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TITLE: Resuscitation Strategies for Burn Injuries Sustained in Austere Environments to Improve Renal Perfusion and Function

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our overall hypothesis is that oral or intravenous resuscitation results in distinct improvements in burn-induced SIRS and AKI. Specifically, while oral resuscitation (i.e., drinking) helps in reducing SIRS, MOD and AKI post-burn injury, we predict it will not be as effective as the gold standard IV fluid resuscitation which may relate to fluid volume requirements that cannot be met orally. Moreover, we hypothesize that IV blood products (e.g., fresh frozen plasma) will improve organ perfusion and outcomes when compared to crystalloids, and thus reduce total fluid requirements. Resuscitation strategies will vary in ameliorating burn induced renal perfusion and dysfunction because of a differential effect on circulating cytokines and granulocytes. Subsequently, markers and byproducts of oxidative stress will increase as renal perfusion decreases. Information from the studies described in this proposal will elucidate what effect low volume post-burn resuscitation strategies have on the mechanisms of oxidative stress and systemic and local inflammation. This will not only provide information on the ensuing SIRS, MOD, and AKI, but also allow for future testing of therapies to modulate these mechanisms. The ultimate goal is to improve outcomes after extensive burn in austere environments where large volumes of fluid are not available and the casualty is delayed in transport to a treatment facility

15. SUBJECT TERMS

NONE LISTED

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Table of Contents

1. INTRODUCTION

Our overall hypothesis is that oral or intravenous resuscitation results in distinct improvements in burn-induced systemic inflammatory response syndrome (SIRS) and acute kidney injury (AKI). Specifically, while oral resuscitation (i.e., drinking) helps in reducing SIRS, multi organ dysfunction (MOD) and AKI post-burn injury, we predict it will not be as effective as the gold standard intravenous (IV) fluid resuscitation which may relate to fluid volume requirements that cannot be met orally. Moreover, we hypothesize that IV blood products (e.g., fresh frozen plasma) will improve organ perfusion and outcomes when compared to crystalloids, and thus reduce total fluid requirements. Resuscitation strategies will vary in ameliorating burn induced renal perfusion and dysfunction because of a differential effect on circulating cytokines and granulocytes. Subsequently, markers and byproducts of oxidative stress will increase as renal perfusion decreases. Information from the studies described in this proposal will elucidate what effect low volume post-burn resuscitation strategies have on the mechanisms of oxidative stress and systemic and local inflammation. This will not only provide information on the ensuing SIRS, MOD, and AKI, but also allow for future testing of therapies to modulate these mechanisms. The ultimate goal is to improve outcomes after extensive burn in austere environments where large volumes of fluid are not available and the casualty is delayed in transport to a treatment facility.

2. KEYWORDS

Burn, prolonged field care, enteral, rehydration salts, intravenous, resuscitation, swine models, crystalloid, colloid, third spacing

3. ACCOMPLISHMENTS

a. What were the major goals of the project? (Goals to be accomplished and status.)

Specific Aim 1: Determine the effectiveness of gastroenteral resuscitation in mitigating SIRS, MOD and AKI. (0-10 months)

- Objective 1a: Identify the effect of gastroenteral resuscitation on renal perfusion and AKI. (0-9 months) Large TBSA contact burn wound will be created using 9x15cm brass probes heated to 100°C on the dorsum, flanks, and hind limbs dorsum of Yorkshire pigs and treated with current standard of care wound dressings. Burn-induced SIRS will be characterized through routine blood collection by standard physiological parameters. Renal perfusion will be quantified via contrast enhanced CT angiography. AKI will be identified will blood chemistry analysis (e.g., creatinine) and urinalysis. By definition, all of these procedures are performed concurrently with animal experiments.
- Objective 1b: Identify the effect of gastroenteral resuscitation on systemic and local inflammation. (6-10 months) Serum and tissue biopsies collected at different time points will be analyzed for pro- and anti-inflammatory cytokines using ELISA techniques. Additionally, immunohistochemical techniques will be used to identify infiltrating immune cell populations, and to elucidate MOD in biopsies of kidneys, lungs, liver and intestine taken upon euthanasia.

Specific Aim 2: Determine the effectiveness of limited volume i.v. resuscitation for mitigating SIRS, MOD and AKI.

