

Supplementary Online Content

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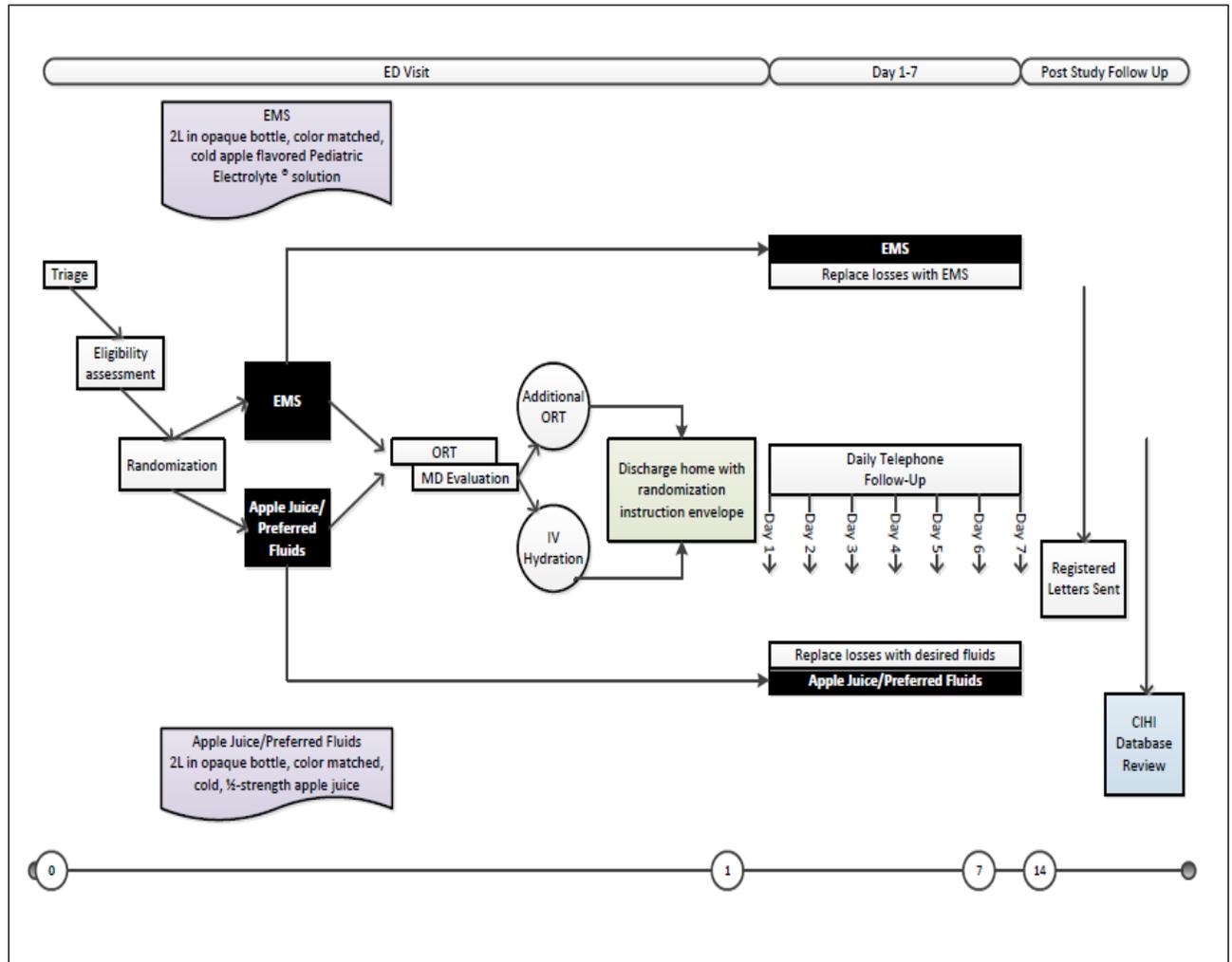
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Schematic Representation of Study Flow and Procedures



EMS, Electrolyte Maintenance Solution; ORT, Oral Rehydration Therapy; IV, Intravenous; CIHI, Canadian Institute for Health Information; ED, Emergency Department.

eAppendix 1. Pharmacy Dispensing Procedures

Is Electrolyte Maintenance Solution (EMS) (Pediatric Electrolyte Solution®) Required (vs. Fluids as Tolerated = FAT i.e. ½ strength Apple Juice) in low risk Children with Gastroenteritis?

SickKids IIT, SickKids Sponsor

Short Title: EMS vs. FAT

(aka Pediatric Electrolyte Solution® vs. ½ strength Apple Juice) in mild Gastroenteritis in Emerg

PRINCIPAL INVESTIGATOR: Dr. Stephen Freedman pager:

PURPOSE:

To determine if Fluid as Tolerated (using ½ strength apple juice) is no worse than standard Electrolyte Maintenance Solution (using Pediatric Electrolyte Solution® apple flavor) in children with “none-some” mild dehydration secondary to mild GI illness (vomiting or diarrhea) in children age 6 months to 5 years.

DESIGN:

- Single Centre, randomized (master table done by RSP), controlled (the EMS arm is the control arm), blinded, study.
- Children will be randomized in a 1:1 ratio of treatment arm (1/2 strength apple juice) to control arm (Pediatric Electrolyte Solution® Apple flavor), random block sizes.
- Initially Double-blind (pharmacy is un-blinded, all study staff blinded, family blinded initially while in hospital but will be given an unblinding envelope upon discharge from ED in case they need to use/purchase additional rehydration solution).
- Pediatric Electrolyte Solution® only has a 48 hour expiry date once opened/repackaged. In order to provide each subject with a “kit” that has a full 48 hour expiry, Central Pharmacy technicians will do the last step (should take 8 to 12 minutes) in making the “kits”.
 - RSP will have prepared sequentially numbered “pre-kits” with all ingredients and tools to make the final “kits”.
 - Central Pharmacy technicians, upon receipt of a telephone call from Emerg requesting a specific numbered kit, will locate the “pre-kit” in the fridge, open the original solution package (or prepare ½ strength apple juice according to instructions), pour it into the 500ml opaque labeled bottles, have a second tech check, sign the worksheet and call Emerg to pick up.
 - There will not be any patient specific prescription nor any computer entries for this study. No Central Pharmacist involvement required.
 - Emerg will need their kit in a short turn around ie 15-20 minutes.
 - If the Central tech does not have 8-12 min to make the “kit”, they may ask RSP technicians, if available, for help.
 - Recruitment will take place from 8am to midnight, Monday to Sunday (6 days per week, but variable).

PROCEDURE:

1) PRESCRIPTIONS/KITS

- There will be no patient specific prescriptions given to Pharmacy for this study.
- RSP pharmacy will make sequentially numbered (according to the master randomization table) “pre-kits”.
- Upon request from Emerg, Central pharmacy techs will do the last step to convert the “pre-kit” to a “kit” with a full 48-hour expiry date.
- Study staff (not pharmacy) will be responsible for keeping a log of patients randomized into study and corresponding “kit” number assigned.

2) PATIENT ELIGIBILITY

- This study is open to children aged 6 to 60 months, > 8kg, presenting to the emergency department with mild gastroenteritis (vomiting and diarrhea) and none-some dehydration (low risk patients).
- Pharmacy will not be receiving copies of the doctor's orders ∴ No need for pharmacy to enroll/randomize individual pts.

3) DOSE :

- Blinded solution (EMS or FAT): 10mL/kg replacement for each watery stool and 2mL/kg replacement for each episode of emesis until resolved.
 - Study subjects will be provided with 2L of blinded study drug (study assessor is blinded, family will not be blinded).
 - If more than 2L are needed within the study period ie before the vomiting or diarrhea resolves, parents will be encouraged to purchase Pediatric Electrolyte Solution® (if randomized to EMS) or any Fluid as Tolerated (if randomized to FAT).

4) COMPUTER ENTRY (RX3000)

- There will be no need for individual computer entries. We supply numbered “kits” to RA after receiving a telephone request.

5) DISPENSING

- There will be no patient specific dispensing for this study.
- When the Study Coordinator or Research Assistant needs a new “kit”, they will call to the Central Pharmacy technician x6473.
 - Central Pharmacy technicians will do the last step (should take 8 to 12 minutes) in converting a “pre-kit” to a “kit”.
 - RSP will have prepared sequentially numbered “pre-kits” with all ingredients and tools to make the final “kits”.
 - Central Pharmacy technicians, upon receipt of a telephone call from Emerg requesting a specific numbered kit, will locate the “pre-kit” in the CENTRAL PHARMACY fridge, open the original solution package (or prepare the ½ strength apple juice as per instructions), pour it into the 500ml opaque labeled bottles, have a second tech check, sign the worksheet and call Emerg to pick up (see details on worksheet that is located in the “pre-kit”).
- Emerg will need their kit in a short turn around ie 15-20 minutes.
- The study solutions are more palatable when drunk cold. However, each of the solutions is stable at Room Temperature.
- There is only enough space in the fridge to store 2-3 “pre-kits” at a time. Additional “pre-kits” will be located in RSP.
 - If a central tech takes the last “pre-kit” out of the Central Pharmacy fridge, they should locate the next 1-2 sequentially numbered “pre-kits” from the Room Temp shelves and place them in the Central Pharmacy refrigerator.
- RSP tech will check every morning (Mon to Fri) for number of “pre-kits” in Central Pharmacy fridge and replace any that were used from the Room Temp supply of pre-kits.
- Pre-Kits will be made weekly by RSP staff according to the need/enrollment when extra RSP technician staff are available.
- If the Central tech does not have 8-12 minutes to make the “kit”, they may ask RSP technicians, if available, for help.

6) KIT MAKING:

- See details on the “Pre-Kit/Kit” making worksheets (there are 2 different worksheets, one for the EMS arm, one for the FAT arm; the appropriate worksheet, according to the master randomization table, will have been put in the “pre-kit” by RSP, most details will already filled out by RSP during pre-kit making process)
- Numbered “Pre-Kits” will be made ahead of time by RSP according to patient randomization number and incorporating the appropriate treatment allocation according to the master randomization table.

7) **PRE-KIT STORAGE:**

- Though the pre-kits do not have to be kept cold, a supply of refrigerated “pre-kits” will be located in the Central Pharmacy fridge, bottom shelf nearest the Central IV room.
- Lynn will request a copy of the Weekly Fridge wheel for the Central Pharmacy fridge from the Central Pharmacy Senior Technician.
- Central pharmacy technicians will select the assigned “pre-kit” number from the Central Pharmacy fridge and convert it to a Kit when requested from Emerg Study staff.

8) **SUPPLIES**

- **Pediatric Electrolyte Solution®** –1L bottles apple flavour (to be repackaged into 4 x 500mL white opaque bottles)
 - Boxes of 8 x 1L bottles
 - Life brand manufactured for Shoppers Drug Mart by Pharmascience (the parent company of Pendopharm).
 - Pediatric Electrolyte® Solution is marketed in Canada, available as a non-prescription product. NPN #02219883.
 - Unopened bottles to be stored at room temperature or refrigerated (exact temperature not specified)
 - Once opened reduce expiry to 48hr expiry (refrigerated).
 - RSP tech will order stock from SDM as needed to make “pre-kits”. SDM only orders 1x/week, plan accordingly
- **Apple Juice** - 1L slim tetra packs (to be repackaged into 4 x 500mL white opaque blinded bottles) Fairlee Item #7547955
 - brand chosen is Fairlee (since this is the purchasing contract with Nutritional Services at SK).
 - Apple Juice will be diluted 1:1 with Sterile Water for Irrigation to obtain ½ strength AJ at time of converting the “pre-kit” to “kit”.
 - Unopened tetra packs may be stored at room temperature or refrigerated (exact temperature not specified)
 - Once opened reduce expiry to 48hr expiry (refrigerated) in order to maintain blinding.
 - RSP will order from Sysco via SK Nutritional services as needed to make “pre-kits”.
 - Shipping document must be provided by Nutritional Services to RSP
 - Provide Nutritional Services with Pharmacy Cost Centre # **7144005000** to bill the apple juice RSP will bill back to Study Fund)
- **Sterile Water for Irrigation**
 - 1L containers, stores item # 15141
 - used to dilute the full strength apple juice 1:1 to half strength apple juice at time of converting the “pre-kit” to “kit”.
 - RSP tech will order stock from PMM as needed to make “pre-kits”, stores open daily 1:30-3:30pm only.
- **Food colouring drops** (red and yellow)
 - Club House brand
 - used to colour match as close as possible the ½ strength apple juice to the colour of the Pediatric Electrolyte Solution®.
 - RSP staff to purchase from grocery store and submit bill to Linda Cavan for reimbursement
- **Brown Handle Bags:** Size: 8”x4 ½”x10”
 - Used to hold the 4x500mL white opaque bottles for “kits”
 - RSP tech to order from George in PMM who will get from
- **White Opaque Bottles:** 500mL size
 - PMM to order from appropriate supplier

9) **UN-BLINDING**

- Research Support Pharmacy/Central Pharmacy staff making kits will be unblinded.
- All other study personnel (including PI, treating MD, RA, CRA, subject/parents) will be blinded up until the point of discharge from Emerg.

- At time of discharge from Emerg, the caregiver will be given an “Unblinding” envelope that states what liquids their child should receive once they run out of the 2L of study supplied liquid. The caregiver will be instructed not to reveal the group to the study personnel during any follow-up visit or call.
 - RSP pharmacy will prepare these “unblinding envelopes” on behalf of the PI.
 - The PI will provide all documents to be included in envelope.
 - These documents include:
 - Caregiver Diary
 - Discharge Instruction Letter: Unblinding Document for Families
 - General discharge letter from aboutkidshealth
 - RSP will design labels for the outer envelope, indicating Subject Randomization # and will include the appropriate documents according to the Master Randomization Table
- **Emergency Unblinding** MAY be requested by the Emergency physician in the case that the subject experiences an adverse event that will be treated differently by knowing which arm of the study the subject was randomized to. The Emerg physician should contact PI to authorize Emergency Unblinding. If PI agrees, the Emergency physician will contact the Research Support Pharmacy (or 24 hour pharmacy) to receive the allocation. Documentation of such, in writing (email is acceptable), should follow within 24 hours. Every attempt will be made to keep the PI and study personnel blinded. It is not anticipated that Emergency Unblinding will be required.
- If a subject is still in Emerg and they do not like the liquid they are taking and want to switch, follow page 9 of the protocol: “In the ED however, it is not feasible to provide more than one intervention and one control solution. However, if, following the initial assessment by the responsible physician, the child’s oral consumption is felt to be inadequate (whether they are randomized to the FAT or EMS groups), the physician may choose to have the child consume an alternate solution. This will allow us to expand the choice of liquids offered to the FAT group, maintain blinding, and also not administer intravenous fluids unnecessarily (ie. when the physician’s usual practice would be to offer an alternative to EMS when its consumption is insufficient). Should an alternative solution be provided, it will be recorded and the solution provided documented. If crossover occurs, EMS to FAT or FAT to EMS, this will be classified as a treatment failure. We do anticipate that crossover of EMS to FAT will be more common as the FAT group will most likely be provided an alternative FAT solution (ie. not EMS).” i.e. the MD can choose to give what he/she wants in an unblinded manner to the child and we will record cross-overs and count those as treatment failures.
- If you get a request for unblinding, take the caller’s information and leave a note for the RSP pharmacists to follow up on the next business day.

10) RETURNS

- RA will advise the parents to bring back the remaining contents at the follow up visit
- RA will measure and record returns then return to pharmacy for destruction only. RSP will not verify the return count.
- Place all returned "used kits" in a box in back corner of 24hr Pharmacy until authorized by RSP pharmacist or PI to record and destroy.

eAppendix 2. ½-Strength Apple-Juice/Preferred Fluids Instruction

Your child has been assigned to drink fluids as tolerated. Should your child not like the solution we have provided then you may provide your child with any fluids they desire to drink. You should give your child the liquid we have provided to you (apple juice diluted 1:1 with water) to replace all fluid losses (vomiting or diarrhea). For each episode of diarrhea please give him/her 10 ml/kg and for each episode of vomiting please give 2 ml/kg. Your child should resume a normal diet as soon as possible.

DO NOT you give your child Electrolyte Maintenance Solutions (such as Pedialyte, Enfalyte, Gastrolyte, Cera) to drink unless instructed to do so by a healthcare provider.

Only you should know what type of liquid your child has been given to drink. Please do not tell anyone at the hospital what type of liquid your child has been given to drink, unless it is an emergency.

If you have questions you can contact the study nurse at XXX-XXX-XXXX.
Please do not tell him/her what liquids your child is taking.

Please return all unused liquids and the completed diary to the study nurse when you return for your follow-up visit.

eAppendix 3. Electrolyte Maintenance Solution Discharge Instruction

Your child has been assigned to drink Electrolyte Maintenance Solution (EMS). You should give your child the liquid we have provided to you (Pedialyte) to replace all fluid losses (vomiting or diarrhea). For each episode of diarrhea please give him/her 10 ml/kg and for each episode of vomiting please give 2 ml/kg. Should your child not like the solution we have provided than you may purchase Pedialyte with a different flavour or you may use a different solution such as Enfalyte, Gastrolyte, or Cera. Your child should consume a normal diet as soon as he/she is able to tolerate it., If your child vomits, then administer the Electrolyte Maintenance Solution only for 4 hours after which time you can resume a normal diet. However while the diarrhea or vomiting persists, please continue to replace all diarrhea and vomiting losses with an Electrolyte Maintenance Solution.

DO NOT you give your child soda pop (carbonated beverages such as ginger ale), fruit juice (apple, orange, grape) or water to replace their losses (vomiting or diarrhea).

Only you should know what type of liquid your child has been given to drink Please do not tell anyone at the hospital what type of liquid your child has been given to drink, unless it is an emergency.

If you have questions you can contact the study nurse at XXX-XXX-XXXX.
Please do not tell him/her what liquids your child is taking.

Please return all unused liquids, to the study nurse when you return for your follow-up visit.

eAppendix 4. Telephone Criteria for Emergency Department Return Visit

Telephone Criteria for ED Revisit¹

1. Fever $\geq 39.0^{\circ}\text{C}$ for > 48 hours following initial assessment
2. Visible blood in stool
3. High output, including frequent (> 10) and substantial volumes of diarrhea (large according to caregiver)
4. Persistent vomiting, including frequent (> 5) and prolonged (> 2 days)
5. Caregiver report of signs of dehydration (ie. sunken eyes, decreased tears, dry mucous membranes, decreased urine output)
6. Change in mental status (ie. irritability, apathy, lethargy)
7. Inability of the caregiver to administer oral rehydration therapy

eAppendix 5. Figure 2 Statistical Model

The curve in Figure 2 was generated from the estimated parameters (log-odds ratios and corresponding variances and covariances) from the following logistic regression model:

$$\text{Log-odds} = \theta_0 + \theta_1 * \text{group} + \theta_2 * \text{age} + \theta_3 * \ln(\text{age}) + \theta_4 * \text{group} * \text{age} + \theta_5 * \text{group} * \ln(\text{age}).$$

Therefore, $\text{OR}(\text{age}) = \exp\{\theta_1 + \theta_4 * \text{age} + \theta_5 * \ln(\text{age})\}$.

Using the score statistic the combined test of significance for the (i) interaction and (ii) the non-linearity of the interaction is a chi-squared with 2 degrees of freedom of 8.63, with $P = 0.01$. The null hypothesis for this test is $H: \theta_4 = \theta_5 = 0$.

eTable 1. Eligibility Criteria

Inclusion

1. Ontario resident: required for Canadian Institute for Health Information (CIHI) follow-up data to be available
2. Age 6 – 60 months
3. Presented to The Hospital for Sick Children emergency department for care
4. ≥ 3 episodes of vomiting (defined as forceful expulsion of stomach contents) or diarrhea (defined as watery stool, able to take the shape of a container²) in the preceding 24 hours
5. < 96 hours since onset of vomiting or diarrhea
6. Weight ≥ 8 kg
7. Minimal dehydration defined by a Clinical Dehydration Scale score < 5 ³⁻⁷
 - i. It is recognized that distinguishing between mild and moderate dehydration is difficult, thus it is no longer recommended.¹ As such, we employed a dehydration score developed and validated and which was in use in our ED to classify children as none-some (score 0 – 4) dehydration versus moderate-severe (5 – 8).⁵⁻⁷ This score was assigned by trained triage nurses.
8. Capillary refill < 2 seconds⁸
9. Eligible for initiation of oral rehydration therapy at triage
 - i. Absence of bulging fontanelle
 - ii. Absence of bilious vomiting
 - iii. Absence of blood in diarrhea or vomit
 - iv. Absence of abdominal pain (if present reported as periumbilical in location)
 - v. Absence of abdominal distension
 - vi. Absence of acute disease requiring alternate treatment
 - vii. Absence of significant co-existing disease (e.g. prematurity, cardiac, renal, neurological, metabolic, endocrine, immunodeficiency, trauma or history of ingestion)

Exclusion Criteria

1. History of chronic gastrointestinal disease (e.g. inflammatory bowel disease, celiac disease) or other diseases that place the child at increased treatment failure risk
2. Prematurity with corrected postnatal age < 30 weeks
3. History of bilious vomiting, hematemesis, hematochezia, or clinical concern for acute abdomen
4. Responsible physician judged the child to require immediate intravenous rehydration
5. Insurmountable language barrier - consent and/or follow-up is not possible.

eTable 2. Reasons Provided for Declining Consent (N=225)

Not interested in participating in clinical trial	134 (60%)
Dislikes apple juice	24 (11%)
Does not want or unable to participate in study follow-up	17 (8%)
Prefers to administer electrolyte maintenance solution	14 (6%)
Parental fatigue	12 (5%)
Breastfed only	12 (5%)
Does not want to administer electrolyte maintenance solution	6 (3%)
Prefers intravenous rehydration	3 (1%)
Other	3 (1%)

eTable 3. Comparison Between Those Who Consented (N=647) and Those Who Declined to Participate (N=225)

	Consented (N=647)	Declined Consent (N=225)
Age – months, mean (SD)	28.3 (15.9)	25.4 (14.5)
Ondansetron administered – no. (%)	436 (67.4)	91 (40.4)
Intravenous rehydration – Index visit – no. (%)	25 (3.9)	12 (5.3)
Hospitalization – Index visit – no. (%)	7 (1.1)	4 (1.8)
Unscheduled emergency department visit – no. (%)	44 (6.8)	25 (12.5)

The institutional ethics review board did not permit the collection of any additional data.

eTable 4. Detailed Description of Crossover in Emergency Department

	Electrolyte Maintenance Solution	Apple Juice – Fluid as Tolerated
Milk	4	
Water	4	
Apple Juice	1	
Pedialyte®		2
Breastfed*	1	3

*Breastfeeding was not considered as a ‘crossover’.

eTable 5. Unadjusted Data^a, Vomiting and Diarrhea Frequency

Characteristic	½-Strength Apple Juice/Preferred Fluids Therapy			Electrolyte Maintenance Solution Therapy		
	No.	Mean	99% CI	No.	Mean	99% CI
Vomiting, No. of Episodes						
Day #1	186	1.09	0.88, 1.31	210	1.11	0.90, 1.31
Day #2	186	0.50	0.43, 0.57	210	0.45	0.39, 0.50
Day #3	186	0.24	0.22, 0.26	210	0.37	0.33, 0.41
Day #4	186	0.15	0.14, 0.16	210	0.19	0.17, 0.20
Day #5	186	0.032	0.031, 0.033	210	0.057	0.055, 0.060
Day #6	186	0.011	0.011, 0.011	210	0.019	0.019, 0.020
Day #7	186	0.011	0.011, 0.011	210	0.019	0.019, 0.020
Diarrhea, No. of Episodes						
Day #1	209	1.98	1.60, 2.36	213	2.05	1.66, 2.45
Day #2	209	1.13	0.97, 1.30	213	1.59	1.32, 1.86
Day #3	209	0.55	0.49, 0.60	213	0.99	0.86, 1.12
Day #4	209	0.30	0.28, 0.32	213	0.53	0.48, 0.58
Day #5	209	0.19	0.18, 0.20	213	0.30	0.28, 0.32
Day #6	209	0.072	0.069, 0.074	213	0.21	0.19, 0.22
Day #7	209	0.057	0.056, 0.059	213	0.15	0.14, 0.16

^a Analyzed employing a Poisson model.

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