AWARD NUMBER: W81XWH-21-1-0364

TITLE: Far-Forward, Fluid First, (4F) Enteral Resuscitation (EnteroResus) for Moderate-Size Burns (20%-40% TBSA): A Hybrid Type I Effectiveness-Implementation Study

PRINCIPAL INVESTIGATOR: Barclay T. Stewart

CONTRACTING ORGANIZATION: University of Washington, Seattle, WA

REPORT DATE: October 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	01Sep2021 – 31Aug2022

4. TITLE AND SUBTITLE

Far-Forward, Fluid First, (4F) Enteral Resuscitation (EnteroResus) for Moderate-Size Burns (20%-40% TBSA): A Hybrid Type I Effectiveness-Implementation Study

5a. CONTRACT NUMBER
W81XWH-21-1-0364

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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SEATTLE WA 98195-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Short- and long-term outcomes of soldiers and civilians with burn injuries are greatly impacted by the care provided in the first hours and days after injury, particularly fluid resuscitation.(1-3) Profound inflammation-induced capillary leak syndrome (CLS) is a hallmark of moderate and severe burn injury.(4) If un- or under-treated, CLS results in dehydration, hypovolemic shock, wound progression, organ failure and death. Patients with burn injuries ≥10-20% total body surface area (TBSA) are typically resuscitated with intravenous (IV) fluids to prevent these sequelae. However, in austere settings, patients often present to medics, health posts, and first-level hospitals that do not have the resources to provide goal-directed IV fluid resuscitation.(5) To address the complexity of goal-directed IV fluid resuscitation while acknowledging resource constraints in LMICs, burn care experts have recommended implementation of enteral resuscitation-based protocols.(6-11) burn injured soldiers and civilians around the world. We plan to perform a hybrid effectiveness-implementation cluster-randomized controlled trial of enteral resuscitation to IV resuscitation in Ghana. The first year has been focused on developing materials (e.g., study protocol revisions, resuscitation protocols, documentation, educational/training materials, DSMB documents), navigating the labyrinth of US and Ghanaian regulatory bodies with conflicting priorities/perspectives (e.g., eligibility of children, safety of enteral resuscitation, role of IV fluids in the intervention clusters), establishing agreements and infrastructure to facilitate the project (e.g., sub-contracts, financial sharing platform), and bringing co-investigators and sites to speed on research operations. With these initial steps and processes in place, we will overcome the regulatory hurdles, onboard sites and begin enrollment within the coming year.

15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRDC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	Unclassified	27	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION:

Burn-injured warfighters, like most people injured in the world, often lack access to timely resuscitation due to logistical and security challenges, operational stresses, limited burn care expertise, and low-resources. This is particularly the case in prolonged field care scenarios, multiple casualty incidents, shipboard incidents, in low- and middle-income countries (where 90% of the world's burn injuries occur), and even in rural America. When burn-injured patients do not receive timely and appropriate resuscitation, they are markedly more likely to experience acute kidney injury (renal failure), wound progression, sepsis and multiple organ dysfunction, and death. Therefore, there is an urgent need for simple, operationally advantageous, safe, and effective resuscitation strategy tailored for low-resource settings.

One such proposed strategy is enteral resuscitation, or the administration of oral rehydration solution via drinking or an nasogastric tube. Although remote case series and small controlled studies have demonstrated the safety and efficacy of enteral resuscitation for burn injuries, there has not been a large effectiveness trial or study of its implementation to inform guidelines. Therefore, we aim to: i) compare the effectiveness of an enteral resuscitation bundle (4F EnteroResus) to enhanced standard of care (IV resuscitation) for patients with moderate burns (10-60% TBSA) at first-level (district) hospitals in Ghana; and ii) identify the challenges and facilitators to enteral and IV resuscitation protocol implementation, compliance and sustainability.

2. KEYWORDS:

Burn injury, low-resource settings, resuscitation, enteral resuscitation, oral rehydration solution

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Establish a research network that includes first-level hospitals within the catchment of major burn centers (i.e., referral hospitals) in Ghana to participate in the study.
    a. Coordinate central and local protocol submissions, approvals and agreements and develop SOPs/training materials to harmonize care across participating centers.
    b. Organize a network of first-level and referral hospitals that commonly care for burn injuries to maximize enrollment.
    c. Establish local advisory groups and DSMB to inform protocol, monitor the study, and facilitate dissemination.
    d. Prepare processes and sites for enrollment, data collection, and data transfer.
2. Randomize participating first-level hospitals to provide 'Far-Forward, Fluid First,' (4F) Enteral Resuscitation (EnteroResus) bundle vs enhanced standard of care bundle (i.e., organized IV resuscitation) for patients with moderate burn injuries (10-60% TBSA).
    a. Compare the 4F EnteroResus with enhanced standard of care with regard to successful resuscitations, acute kidney injuries, shock, electrolyte disturbances and over-resuscitations; and
    b. Compare the 4F EnteroResus with enhanced standard of care with regard to gastrointestinal intolerance, aspiration, pneumonia, sepsis and death.

What was accomplished under these goals?

We have built a strong community of collaborators ready to participate in the trial, including Ghanaians with experience in cluster-randomized and implementation trials, burn care experts from the largest four burn care facilities in Ghana, and clinical leads at first-level hospitals identified by the burn care experts as being district hospitals with high incidence of burn injury referrals. We met bi-weekly in the first few months of the year and monthly since to refine the protocol consistent with the capabilities of each center and the burn care standards in Ghana. Additionally, we have organized a DSMB and a burn advisory group to help us navigate the complexities and asks of the regulatory agencies.

The latter has been quite complex and has led to significant delays. There is no central IRB in Ghana, therefore, we have had to submit our application, respond to reviews, and resubmit our application to: Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics, Ghana Health Service Ethical Review Board, and each of the participating referral hospitals (namely Komfo Anokye Teaching Hospital, Tamale Teaching Hospital, 37 Military Hospital, Eastern Regional Hospital). During this process, we were confronted with several unexpected challenges. The first was the need to include children, who were deemed by the IRBs as key stakeholders in burn injury and the likely key beneficiaries of the intervention should it be effective. This required major revisions and resubmissions that led to additional questions regarding safety, monitoring, and oversight. These additional changes then led us to change our approach form a parallel submission approach to each of the Ghanaian IRBs to a serial approach to avoid complex revisions while other regulatory agencies are reviewing a now outdated draft. This has come at the expense of significant delay in our anticipated enrollment but will ensure that we meet all regulatory requirements and build trust in the research ethics community in Ghana. The second unexpected challenge was the requirement to have the protocol reviewed by the Ghanaian FDA. This was requested by the Ghana Health Service and Komfo Anokye Teaching Hospital IRB because we are using WHO ORS, which is considered a drug. The application for this has been completed and is being submitted this coming week. The third unexpected challenge was the mandate for us to purchase an insurance plan for the liability of the investigators and damages and care for study patients. While this is somewhat common for trials in many high-income countries, this is not common in Ghana. After consultation with multiple insurance companies and estimating rates of adverse events based on prior observational studies and burn care generally in Ghana with the help of our advisory group, we were able to identify company and create a plan/premium that were agreeable by all parties. The insurance coverage was approved by Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics. Another challenge encountered was the ask by two review bodies for building capacity for remote enrollment. This was not part of our design initially, but we created a plan and the documents required to do remote enrollment in a hub-spoke model to accommodate the multiple languages of patients across the country/sites. These and other regulatory challenges led us to hiring an international multicenter trial and regulatory expert from the Institute for Translational Health Sciences. She and her team have and continue to help us reduce delays as we navigate the web of ethical and regulatory approvals.

Another more complex challenge that we encountered was the development and operationalization of the sub-contract between University of Washington and Kwame Nkrumah University of Science and Technology. The sub-contract was primarily required to pay the IRB submission fees ahead of any other research or personnel expenses. While our intuitions have

worked together for years, there has not been a formal sub-contract of this size. It took several months of work involving our respective accounting and grants offices but was completed. We were able to process some IRB fees through brining money with me during field visits. However, larger monies were required to be processed through the sub-contract system (e.g., fee for the Ghanaian FDA submission). The shared invoicing platform between our institutions has been created and the money should be available for invoicing and payment starting the first week of September.

Despite the delays, we have received favorable final reviews and conditional approvals from Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics and the University of Washington IRB. The conditional approvals are contingent upon the approvals from the other Ghanaian regulatory bodies listed above. We have communicated with HRPO who have asked that we obtain all approvals prior to HRPO submission. We will continue to keep them posted with updates regarding the regulatory labyrinth in Ghana.

Additionally, the delays have given us time to develop research documentation tools, SOPs, communication tools, and REDCap database. Further, one of the reviews from Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics was related to the poor palatability of ORS, which might prevent its successful use for patients cared for in the intervention arm. In addition to sharing data from a US Military study on this exact topic, we were able to complete a single-blind, age-stratified study of oral rehydration drinks' palatability in comparison to one another (and to the findings from the US Military study) to identify a formulation that would be most acceptable for use in Ghana as well as by others in low-resource settings. This rapid study was appreciated by the review board and has since been published.

We have visited and held mock resuscitations and enrollments with participating referral hospital partners and staff. Additionally, we have been able to use lessons learned from a smaller pilot trial of enteral resuscitation for burn injuries in Nepal to identify and raise potential problems with our protocol with our Ghanaian partners and adapt the protocol for success. During these visits and with consultation of the Ghana Health Services Deputy Director General, we have identified the target first-level hospitals for randomization once we have all regulatory approvals.

What opportunities for training and professional development has the project provided?

Training has been focused on:

1. Education of research partners regarding burn resuscitation standards, enteral resuscitation, and study protocols.

2. Research ethics, standards and integrity using the CITI training modules for new researchers involved in the study (all but Ghanaian co-investigator, Dr. Adam Gyedu).

3. Global health research and leadership offered by University of Washington Department of Global Health for affiliated researchers.

4. Harborview Injury Prevention and Research Center Works in Progress meetings to highlight research protocol development, data analysis and interpretation, dissemination strategies.

5. Study leaders (Dr. Adam Gyedu and myself) regarding regulatory complexities by way of UW Institute of Translational Health Sciences consultations.

How were the results disseminated to communities of interest?

While we have been keeping our research partners and regulatory bodies up to date, there we have not yet been able to enroll participants and there are no results to disseminate. However, we have formed our burn advisory group in Ghana comprised of burn care providers, pediatrician and pediatric surgeon, experienced researchers, local professional society leaders. These individuals will help us with a dissemination strategy when we are ready to develop one ahead of enrollment.

We did disseminate the results of the palatability study to this group and the Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics. Additionally, this has been published.

We have shared our experience and current data regarding enteral resuscitation from our pilot project in Nepal and the palatability study at conferences (e.g., 2022 American Burn Association, 2022 International Society for Burn Injuries, 2022 Schilling Lecture Series, 2022 Military Health Research Symposium, 2022 African Federation of Emergency Medicine in Ghana). We will use these and other platforms for additional results dissemination once we are able to begin enrollment.

What do you plan to do during the next reporting period to accomplish the goals?

We now have a clear path to regulatory approvals due to: i) pre-consultations with each body who that has provided us with preliminary feedback that has shaped all of our submissions; ii) multiple IRB revisions that has yielded a very strong and detailed protocol; iii) conditional approvals from major bodies in the US (University of Washington) and Ghana (Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics) and positive pre-reviews from Ghana Health Service, Ghana FDA and HRPO; iv) and understanding of the order in which the submissions, conditional approvals, and approvals are needed. We are wholly focused in the near-term on approval from all necessary bodies so that we can begin onboarding sites and enrolling participants.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
What was the impact on other disciplines? What was the impact on technology transfer? What was the impact on society beyond science and technology?

We are yet to generate findings that will make an impact, although we anticipate the potential for enteral resuscitation significantly augment burn care in low-resource settings and be more easily implemented as a direct result of the protocol, findings, and lessons learned from this project.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

The challenges and changes encountered are detailed above and listed below:

1. Timeline as a result of the regulatory delays we are navigating. We did not anticipate the complexity of the regulatory environment in Ghana.
    a. In response, we have hired regulatory expertise from Institute of Translational Health Sciences to assist us with more rapidly achieving approvals and initiating enrollment.
2. Inclusion of children
    a. Our initial plan was to focus on adults. However, Ghanaian IRBs requested that we include children since they would be the primary beneficiaries of such an intervention in Ghana (large proportion of people who are burn injured and do not have IV access). We have gotten this approved by University of Washington and discussed this with HRPO ahead of final submission.
    b. We have updated our protocols and documentation to reflect differences in pediatric and adult burn care and documentation.
3. Evaluation of palatability/acceptability of oral rehydration drinks
    a. The Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics was concerned about the acceptability of plain ORS as a resuscitation drink.
    b. We designed, had approved, completed, and published a single-blind study of the palatability of different oral rehydration drinks to ensure that we used the most acceptable formulation for Ghanaians. The findings were consistent from those generated at the Institute of Surgical Research among US Military personnel, which suggests generalizability in the use of citrus flavored ORS formulations.
4. Creating a process for remote enrollment
    a. We initially expected that this cluster-randomized study would be an Exception to Informed Consent (EFIC) trial. However, this mechanism is not available in Ghana. Therefore, we created a plan for site-specific enrollment by trained staff at each first-level hospital.
    b. Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics also asked that we change from a site-specific enrollment to centralized remote enrollment to ensure consistency and integrity in the enrollment process.
    c. We created a process for this, which has been conditionally approved by Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics. We will rehearse and conduct many mock enrollments to work out all kinks in the process once all approvals are achieved.
5. Expanding eligibility to patients with full-thickness injures ≥10% and total injury size

<60% total body surface area (TBSA)

a. The study was originally designed to include only individuals with 20-40% TBSA burn injuries. However, since patients with 10% full-thickness (at least 3rd degree) injuries, particularly children, usually require some resuscitation and prior studies have shown that enteral resuscitation can be performed safely for patients with up to 60% TBSA injuries, we expanded our inclusion criteria on the recommendation of our Ghanaian burn advisory group.
b. In addition to providing more generalizable results, this will also increase the rate of enrollment given that a larger number of people will be eligible.

Actual or anticipated problems or delays and actions or plans to resolve them

Actual and anticipated problems and delays have been outlined above. We have returned to biweekly meetings now that we have a path to regulatory approval to facilitate preparations for site onboarding, staff training and enrollment practice ahead of full approval and actual enrollment. We have hired a regulatory consultant to help us more deftly navigate the complex regulatory environment in Ghana and between the US and Ghana and HRPO specifically. We have established working relationships between this trial group in Ghana and our project in Nepal to help share lessons learned with novice trialists and enteral resuscitation specifically. We anticipate that these working relationships and the ideas generated among them will assist this Ghanaian project in avoiding some of the clinical pitfalls we have encountered in Nepal.

Changes that had a significant impact on expenditures

We have done all possible to reduce/limit/restrict expenditures until enrollment. We have all agreed that we will do the work necessary to achieve approvals without salary in order to save the money available for research expenses, our added time during enrollment, and potentially a no-cost extension should we need one. Therefore, we have spent marked less this year than predicted, and will continue to do so until approvals have been achieved.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Human subjects

Significant changes in use or care of human subjects

We have been asked by our Ghanaian burn advisory group and Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics to include children in the protocol. We have made adjustments to the protocol and have had these reviewed by a pre-consultation with HRPO to ensure that we meet all US federal regulations

regarding the inclusion of children (including direct benefit). This has all been added to our protocol, submitted to Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics and University of Washington and approved by the latter two bodies. We await reviews from Ghana Health Service, Ghana FDA and HRPO. The hospital reviews in Ghana will be short and will fall in line with Kwame Nkrumah University of Science and Technology Committee for Human Research and Publication Ethics and Ghana Health Service.

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

6. PRODUCTS:

- **Publications, conference papers, and presentations.**
  The following are related to this work and build expertise and opportunities for dissemination of the planned trial, but were not funded by this contract directly:
  1. 2022 American Burn Association (Presentation) – Development and implementation of enteral resuscitation in a low-resource setting.
  2. 2022 International Society for Burn Injuries (Presentation) – Results from an implementation trial of enteral resuscitation in Nepal,
  3. 2022 Schilling Lecture Series (Presentation) – Resuscitation in Austere Settings: the role and study of enteral resuscitation,
  4. 2022 Military Health Research Symposium (Presentation) - Pilot randomized, controlled trial
     of enteral resuscitation for major burn injuries in Nepal,
  5. 2022 African Federation of Emergency Medicine (Presentation) – State of the art burn resuscitation and care.

- **Journal publications.**

  Gyedu A, Mehta K, Baidoo H, Addo D, Abdullah M, Mesic A, Samosorn A, Cancio LC, Nakarmi K, Stewart BT. Preferences for oral rehydration drinks among healthy individuals in Ghana: A single-blind, cross-sectional survey to inform implementation of an enterally based resuscitation protocol for burn injury. Burns. 2022 May 20:S0305-4179(22)00124-3. doi: 10.1016/j.burns.2022.05.016. Epub ahead of print. PMID: 35715342.

- **Books or other non-periodical, one-time publications.**

Stewart, BT and Rai, S. Burn Care in Austere Settings. Surgical Clinics of North America (in production)

- **Other publications, conference papers and presentations.**
- **Website(s) or other Internet site(s).**
- **Technologies or techniques.**

  Enteral resuscitation protocol (this has not been published or presented before). We are going to turn this into a technique manuscript for submission as well.

- **Inventions, patent applications, and/or licenses.**
- **Other Products.**

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS What individuals have worked on the project?

Name: Barclay Stewart
Project Role: PI
Nearest person month worked: 2
Contributions (no change): Overall strategy and coordination, regulatory decision-making, drafting and final reviews of materials ahead of submission, meetings with all involved, meetings with regulatory bodies

Name: Charles Mock
Project Role: Co-Investigator
Nearest person month worked: .5
Contributions (no change): Mentorship for Drs Stewart and Gyedu

Name: Adam Gyedu
Project Role: Site PI - Ghana (KNUST)
Nearest person month worked: 3
Contributions (no change): Development and execution of strategy in Ghana, supporting regulatory decision-making, drafting and final reviews of materials ahead of submission, meetings with all involved, meetings with regulatory bodies

Name: Etuh Ighohwo
Project Role: Co-Investigator – Ghana (Tamale Teaching Hospital)
Nearest person month worked: 1
Contributions (no change): Participating in burn advisory group meetings, participating in study meetings, reviewing protocols and SOPs, identifying and coordinating with first-level hospitals, identifying study staff for hiring once approved

Name: Paa Ekow
Project Role: Co-Investigator – Ghana (Komfo Anokye Teaching Hospital)
Nearest person month worked: 1
Contributions (no change): Participating in burn advisory group meetings, participating in study meetings, reviewing protocols and SOPs, identifying and coordinating with first-level hospitals, identifying study staff for hiring once approved

Name: CMD Kwesi Nsaful
Project Role: Co-Investigator – Ghana (37 Military Hospital)
Nearest person month worked: 1
Contributions (no change): Participating in burn advisory group meetings, participating in study meetings, reviewing protocols and SOPs, identifying and coordinating with first-level hospitals, identifying study staff for hiring once approved

Name: Forster Amponsah
Project Role: Co-Investigator – Ghana (Eastern Regional Hospital)
Nearest person month worked: 1
Contributions (no change): Participating in burn advisory group meetings, participating in study meetings, reviewing protocols and SOPs, identifying and coordinating with first-level hospitals, identifying study staff for hiring once approved

Name: Kajal Mehta
Project Role: Research fellow
Nearest person month worked: 3
Contributions (no change): Drafting protocols, refining protocols and SOPs given ongoing work and experience from sister study in Nepal, building REDCap database

Name: Aldina Mesic
Project Role: Research fellow
Nearest person month worked: 3
Contributions (no change): Drafting protocols, providing implementation science guidance, developing and testing interview guides and qualitative analysis plan

Name: Jane Edelson
Project Role: Research coordinator and regulatory consultant
Nearest person month worked: 1.5
Contributions (addition): Coordinating regulatory efforts, meeting with regulatory bodies, providing insights and expertise on international multicenter trials

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

No

What other organizations were involved as partners?

As detailed above, we have connected our Ghanaian and Nepali research partners working on

similar projects about enteral resuscitation to generate synergy and avoid shared pitfalls that slow research progress and reduce clinical effectiveness. The partners in this case are Dr. Shankar Man Rai, Dr. Kiran Nakarmi, Dr. Raslina Shresthsa, phect NEPAL, Nepal Cleft and Burn Center at Kirtipur Hospital.

These partners have provided only in-kind intellectual support and are all located in Nepal.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: None

QUAD CHARTS:

Far Forward, Fluid First Enteral Resuscitation (4F EnteroResus)

MB200003 - W81XWH-21-1-0364

PI: Barclay Stewart, MD PhD **Org:** University of Washington (UW) **Award Amount:** $ 1,500,000

Study/Product Aim(s)

Our **goals** are to: i) evaluate the effectiveness of enteral resuscitation in austere settings, and ii) understand challenges and facilitators to enteral resuscitation so we can accelerate its uptake and generate more effective implementation strategies. Specifically, we aim to:

Specific Aim 1. Compare the effectiveness of an enteral resuscitation bundle (4F EnteroResus) to enhanced standard of care (IV resuscitation) for patients with moderate burns (10-0% TBSA) in Ghana.

Specific Aim 2. Identify the challenges and facilitators to enteral and IV resuscitation protocol implementation, compliance and sustainability.

Approach

We will perform a hybrid type I effectiveness-implementation cluster randomized trial with first-level hospitals across Ghana. Hospitals will be randomized to enterally based or intravenous (IV) resuscitation. We will collect resuscitation, complication, outcome and implementation data to inform guideline development and dissemination of enteral resuscitation for use in austere settings.

Far-forward enteral resuscitation for burns is operationally advantageous & has the potential to:

- ***Reduce delays in resuscitation***
- ***Prevent and treat hypovolemic shock***
- ***Avert preventable deaths and disabilities***

…if it can be successfully implemented in austere environments.

Accomplishments to date: long-standing, productive collaboration between UW, Kwame Nkrumah University of Science and Technology, and Ghana Health Service. Substantial published and our unpublished data regarding the safety and efficacy of enteral resuscitation inform implementation strategies for this trial and its protocols. Study of ORS palatability completed to inform implementation of enteral resuscitation.

Timeline and Cost

Activities CY	21	22	23	24
Regulatory, IRB, hiring staff				
Material development and training				
Enrollment, data collection, interviews				
Interim and complete data analysis and dissemination				
Estimated Budget ($K)	**386**	**358**	**366**	**390**

Goals/Milestones

CY21-22 Goal – Regulatory, IRB, hiring staff

☐Obtain ethical and institutional approvals (Ghanaian/KNUST IRB conditional approval granted)

☐Recruitment and training of research staff

CY22 Goal – Material development and training, enrollment

☐Develop training and protocol materials with Ghanaian stakeholders

☐Enroll hospitals, collect data, perform implementation interviews

CY23 Goal – Continue data collection

☐ Collect patient and implementation data

CY24 Goal – Data analysis and dissemination

☐ Perform a priori and post hoc analyses

☐ Report and disseminate findings in accordance with transition plan

Comments/Challenges/Issues/Concerns

- Multiple and complex IRB processes within Ghana and US
- In-depth stakeholder input positively impacted protocols, but required new IRB

Budget Expenditure to Date

Projected Expenditure: $386,000

Actual Expenditure: $43,307(salary support held until IRB approvals)

9. APPENDICES:

Gyedu A, Mehta K, Baidoo H, Addo D, Abdullah M, Mesic A, Samosorn A, Cancio LC, Nakarmi K, Stewart BT. Preferences for oral rehydration drinks among healthy individuals in Ghana: A single-blind, cross-sectional survey to inform implementation of an enterally based resuscitation protocol for burn injury. Burns. 2022 May 20:S0305-4179(22)00124-3. doi: 10.1016/j.burns.2022.05.016. Epub ahead of print. PMID: 35715342.

BURNS XXX (XXXX) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Preferences for oral rehydration drinks among healthy individuals in Ghana: A single-blind, cross-sectional survey to inform implementation of an enterally based resuscitation protocol for burn injury

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ARTICLE INFO

Accepted 13 May 2022

Keywords:
Enteral resuscitation
Burn
Implementation
Acceptability
Low- and middle-income countries

ABSTRACT

Background: Enterally based resuscitation for major burn injuries has been suggested as a simple, operationally superior, and effective resuscitation strategy for use in austere contexts. However, key information to support its implementation is lacking, including palatability and acceptability of widely available rehydration drinks.

Methods: We performed a single-blinded, cross-sectional survey of 60 healthy children (5–14 years), adults (15–54 years) and older adults (≥55 years) to determine palatability and overall acceptability of five oral rehydration solutions (ORS) and a positive control drink (Sprite Zero®) in Ghana. Quantitative data were described and differences between our control drink and the others across age groups were visually examined with Likert plots. Qualitative responses were analyzed using a content analysis framework.

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https://doi.org/10.1016/j.burns.2022.05.016

Results: Twenty participants in each age group completed the study. Participants were as young as 5 years and as old as 84 years. Nearly two thirds of the sample identified as male (n = 38, 63% of all participants). The positive control was reported to taste 'good or 'very good' by the majority of participants (89%) followed by lemon-flavored ORS (78%) and orange-flavored ORS (78%). Conversely, homemade and low-osmolarity ORS were reported to taste 'good' or 'very good' by only 20% and 15% of participants, respectively. There were no major taste differences across the age groups. However, children more frequently reported positively (i.e., tastes 'good' or 'very good') about flavored and sweet drinks than did adults and older adults. When faced with the hypothetical situation of being critically injured and needing resuscitation, participants tended to be more agreeable to consuming all the drinks, even low-osmolarity and homemade ORS.

Conclusions: These findings can be used to support the development of protocols that may be more acceptable among patients undergoing enterally based resuscitation, thus improving the effectiveness of the treatment. Specifically, enterally based resuscitation should likely include citrus-flavored ORS when available, given superior palatability and the fact that different flavor additives for patients of different ages do not seem necessary.

1. Introduction

Major burn injuries benefit from early fluid resuscitation to prevent deaths and disabilities that result from systemic inflammation, a capillary-leak syndrome and hypovolemic shock [1]. However, delays in resuscitation are common and result from resource limitations, challenging operational environments, and limited expertise [2,3]. These delays are very common for people injured in austere contexts including many areas of low- and middle-income countries, rural areas in high-income countries, multiple-casualty incidents, and military environments (e.g., prolonged-field-care scenarios, shipboard incidents). In such contexts, the mortality rate for major burn injuries is generally three or more times higher than in well-resourced burn centers in high-income settings [4,5]. Therefore, a a simple, operationally superior and effective resuscitation strategy is needed for use in austere contexts proximate to patients who need it most [6].

Enterally based resuscitation involves fluid administration through drinking or via a nasogastric tube to restore or maintain intravascular volume and prevent hypovolemic shock. For other hypovolemic conditions (e.g., dehydration from acute watery diarrhea), enterally based resuscitation has proven to be highly effective for resuscitating patients, and thus is advocated by the World Health Organization (WHO) [7]. Enterally based resuscitation typically utilizes WHO Oral Rehydration Salts (ORS) reconstituted with clean water. ORS is a mix of specific ratios of glucose and electrolytes to optimize intestinal fluid absorption. The sodium-glucose cotransporter, SGLT1, stoichiometrically transports two sodium ions and one glucose molecule together across the cell membrane. ORS includes both sodium and glucose because, without glucose, intestinal sodium and water are not actively absorbed [8]. Other functional factors (e.g., pyruvate, prebiotics), flavors and aromas have been added to commercially available ORS solutions to promote intestinal functions, optimize osmolarity, and increase palatability [9–13].

Palatability is a major factor that limits intake, although very dehydrated patients often drink large volumes of 'salty' ORS in the attempt to replace perceived sodium loss. Several small clinical studies have demonstrated that enterally based resuscitation for acute burn injury is safe and efficacious in controlled settings, but limited data are available on the specific formulation to use, how to administer it and how to troubleshoot poor intake. Such limited knowledge prevents the successful operationalization of acceptable, feasible and effective enterally based resuscitation in real-world scenarios.

The aspect of palatability and its impact on burn-injured patients consuming large volumes of ORS over days is not well understood and could strongly impact the success of enterally based resuscitation. In a recent study of rehydration solution palatability among U.S. service members, Gatorade® and Drip-Drop® rehydration drinks were more palatable compared to WHO ORS, Cerasport®, and CeraLyte 70® [6]. However, most of the drinks tested have limited availability in the global context, are too expensive, or do not meet the physiological requirements to promote optimal intestinal absorption. For example, Drip-Drop® is 18 times more expensive than WHO ORS. Some solutions are hyper- or hypo-osmolar or contain incorrect ratios of sodium to glucose. Additionally, palatability and preference may differ significantly across cultures. Many people in low- and middle-income countries have received WHO ORS since childhood for the treatment of dehydration from enteritis and are more accustomed to the taste and aroma. However, WHO ORS is rarely consumed in high-income settings. It is important to generally understand the preferences among specific consumers, and to learn about geographic and age-related preferences of potential consumers of enterally based resuscitation.

Therefore, we aimed to examine the palatability of and preference for widely available rehydration drinks among individuals from multiple age groups in Ghana. Our hypothesis is that flavored ORS will be more acceptable than unflavored ORS, particularly among children. Ghana is the site

of a large, cluster randomized, effectiveness-implementation trial of enterally based resuscitation for major burn injuries. The examination of palatability and preference was determined to be a key responsibility of investigators ahead of protocol design and implementation. By understanding this important aspect of enterally based resuscitation, we aimed to gain insight into how to best operationalize the resuscitation of people with burn injuries not only in Ghana, but potentially in other contexts globally.

2. Methods

2.1. Study design and participants

The study is a single-blinded, cross-sectional survey of healthy individuals to understand palatability of and preferences for four oral rehydration drinks. These drinks were selected to represent formulations widely available globally and with common flavor additives. A popular clear-liquid beverage was also tested as a control based on recommendations from a local research consumer advisory group. The five drinks trialed were:

1) UNICEF low-osmolarity ORS (most common ORS globally, and ORS on the WHO Essential List of Medications);
2) Commercially available, orange-flavored ORS;
3) Commercially available, lemon-flavored ORS;
4) Homemade ORS as recommended by WHO; and
5) Sprite Zero® (positive control, The Coca-Cola Company, USA).

Homemade ORS was prepared in the following way. Study members washed their hands and containers with scent-free soap and water. The containers were well rinsed to ensure no soap residue was left behind. One liter of clean water was placed into a container along with half of a teaspoon of table salt and 6 teaspoons of granulated table sugar. The mixture was stirred until the solutes were dissolved. We selected Sprite Zero® as a positive control given that it is available in nearly all countries globally, recommended by our local institutional review board (IRB), and well known to readers to allow a point of reference. The IRB recommended against control beverages with high glucose/fructose concentrations (e.g., Sprite®, Lucozade®) given risk of administration to people with diabetes mellitus and beverages that have been reported to become contaminated during local processing (e.g., fresh coconut water) [14]. We did not add non-nutritive sugar substitutes or artificial sweeteners (e.g., aspartame, saccharin, stevia, sucralose) to ORS formulations given that these are not widely available in low-resource or first-level hospital settings [15]. The Sprite Zero® was allowed to decarbonate to allow apposite comparisons. Contents of the drinks above and those used in the aforementioned Burmeister et al. study [6] are provided in Table 1.

Individuals ≥5 years of age were purposively sampled from a major pedestrian and transit area in Kumasi, Ghana to ensure representation from people with diverse socioeconomic stations, locations and age groups. The sample was stratified to obtain representation from children (age 5–14 years), adults (age 15–54 years) and older adults (age ≥55 years). Individuals who were unable to taste or smell or respond with their experience and preferences were excluded. Individuals were also excluded if they reported diabetes mellitus or oropharyngeal or gastroesophageal disorders that prohibited safe consumption of thin liquids; or if they were unable to demonstrate understanding of the study and/or to provide informed consent or assent. Participation was voluntary. Eligible adult participants were asked to provide informed consent, and assent was sought from children after seeking informed consent from their parents or guardians. Based on prior work by Burmeister et al. on the palatability of rehydration drinks among U.S. service members [6], accepting a type I error rate of 0.05 (α) and absolute error of 1 (d), and a difference in means of matched overall acceptability responses between control and experimental rehydration drinks of 0.75, we aimed to enroll 20 participants in each of our target age groups to give an actual power of 0.953 (G*Power v3.1; Düsseldorf, Denmark). Participants were remunerated with GHS 10 (i.e., US$1.30, €1.25) in mobile phone credit for their time. The study was approved by the Kwame Nkrumah University of Science and Technology (KNUST) Committee for Human Research and Publication Ethics.

2.2. Study procedures and survey

Participants were presented with the five drinks contained in sample cups with lids in random order. The sample cups were opaque and had opaque lids to prevent bias from visual inspection and served as participant blinding. Each cup was filled with 50 mL of drink. The sample cups were labeled with a code (A, B, C, D, or E) with the contents of the cups known only to the research team. Drinks were served at ambient temperature (around 85 °F) to imitate real-world experiences. Salt-free crackers and water were used to cleanse the palate between tastings. The participants were surveyed after each tasting and then again while reflecting on all the drinks. Drink/tasting order was cycled to avoid effects of the taste of one drink on another tasted immediately after (i.e., one participant started with A, the next with B, and so on).

The survey (Appendix 1) consisted of 9 items. It captured quantitative information regarding key characteristics including saltiness, sweetness, viscosity, and overall palatability using a 1–5 Likert scale. Further, concerted efforts were made to ensure that the results would be directly comparable to the Burmeister et al. palatability study performed among U.S. service members [6]. Specifically, four items were used to obtain information on specific taste characteristics of each drink and four items were used to elicit preferences for each drink including how much participants enjoyed each drink, whether they would purchase the drink, and whether they would consume the drink if needed while ill. After each drink sample and before cleansing the palate, an open-ended item on the survey asked participants to explain their responses regarding their taste scoring. Once all samples were completed, the last item asked participants to rank the drinks in order of preference, from most to least favorite. No prompts were provided other than an explanation of the scale to avoid acquiescence and social desirability biases.

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Table 1 – Characteristics and composition of oral rehydration solutions (ORS), other rehydration drinks, and control drinks.

Study indicator	Drink preparations	Carbohydrate	Sodium	Chloride	Potassium	Magnesium	Base	Osmolarity	Other relevant additives
	Oral rehydration solutions								
	WHO ORS[a]	20	90	80	20	0	30	311	
	Reduced osmolarity ORS	16	60	60	20	0	30	240	
	ReSoMal	105	45	40	40	3	10	240	Zinc, copper
	Flavored ORS	20	75	65	20	0	10	245	Flavor (orange, lemon)
	ESPGHAN ORS[b]	16	60	60	20	0	30	240	
	Homemade ORS[c]	23	55	88	0	0	0	250	
	Pedialyte®	25	45	35	20	4	30	250	Flavor
	DripDrop®	30	60	0	20	13	150	235	Flavor
	Other rehydration drinks								
	Coconut water (mature)[d]	1	33	52	51	16	19	288	
	Cerasport®	0	35	0	10	0	5	135	Flavor
	CeraLyte 70®	0	70	0	20	0	10	260	Flavor
	Control drinks								
	Sprite Zero®	0	8	6	1	1	30	658	Flavor, others
	Gatorade®	58	20	11	3	0	0	299	Flavor, others

[a]WHO – World Health Organization; [b]ESPGHAN – European Society for Pediatric Gastroenterology, Hepatology and Nutrition; [c]The composition of homemade ORS varies markedly from maker to maker. Additionally, some recipes call for other ingredients such as baking soda, pre-cooked cereals, coconut water, zinc solution or dissolvable tablets. These are not included in this table.; [d]The composition of coconut water varies by age of coconut and growing environment.; Carbohydrates are presented as g/L, electrolytes and base as mEq/L, and osmolarity as mOsm/L.

2.3. Data management and analysis

Responses on the surveys were collected on paper surveys and doubly transcribed into Excel. Discrepancies were arbitrated with the original survey form. Responses were described. Assessment of central tendency bias was performed. Differences between our control drink and the others and preferences across age groups were visually examined with Likert plots [16]. Likert plots are diverging stacked bar charts aligned at the neutral response. Deflections to the right represent the frequency of positive responses and deflections to the left represent negative responses. Additionally, overall acceptability of each rehydration drink [responses to a Likert scale from 1 (most acceptable) to 5 (least acceptable)] was examined with medians and percent agreements. The Wilcoxon matched-pairs signed rank test was used to examine medians between participants' responses to acceptability of each drink and medians of (i) the positive control and (ii) low-osmolarity ORS as the comparator responses, respectively. Responses to the open-ended items were analyzed using a content analysis framework and a phenomenological approach. Lastly, data from the article on palatability of rehydration drinks among U.S. service members by Burmeister et al. [6] were compared to responses from our sample.

3. Results

3.1. Participants

Twenty participants in each age group (i.e., children, adults, older adults) completed the study (Table 2). Only two adult individuals were approached but declined to participate (97% response rate). Participants were as young as 5 years and as old as 84 years. Nearly two thirds of the sample identified as male (n = 38, 63% of all participants).

3.2. Palatability

The positive control, Sprite Zero®, was reported to taste 'good or 'very good' by most participants (89%), followed by lemon-flavored ORS (78%) and orange-flavored ORS (78%) (Fig. 1). Conversely, homemade and low-osmolarity ORS were reported to taste 'good' or 'very good' by only 20% and 15% of participants, respectively. Further, 63% and 58% of participants reported that homemade and low-osmolarity ORS were 'bad' or 'very bad', respectively. Note that reports of 'bad' or 'very bad' taste were rare for the other drinks (lemon-flavored ORS 12%, orange-flavored ORS 10%, Sprite Zero® 7%).

Although most responses to the open-ended prompt after each sample, 'Why did you respond as you did?' were similar, some responses were potentially informative. For example, participants liked the taste of fruit in the drink samples (e.g., orange, lemon, citrus generally) even if they commented specifically about how salty the taste or aftertaste was. Additionally, one participant commented, *'[Orange-flavored ORS] reminds me of Fanta®'* (The Coca-Cola Company, USA), an orange-flavored soda often consumed at social gatherings in Ghana. Sweet flavors were valued more than salty flavors. The combination of sweet and salty flavors was generally well-accepted (e.g., *'The taste is somewhat okay'*, *'I like the flavour'*, *'Salty but nice'*, *'Sweet taste, salty aftertaste, great flavor'*). Responses about low-osmolarity ORS were almost universally about the dominant salt flavor and being *'tasteless'*, *'plain'* or *'dilute'*. Although comments about homemade ORS were similar to those regarding low-osmolarity ORS, other comments were unique. As an example, participants thought that the homemade ORS tasted like *'coconut water'*. Coconut water is often consumed from street vendors and at home preferentially for rehydration and refreshment. Others associated the taste of with a *'drug'* (i.e., medical intervention or medication such as ORS) for diarrhea and noted that it was unpleasant but occasionally necessary. Importantly, no participant commented on the viscosity, temperature, or aroma of any drink.

We found no major taste differences across the age groups. However, children more frequently reported positively (i.e., tastes 'good' or 'very good') about flavored and sweet drinks than did adults and older adults.

Table 2 – Demographics of study population.

	n	%	Range
Age; median (IQR)[a]	27	[5–64]	[5–84]
Age group; years			
5–14	20	[33]	[5–13]
15–54	20	[33]	[22–53]
≥ 55	20	[33]	[55–84]
Gender			
Male	38	[63]	–
Female	22	[37]	–

[a] IQR – interquartile range.

3.3. Preference

Participants generally 'agreed' or 'strongly agreed' that they enjoyed flavored ORS, would drink it regularly and even purchase it at frequencies comparable to Sprite Zero® (Fig. 2). Conversely, only a minority of participants 'agreed' or 'strongly agreed' to the same when considering low-osmolarity or homemade ORS. However, when faced with the situation of being critically injured and needing resuscitation, participants tended to be more agreeable to consuming all the drinks, even low-osmolarity and homemade ORS.

3.4. Overall acceptability ranking

Overall, 78% of participants found the positive control to be 'most acceptable' or 'acceptable' (Table 3). Orange-flavored ORS was found to be 'most acceptable' or 'acceptable' by 62% of participants. Lemon-flavored ORS was found to be 'most acceptable' or 'acceptable' by 48% of participants. Low-osmolarity ORS and homemade ORS were found to be 'most acceptable' or 'acceptable' by 5% and 7% of participants, respectively. All rehydration drinks were found to be less acceptable than the positive control (all $p < 0.001$). Orange-flavored ORS, lemon-flavored ORS, and the positive control were more acceptable than low-osmolarity ORS (all $p < 0.001$). We found no difference in acceptability responses between low-osmolarity ORS and homemade ORS ($p = 0.96$).

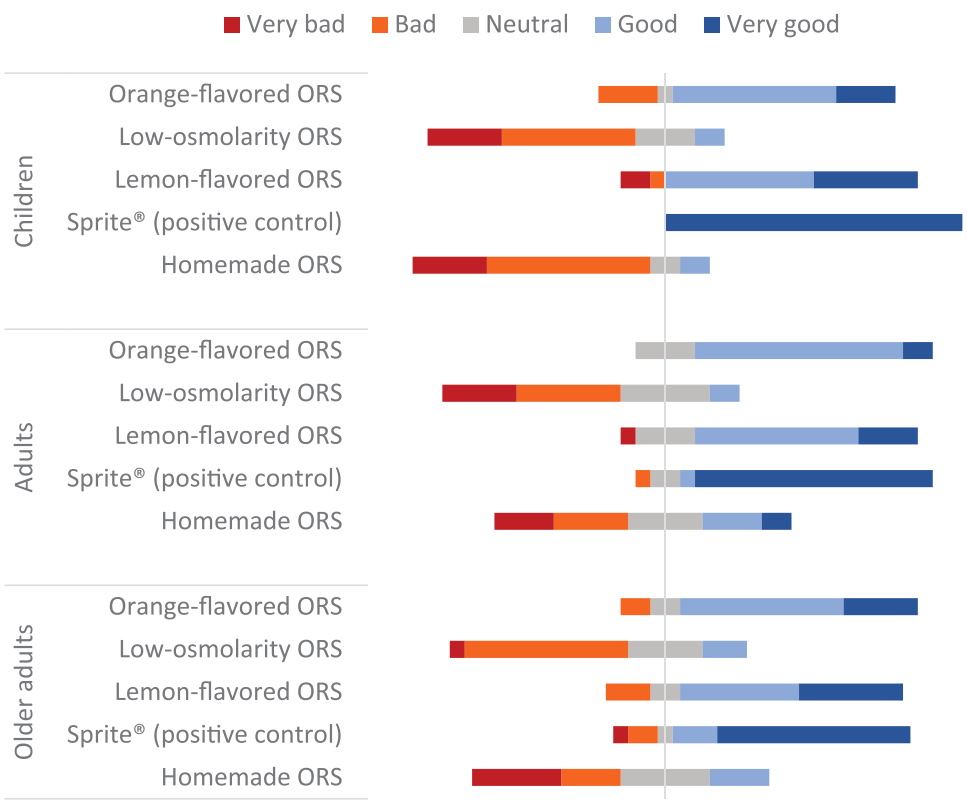

Fig. 1 – Healthy participant-reported taste experience by age group regarding rehydration drinks. ORS – oral rehydration solution; Sprite Zero® was allowed to decarbonate and used as a positive control.

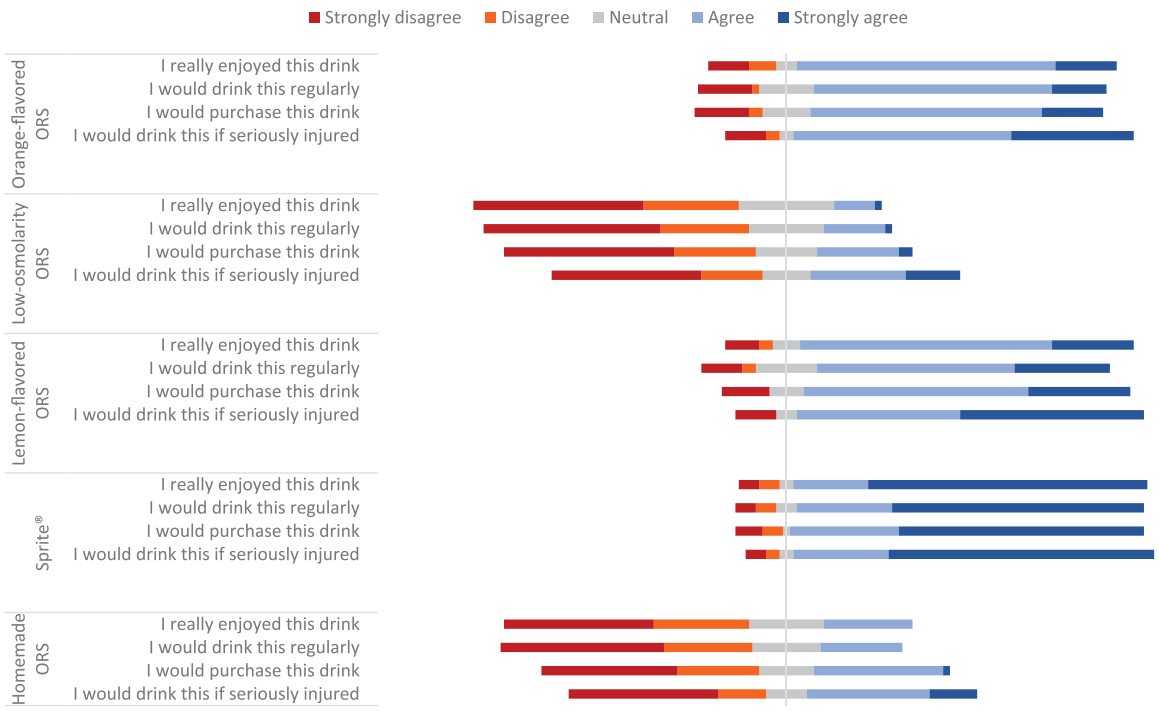

Fig. 2 – Healthy participant-reported preferences regarding rehydration drinks. ORS – oral rehydration solution; Sprite Zero® was allowed to decarbonate and used as a positive control.

When asked to rank drinks from most to least favorable for drinking in large quantities while injured, participants preferred orange-flavored ORS over lemon-flavored ORS followed by low-osmolarity ORS and homemade ORS (Fig. 3). Although we found slight differences across the age groups (e.g., adults preferred homemade ORS to low-osmolarity ORS), the rank was generally the same. We found no acceptability differences reported by those who identified as males or females.

3.5. *Comparison with U.S. service members*

Responses from forty U.S. service members extracted from the article on palatability of rehydration drinks by Burmeister et al. [6] were compared to those of our sample. Similar to our sample, service members preferred the positive control (i.e., Gatorade®; PepsiCo, USA) with more glucose than typical rehydration drinks with higher sodium:glucose ratios. Citrus-flavored drinks were preferred to WHO ORS in both populations (e.g., low-osmolarity or homemade ORS). Less than 25% of participants from both samples reported that they would regularly drink or purchase an unflavored rehydration drink.

4. Discussion

This study aimed to examine the palatability of and preference for widely available rehydration drinks among individuals from multiple age groups in Ghana. It was clear that taste of rehydration drinks is an important consideration when working to optimize the acceptability of enterally based resuscitation. First, citrus-flavored ORS solutions were markedly more palatable and preferred when compared to non-flavored ORS solutions (e.g., low-osmolarity and homemade ORS formulations). Second, we found little variation in taste and preference across age groups. Lastly, participants generally stated that they would be more agreeable to each of the rehydration drinks if they were critically injured and in need of resuscitation. Each of these findings can be used to guide the design and development of enterally based resuscitation protocols.

Enterally based resuscitation requires less technical expertise and fewer resources than does intravenous resuscitation in austere contexts. Furthermore, it is operationally advantageous for three reasons.

i) No need for sterile crystalloid bags or bottles (i.e., low weight, low cube);
ii) No need for starting or maintaining peripheral or central intravenous or intraosseous access, particularly among dehydrated patients in the pre-hospital or first-level hospital settings; and
iii) Potential for lay-person administration (i.e., self, buddy, family member, low-skilled healthcare worker).

However, the advantage of enterally based resuscitation is lost if burn-injured patients find the solution to be unpalatable and refuse to consume it continuously and/or in sufficient volumes. Therefore, the findings from both this and the Burmeister et al. study [6] suggest that citrus-flavored

Table 3 – Summary of acceptability of rehydration drinks.

	Median response	% of participant responses					p_1-value	p_2-value
		Most acceptable	2	3	4	Least acceptable		
Orange-flavored ORS	2	25	37	30	7	2	<0.001	<0.001
Low-osmolarity ORS	4	2	3	7	47	42	<0.001	-
Lemon-flavored ORS	3	8	40	32	12	8	<0.001	<0.001
Positive control	1	63	15	18	3	0	-	<0.001
Homemade ORS	4	2	5	13	33	47	<0.001	0.96

ORS – oral rehydration solution; p1-value – results of Wilcoxon Matched-Pairs Signed Rank Test with the positive control as the comparator responses; p2-value - results of Wilcoxon Matched-Pairs Signed Rank Test with the low-osmolarity ORS as the comparator responses.

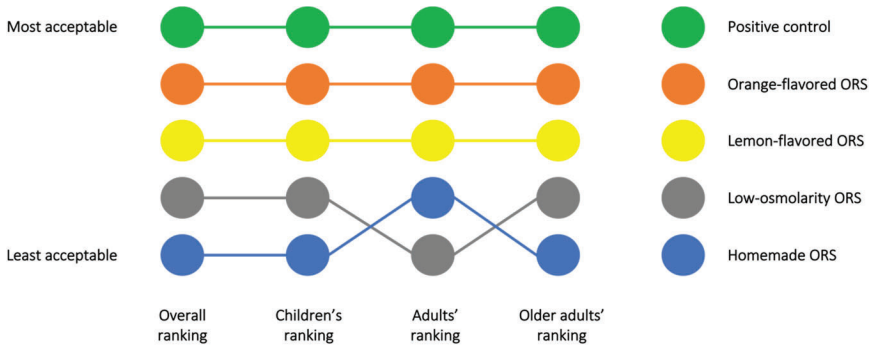

Fig. 3 – Overall rank of rehydration drink from most to least acceptable. Sprite Zero® was allowed to decarbonate and used as a positive control.

ORS formulations be used for enteral resuscitation to balance the physiological benefits of precise sodium:glucose ratios, palatability, and ubiquitous availability. Citrus-flavored ORS formulations can be found in pharmacies, hospitals, clinics and government stores in almost every country around the world.

The specific sodium:glucose ratio for an optimal pro-absorptive effect is unknown. However, most in vitro and clinical studies suggest that a ratio between 0.64 and 0.82 is ideal [17]. Interestingly, this ratio corresponds to approximately 3 sodium ions and 4 glucose molecules, which is substantially different than the optimal ratio of the SGLT-1 protein (i.e., 2 sodium ions and 1 glucose molecule). It is thought that glucose is the rate limiting factor for SGLT-1 pump activity given the extracellular abundance of sodium. However, higher concentrations of glucose, particularly when administered in resuscitation volumes, cause an intraluminal hyperosmolar state and can worsen hypovolemia. Therefore, ensuring that enterally based resuscitation protocols use solutions with an optimal sodium:glucose ratio while balancing palatability is vitally important.

In addition to flavor additives, other additives have been considered for promoting gut functions. These include pyruvate, lactate, carbachol, micronutrients, and prebiotics [6,9,10,13,18–22]. While pre-clinical studies suggest potential benefits in isolation, the safety and effectiveness of these additives for promoting rapid plasma expansion, supporting mucosal health, priming innate mucosal immune function, and supporting healthy gut microbiomes despite critical injury have not been confirmed.

Globally, children are most likely to sustain a burn injury and are also the most challenging patient group for securing and maintaining intravenous access, particularly when they are dehydrated and being cared for in less-than-ideal operational environments [5,23]. In Ghana, as in many other low- and middle-income countries, the resources and capabilities for basic (e.g., peripheral intravenous fluid administration, monitoring of vitals and urine output) and advanced resuscitation (i.e., central venous fluid administration, advanced monitoring) are critically deficient [24,25]. This is particularly true when one considers the need for pediatric-sized equipment and supplies [26]. Given the above, ensuring that enterally based resuscitation is optimized for pediatric and adult patients is essential. The findings from this study suggest little difference in the tastes and preferences for rehydration drinks between children and adults or older adults. Therefore, protocols should consider the same formulation for both children and adults and focus more closely on the route and rate of administration.

Trials of specific flavor additives to ORS for patients with acute watery diarrhea have been performed [11]. Flavors, such as cola and strawberry, have been shown to be more palatable than other fruits and ORS without flavor additives [11]. However, such additives pre-packaged in ORS sachets are rarely available compared to citrus formulations. Until specific flavors have widespread availability and are promoted through representation in WHO List of Essential Medications, protocols should recommend use of readily available formulations (e.g., citrus-flavored ORS) instead of ones that might be more palatable but less available.

This study addressed palatability and taste preferences to optimize the acceptability of enteral resuscitation. However, many have concerns about gastrointestinal discomfort and intolerance, administration during ileus, worsening intestinal ischemia during times of shock, and aspiration. Multiple small observational studies and one randomized study have demonstrated safety and efficacy of enteral resuscitation in controlled settings. A systematic review of these 12 studies that examined the safety and efficacy of enteral resuscitation in humans with burns reported that enteral resuscitation was [1]: (i) alone sufficient for most patients with 10–40% TBSA burns (i.e., IV fluids were not indicated to maintain end-organ perfusion); (ii) usually able to be administered at rates commensurate with fluid-resuscitation prediction formulas (e.g., Parkland formula); (iii) associated with occasional gastrointestinal intolerance (e.g., nausea, vomiting), but not clinically significant aspiration events; iv) not associated with atypical electrolyte derangements; and (v) ineffective and inappropriate for resuscitation in patients with cardiovascular collapse at presentation due to ileus and concern for intestinal ischemia. Given these findings, the American Burn Association, International Society for Burn Injuries, International Committee of the Red Cross, Joint Trauma System Clinical Practice Guidelines, and Tactical Combat Casualty Care Guidelines all suggest considering enteral resuscitation for moderate-sized burns,

particularly when resources are limited. Most recently, WHO published guidelines for burn care during mass casualty events [27]. Recommendation 7 suggests that oral fluid should be initiated on scene despite concerns from the burn community regarding the risk of organ hypoperfusion and complications when intravenous fluids are not also administered. Recommendation 8 suggests that oral fluids should be administered to thirst for injuries < 20% total body surface area (TBSA) and ORS at a volume of 100 mL/kg/24 h for patients with 20–40% TBSA injuries. For larger injuries, the recommendation suggests intravenous crystalloid at the same volume, and oral intake as able. We found no guidelines for emergency planning agencies regarding the specific rehydration drink to use. This is a clear gap, given the recommendation by WHO of several ORS formulations (e.g., low-osmolarity, standard, homemade), the potential for additives to promote gut function, and the availability of multiple flavor additives to improve palatability. Further, guidelines for the management of fluid resuscitation when issues of intolerance due to taste, aroma or gastrointestinal symptoms arise have not been addressed; these may include use of nasogastric tubes and gavage, augmentation with intravenous crystalloid solution, and/or co-administration with food or enteral feeding. Early data from a single-center effectiveness-implementation randomized trial of enterally based versus intravenous resuscitation for major burn injuries in Nepal (ClinicalTrials.gov Identifier NCT04732624) provides insight. The study suggests, for example, that the effectiveness of enteral resuscitation is largely dependent on how clinical protocols are developed and disseminated, the characteristics of enteral fluid being administered, the route of administration when palatability issues or gastrointestinal symptoms arise, and the availability of local enteral feeding supplies [28].

Despite recommendations for enteral resuscitation in specific contexts, multiple questions remain unanswered, such as: (i) does time of initiation of enteral resuscitation from time of injury affect incidence of ileus or rates of gastrointestinal intolerance?; (ii) what is the impact of concurrent enteral feeding on gastric emptying, gastrointestinal intolerance, and aspiration?; does enteral intake influence total resuscitation fluid given?; does enteral resuscitation (and sparing IV fluid resuscitation) protect the endothelial glycocalyx?; and does enteral resuscitation modulate changes in mucosal blood flow, function of the innate mucosal immune system, and shifts in the gut microbiome and the associated risks of bacterial/bacterial by-product translocation, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), sepsis, and death? Therefore, more prospective, controlled study of both the effectiveness and implementation of enterally based resuscitation is needed to support specific guidelines for use outside of mass-casualty scenarios and for safe and effective protocol implementation.

Although this study provides useful information for developing enterally based resuscitation protocols for global use, several limitations are worth consideration. First, this study recruited healthy individuals. Critically injured individuals may have significant alterations to their taste, smell and ability to tolerate large volumes of marginally or un-palatable rehydration drinks. However, information from the general population regarding the palatability of rehydration drinks must be used to develop enterally based resuscitation protocols ahead of large-scale clinical trials. Further, we worked to purposively sample individuals across age groups to ensure that no major differences in age-related palatability exist. Second, the study population was sampled from a single area in Ghana. However, the area was purposively selected as a major pedestrian and transit area in Ghana to ensure broad representation. Third, people with burn injury indicate markedly larger volumes of rehydration drinks per hour. We only sampled palatability of these drinks at small volumes. Tastes and preferences might change when larger volumes are indicated or consumed. Lastly, to avoid introducing bias from the appearance of rehydration drinks, samples were contained in opaque and lidded cups. Participants were not offered drinks in more practical vessels for resuscitation (e.g., graduated bottles) or via straws. However, we have no evidence that these factors would markedly change the responses provided by the participants. Despite these limitations, the findings allow for reasonable conclusions to be drawn about the palatability of, and preference for, rehydration drinks for enteral resuscitation among a healthy population.

5. Conclusion

Although prospective effectiveness and implementation data are needed to inform enterally based resuscitation for burn injuries, these findings can be used to support the development of protocols that may be more acceptable among end-users. Specifically, enterally based resuscitation should likely include citrus-flavored ORS when available, given superior palatability. Additionally, it does not seem necessary to plan different flavor additives in ORS for patients due to age alone. Given similar findings among U.S. service members, it is likely that these findings are broadly generalizable.

Funding

This study was funded by grant R25-TW009345 from the Fogarty International Center, US National Institutes of Health and Institute of Translational Health Science (grant support UL1 TR002319, KL2 TR992317, and TL1 TR002318 from National Center for Advancing Translational Sciences and NIH). The time to perform this study was supported, in part, by Department of Defense Congressionally Directed Medical Research Programs (CDMRP) Military Burn Research Program (MBRP) Clinical Translational Research Award (W81XWH-20 MB200003). The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the other funding agencies.

Financial disclosure

The authors have no financial conflicts of interest to disclose.

Declaration fo Competing Interest

The authors have no real or perceived conflicts of interest to report.

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