- Objective 2a: Compare the effects of instillation of lactated Ringer's (LR) as calculated by the modified Brooke Formula, versus a limited resuscitation volume paradigm. (10-21 months) Implanted jugular catheters will be used to administer 2 different volumes of LR to explore the consequences of limited volume capabilities likely found in prolonged field care scenarios. Outcomes will be similar to Aim 1 to examine: AKI via blood chemistry, urinalysis, and CT-angiography; SIRS via physiological parameters, blood cell counts, and cytokine (ELISA) analysis; and MOD via blood chemistry and histopathology. As such, results will be directly comparable to those found in Aim 1.
- Objective 2b: Compare the effects of LR with 2 different colloids: 5% albumin and fresh frozen plasma (FFP) on SIRS, MOD, and AKI. (13-21 months) Implanted jugular catheters will be used to deliver limited volumes of FFP and albumin. The volume used corresponds to low-volume resuscitation capabilities in prolonged field care scenarios (approximately 2 units/70kg patient/day).Again, the same volume is used in objective 2a, making the results directly comparable.

b. What was accomplished under these goals? (Detailed progress and results.)

'In short, all goals were met with great success. Specifics are given here:

Objective 1a/1b:

We have met the goals from Objective 1a and 1b. Animal experiments were completed sometime back, and were successful in examining oral resuscitation (water deprivation, ad libitum access to water, ORS at 70mL/kg/d, and ORS at 15mL/kg/d). Specific figures are not included here, as this data is published in scientific journals (See Appendix A). Specifically, using the animal model previously described [1] with specific full-thickness burn depths [2, 3], enteral fluids were shown to be effective at mitigating Acute Kidney Injury (AKI). Since trauma-induced AKI is partly due to inflammation, [4] we also showed that enteral resuscitation has anti-inflammatory effects similar to IV fluids.[5] Moreover, subsequent analysis was performed to show that these changes in AKI were associated with changes in endothelial dysfunction markers.[6] Further information on inflammation was also found, as we showed resuscitation also altered the splenic [7] and adrenal [8] responses post-burn. Specifically, IV fluids (but not enteral fluids) significantly reduce the amount of neutrophils within circulation and in the spleen. Similar results are seen in monocytes, but not for lymphocytes. We also showed that IV fluids affect adrenal integrity.

Taken together, these results indicate that enteral fluids may be a viable option for resuscitation of burn patients. From a safety standpoint, there were no adverse events (e.g., ileus) in our animal experiments, and these fluids were able to reverse acute kidney injury seen after 40% TBSA contact burn. While this method of delivering fluids is very simple and feasible in prolonged field care scenarios, it also may prove to be of benefit along with IV fluids as part of definitive clinical care.[9] This is especially true when considering the shortage of IV fluids seen in the past year because of hurricane-based destruction of manufacturing facilities. As such, one of the most exciting accomplishments emanating from these conclusions is a standardization of a standard operating procedure (SOP) to employ enteral fluids within USAISRs burn center. This SOP has been shared on the Department of Health and Human Services website (see section 6d), as a resource during mass casualty or other such events. Additionally, the knowledge products generated form this objective has inspired an IRB-submission examining the feasibility of enteral fluids within the USAISR burn center. This cannot be understated that the translatability from this modest preclinical work has been realized.

Objective 2a/2b:

We have completed animal experiments from this Aim, and have incorporated some of the circulating biomarkers in comparative reports with those in Aim 1. In terms of IV fluids, similar reversal of AKI was seen when compared with enteral fluids (i.e., non-inferiority). [10] However, what was seen was significant third spacing in the subcutaneous space which was associated with higher weight gain with fluid levels approaching 2ml/kg/%TBSA (Figure 1). Specifically, histological analysis of the subcutaneous fat layer showed that larger amounts of Lactated Ringer's as prescribed by the modified Brooke formula, led to a thicker hypodermal fat layer. The limited-volume fluid types used were: albumin, fresh frozen plasma, lactated ringers, and plasmalyte, all of which were compared with the prescribed modified Brooke levels.

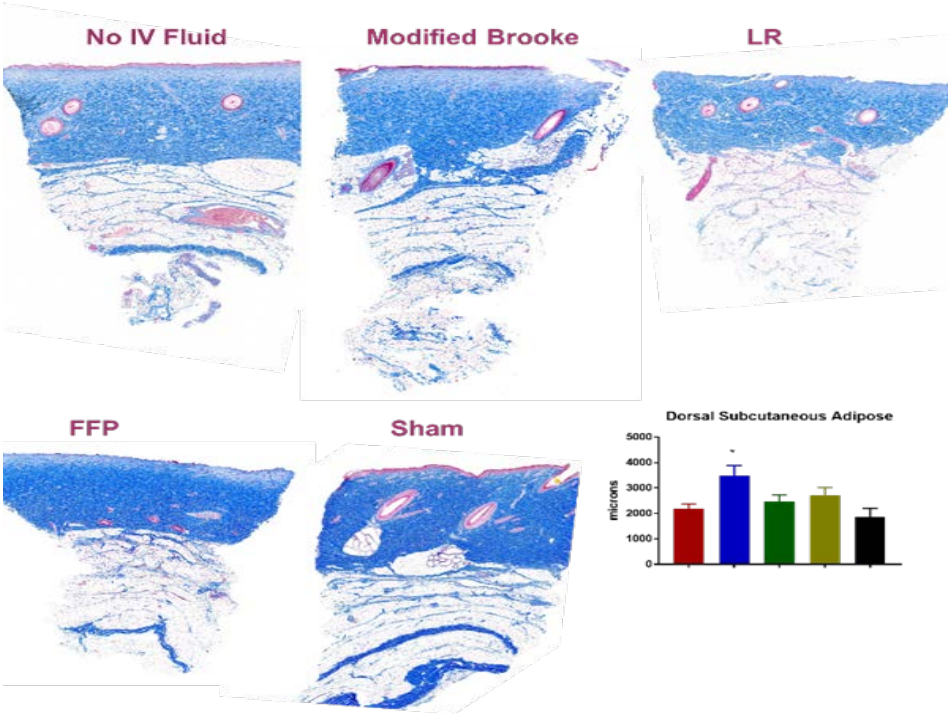

Figure 1. Representative skin biopsies stained with Masson's Trichrome highlights collagen blue, and epidermal/muscle tissues red. Images are shown for dorsal skin burns in all resuscitation groups. One-way ANOVAs were used to determine differences in the dermal and subcutaneous adipose tissue thicknesses. There was a significant effect of fluid on the thickness of the dorsal subcutaneous fat (P=0.0057), with the Modified Brooke formula leading to the thickest subcutis. There were no changes in dermal thickness amongst the groups.

Although renal function or lymphocyte bioenergetics [11] were not altered, we did make several observations of nuanced differences due to fluid type. For example, we showed that cardiac tissue displayed larger reductions in mitochondria when administered colloids.[12] Furthermore we have shown that the volume of crystalloid effects the gut microbiome in a dose-dependent manner.[13] The microbiome is the community of microbes which live in and on our bodies, and it has been shown that the bacterial portion of the microbiome is important for trauma outcomes.[14, 15] Moreover, the cutaneous microbiome is important for wound healing, [16] and the pig model used for the studies described herein has also been characterized.[17] Under the experiments described in this award, we have recently shown that colloids can also impact the gut microbiome, which is associated with changes in liver function. [18] While these knowledge products will not prevent the use of, for example, freeze dried plasma down range, mitigating potential damaging effects of these fluids should be the province of future research.

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

While this project was not intended to specifically provide training or professional development, it has served as a platform for Dr. Burmeister to establish his laboratory, to include mentorship of two postdoctoral fellows who are involved with this project. One of these individuals has been recruited and hired as an assistant professor at University of Texas Medical Branch in Galveston, TX. This speaks to the success mentorship. Mentorship includes design of ex vivo experiments and writing/presentation of abstracts. Additionally, tissue and experiments from this project served as the basis for 4 summer student projects within the last 2 years, 3 of which are published.

d. How were the results disseminated to communities of interest?

Specific presentations have been done at national conferences including Shock, Experimental Biology, American Burn Association, and Military Health Research Symposium. Results were disseminated to the scientific community in the form of manuscripts and oral presentations (see below). The burn center was briefed with internal updates, and creation of an SOP for its employment in the clinic.

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

This is the final report for this award. All told, scientific knowledge products were delivered, and a proof of concept was shown which has led to a clinical trial under review by the USAMRDC IRB (H-19-027), which is being led by Dr. Linda Sousse and funded by C_USAISR_19_2020.

4. IMPACT

a. What was the impact on the development of the principal discipline(s) of the project?

The finding and results from this project indicate that enteral fluids may be of benefit, and it is anticipated that studies into the types and volumes of these fluids will be pursued. Ultimately, this strategy may eventually be employed routinely for the resuscitation of burn patients. In fact, this project has inspired an IRB-approved protocol, which is just getting underway. Moreover, voluntary consumption of oral rehydration solutions has begun in the burn unit, demonstrating the impact on clinical care of burn patients.

b. What was the impact on other disciplines?

Nothing to Report.

c. What was the impact on technology transfer?

As mentioned earlier, these results have been communicated to the burn center. Discussions with Dr. Cancio at the USAISR burn center have led to an SOP which has also been shared with the DHS Assistant Secretary of Preparedness and Readiness (See Appendix B). Additionally, burn providers were briefed on results from this study in a staff development day. Bedside nurses are now on board with supporting a clinical study. The knowledge products and translatability of the information gathered with this proposal has been a raging success.

d. What was the impact on society beyond science and technology?

If the aforementioned clinical study being planned proves to corroborate the animal studies performed thus far, then it is possible that burn centers across the country/world will employ the use of enteral fluids. This would have far-reaching effects, especially in economically disadvantaged areas of the world, or in resource-poor environments (e.g., mass casualty scenarios, prolonged field care).

5. CHANGES/PROBLEMS

a. Changes in approach and reasons for change

Nothing to Report.

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

Nothing to Report.

c. Changes that had a significant impact on expenditures

Despite slightly behind schedule, this project stayed on budget.

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

Nothing to Report.

6. PRODUCTS

a. Journal publications

- Gómez BI, McIntyre MK, Gurney JM, Chung KK, Cancio LC, Dubick MA, Burmeister DM. Enteral resuscitation with oral rehydration solution to reduce acute kidney injury in burn victims: Evidence from a porcine model. PLoS One. 2018;13(5):e0195615. doi: 10.1371/journal.pone.0195615. eCollection 2018. PubMed PMID: 29718928; PubMed Central PMCID: PMC5931460.

a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- Gómez BI, He C, Chao T, Dubick MA, Burmeister DM. Effect of Intravenous Fluid Volumes on the Adrenal Glucocorticoid Response After Burn Injury in Swine. J Burn Care Res. 2018 Aug 17;39(5):652-660. doi: 10.1093/jbcr/iry024. PubMed PMID: 29757442.

a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Chao T, Gómez BI, Heard TC, Smith BW, Dubick MA, Burmeister DM. Burn-induced reductions in mitochondrial abundance and efficiency are more pronounced with small volumes of colloids in swine. Am J Physiol Cell Physiol. 2019 Dec 1;317(6):C1229-C1238. doi: 10.1152/ajpcell.00224.2019. Epub 2019 Sep 18. PubMed PMID: 31532719.

a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 2

d. DoD funding acknowledged

- Gómez BI, Dubick MA, Schmidt EP, Shupp JW, Burmeister DM. Plasma and Urinary Glycosaminoglycans as Evidence for Endotheliopathy in a Swine Burn Model. J Surg Res. 2020 Apr;248:28-37. doi: 10.1016/j.jss.2019.11.006. Epub 2019 Dec 13. PubMed PMID: 31841734.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Gómez BI, Harrington BK, Chao T, Chung KK, Dubick MA, Boggs NA, Burmeister DM. Impact of oral resuscitation on circulating and splenic leukocytes after burns. Burns. 2020 May;46(3):567-578. doi: 10.1016/j.burns.2019.08.019. Epub 2019 Nov 29. PubMed PMID: 31787475.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- Chao T, Gomez BI, Heard TC, Dubick MA, Burmeister DM. Increased oxidative phosphorylation in lymphocytes does not atone for decreased cell numbers after burn injury. Innate Immun. 2020 Jul;26(5):403-412. doi: 10.1177/1753425918805544. Epub 2020 Jan 6. PubMed PMID: 31906760.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- McIntyre MK, Winkler CJ, Gómez BI, Lapierre JP, Little JS, Dubick MA, Nicholson SE, Burmeister DM. The Effect of Burn Resuscitation Volumes on the Gut Microbiome in a Swine Model. Shock. 2020 Sep;54(3):368-376. doi: 10.1097/SHK.0000000000001462. PubMed PMID: 31651724.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Muraoka WT, Granados JC, Gomez BI, Nicholson SE, Chung KK, Shupp JW, Bynum JA, Dubick MA, Burmeister DM. Burn resuscitation strategy influences the gut microbiota-liver axis in swine. Sci Rep. 2020 Sep 24;10(1):15655. doi: 10.1038/s41598-020-72511-8. PubMed PMID: 32973266; PubMed Central PMCID: PMC7515893.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

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

- Burmeister DM, Little JS, Gomez BI, Gurney J, Chao T, Cancio LC, Kramer GC, Dubick MA. Operational Advantages of Enteral Resuscitation Following Burn Injury in Resource-Poor Environments: Palatability of Commercially Available Solutions. J Spec Oper Med. 2019 Fall;19(3):76-81. PubMed PMID: 31539437.
a. Original manuscript
b. Published
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

c. Other publications, conference papers, and presentations

Selected abstracts that have been part of official publications, and/or presented as oral or posted presentations at national scientific and military meetings.

- Belinda I. Gómez, Joshua. S. Little, Tiffany C. Heard, Michael A. Dubick and David M. Burmeister. Limited Volume Resuscitation with 5% Albumin Exacerbates Liver Injury in a 40% TBSA Swine Burn Model. Military Health System Research Symposium 2019 (Kissimmee, FL).

a. Oral
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Little, JS, Gomez, BI, Gurney, J, Cancio, LC, Kramer, GC, