuPH20)
  - rHuPH20 was FDA-approved in Dec 2005 for use with SC hydration
  - Highly purified human enzyme—up to 100 times purer than animal-derived hyaluronidase based on specific activity
  - Increases hydration flow rates 4-fold over SC alone in adults
  - Non-allergic, safe and well tolerated in adults
- No significant adverse events (AEs) in published studies of rHuPH20

Animal versus Human Recombinant Hyaluronidases
- Animal-sourced enzymes are extracted from bull or sheep testes
- Typically <1-5% pure
- Allergic reactions most common
- Some animal products preserved with thimerosal
- Potential risks for animal pathogen transmission

Purity analysis of bovine hyaluronidase preparation by SDS PAGE electrophoresis and Western Blot with anti-RAM PH20 MoAb compared to purified human recombinant
INFUSE-LR: Representative Subject at Baseline and End-Infusion

Placebo
Recombinant hyaluronidase

INFUSE Pediatric Hydration Study: Design and Objectives

- Increased Flow Utilizing Subcutaneously-Enabled (INFUSE) Pediatric Rehydration Study
- Phase IV, open-label, single-arm, multicenter, feasibility study
- Subjects: children with mild to moderate dehydration being admitted to hospital Emergency Departments (EDs)
- Target sample size = 50;
- Study designed to assess effectiveness, safety, tolerability, and ease of use of rHuPH20-augmented SC rehydration

Key Inclusion Criteria

- Body Weight: <42 kg
- Age: 2 months to 10 years
- Need for parenteral fluids because oral rehydration therapy or attempts to establish IV have failed
- 1 to 6 of the following signs and symptoms of dehydration:
  1. General condition (lethargy; drowsiness; postural dizziness; cold, cyanotic extremities; muscle cramps; coma)
  2. Weak radial pulse
  3. Deep or rapid respiration
  4. Diminished skin elasticity
  5. Sunken eyes
  6. Absence of tears
  7. Dry mucous membranes
  8. Little or no urine output
  9. Heart rate >150 bpm
  10. Capillary refill time at fingertip >2 sec

Key Exclusion Criteria

- Severe dehydration, shock, or other life-threatening situation
- IV fluids received in past 24 hours
- Known hyponatremia, hypernatremia or hypokalemia
- Known hypersensitivity to hyaluronidase or a condition precluding SC injection

Study Design and Protocol

- 24 gauge angiocatheter placed SC in anterior thigh or upper back
- 1 mL (150 U) rHuPH20 given SC by push
- Continuous, pump-driven infusion of 20 mL/kg isotonic fluid given SC over 1 hour immediately following rHuPH20 injection
- Subsequent SC hydration continued as needed, for up to 72 hours; rHuPH20 injection repeated every 24 hours
- Number of signs/symptoms of dehydration assessed at baseline and at the end of SC infusion
- Safety and tolerability assessed throughout rehydration period and by telephone contact 3 and 7 days after ED discharge

Effectiveness Endpoints

Primary Effectiveness Endpoint
- Percentage of patients achieving successful rehydration
  - Primarily attributed by investigator to rHuPH20-augmented SC fluid infusion
  - AND
  - Child discharged from ED to home without needing alternative rehydration therapy

Secondary Effectiveness Endpoints
- Change from baseline in number of signs/symptoms of dehydration at the end of SC hydration
- Time from start of infusion to first urine output
- Volume of fluid infused over time
- Time from start of infusion to discharge from ED
- Need for and nature of rescue therapy
- Incidence of readmission or retreatment for dehydration
- Ease of use in investigator’s judgment
- Parent satisfaction with rehydration therapy

**Safety and Tolerability Endpoints**

**Infusion site pain**
- Objective Pain Rating Scale (Faces, Legs, Activity, Cry, and Consolability [FLACC] Scale) for children <3 years: 0 (none) to 10 (worst)
- Faces Pain Rating Scale for children 3 to 10 years: 0 (no hurt) to 5 (hurts worst)

**Infusion site reactions**
- Tenderness, pruritus, swelling, erythema, ecchymosis, and papular rash rated on 4-point severity scales

Infusion site pain and reactions recorded immediately before injection of rHuPH20, immediately after injection of rHuPH20, at 1 h, 2 h, 3 h, 4 h, and 24 h post-infusion, and at end of hydration treatment

Other AEs monitored continuously

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**Results (N=51)**

**Patient Characteristics**
- Age: 0.3–9.8 years (mean = 1.9 ± 1.9 years)
- 43/51 (84%) children were <3 years old
- Gender: 29 males (57%), 22 females (43%)
- Weight: 5.1–31.4 kg (mean = 11.2 ± 5.4 kg)
- Race: Predominantly white (31/51; 61%)
- Ethnicity: Non-Hispanic or Latino (42/51; 82%)
- Mean ± SD number of signs/symptoms of dehydration: 3.5 ± 1.2
- Presenting Diagnosis:
  - Gastroenteritis: 36/51 (71%)
  - Other: 15/51 (29%)
- Catheter site:
  - Thigh: 15
  - Interscapular: 36

**Effectiveness Outcomes**
- 43/51 (84.3%) children were successfully rehydrated per study definition
- 5/51 (9.8%) rehydrated, but admitted due to poor po
- 3/51 (5.9%) “failed”
  - 1 discontinued due to parental withdrawal of consent after 10 hours SC (switched to IV hydration)
  - 1 discontinued due to an AE after 9 minutes (infusion site pain)
  - 1 switched to IV and admitted
- No child required readmission for retreatment of dehydration

**Mean total volume infused**
- 437.3 mL (range 20 to 1938 mL)

**Mean total volume infused per kg**
- 43.3 mL/kg (range 1.4 to 195.8 mL/kg)

**Mean duration of infusion**
- 7.5 hours (range 0.2 to 45.3 hours)

**Median time from start of infusion to discharge from ED**
- 3.4 hours

*Patient who received fluid for 0.2 h was considered a treatment failure.

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**Gorelick Dehydration Scores at Baseline and End of Treatment**

- Baseline: 3.5 ± 1.2
- End of Treatment: 0.5 ± 0.9

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**Other Effectiveness Outcomes**
- Ability to "give a bolus"
  - Median flow rate in first hour: 18.9 ml/kg/hr
  - 38/51 (75%) received > 15 ml/kg within one hour of enrollment
  - Considerable variability between sites
  - Learning curve
  - "Ramping up"
- Mean % body weight change = +1.8% (0.2kg)
Typical Catheter Site Reactions

<table>
<thead>
<tr>
<th>Table 3. Number of Patients with Infusion Site Reactions on Day 1</th>
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</thead>
<tbody>
<tr>
<td><strong>Score Recorded After rHuPH20 Injection but Prior to Fluid Infusion</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Erythema</td>
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<tr>
<td>Tenderness</td>
</tr>
<tr>
<td>Ectopyhema</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Fatus</td>
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</tbody>
</table>

Pain and pruritus were scored as 0, 1, 2, 3, 4, 5, 6, and 7, and 8, 9, 10, 11, 12, 13, and 14 for swelling, erythema, ectopyhema, and pruritus, respectively, in each clinical sign. The total diameter for each clinical sign was scored as: 1 = <2 cm, 2 = 2.5 cm, 3 = 3.5 cm, and 4 = 4.5 cm.

Typical Infusion Site Immediately Before and After Initial Bolus of Isotonic Fluid

Maximum Pain Scores: Post Hylanex versus During Infusion

<table>
<thead>
<tr>
<th>Table 4. Number of Patients with Infusion Site Pain on Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score Recorded After rHuPH20 Injection but Prior to Fluid Infusion</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Number of Patients (n=6)</td>
</tr>
</tbody>
</table>

Maximum Pain Scale (children <3 yrs):
- 0 = No pain
- 1 = Mild discomfort
- 2 = Mild pain
- 3 = Moderate pain
- 4 = Severe pain

Maximum Pain Scale (children 3-10 yrs):
- 0 = No pain
- 1 = Mild discomfort
- 2 = Mild pain
- 3 = Moderate pain
- 4 = Severe pain
- 5 = Extremely severe pain

Systemic Adverse Effects

- Occurred in 9 patients:
  - Mild vomiting (n=2)
  - Mild otitis media (n=1)
  - Mild pyrexia and bronchopneumonia (n=1)
  - Mild pyrexia and mild generalized rash (n=1)
  - Mild abdominal distention (n=1)
  - Mild nasopharyngitis (n=1)
  - Moderate influenza and moderate ear infection (n=1)
  - Mild antibiotic sensitivity and cellulitis (n=1)
- None were considered to be related to rHuPH20 or infusion fluid.
- Cellulitis related to catheter site/break in skin.
Ease of Use: Catheter Placement

- Median time to begin SC fluids after initial needle stick = 2 minutes
- SC access was achieved on first attempt in 44/51 patients (86%); on second attempt in 6/51 patients (12%); and on third attempt in 1/51 patients (2%)*
- No patient required a change of infusion site

* Patient with three attempts had 1st catheter insertion with 1 stick. Twenty minutes later, a 2nd catheter insertion was recorded with 2 sticks; investigator commented ‘1st catheter pulled loose and kinked after Hylenex infused’.

Ease of Use: Acceptance by Clinicians

- Investigators rated the procedure as easy to perform in 49/51 (96.1%)
- Compared to prior experience with IV therapy, investigators rated SC therapy as equally or more effective in 45/49 (91.8%)
- Investigators found SC therapy less difficult than IV therapy in 45/50 (90.0%) cases

Parent Satisfaction and Preferences (N = 48)

- In 43/48 (89.6%) cases, parents were satisfied or very satisfied with SC hydration
- Parents were dissatisfied in 4/48 (8.3%) cases, and very dissatisfied in 1 (2.0%) case
- 45/48 (93.8%) parents felt the procedure was successful
- If they or their child ever needed rehydration therapy in the future, 42/48 (87.5%) said they would opt for SC hydration again
- 34 parents said they or their child had previously had IV fluids and answered a question comparing the two routes. Of these, 31 (91.2%) said the SC hydration experience was the same or better

Conclusions

- rHuPH20-augmented SC infusion of isotonic fluid appears to be safe and effective method of rehydration in appropriately selected infants and young children with mild to moderate dehydration
- Maintenance fluids, typically D51/2NS with KCL, were safely given in multiple subjects following the rehydration phase
- Fluid volumes can be administered in a clinically relevant timeframe without the need for IV placement
- SC access is achieved in the majority of children on the first attempt
- Most parents are satisfied with procedure and would choose it again for their child; investigators generally find it easy to perform
- Manuscript submitted to Pediatrics 12/08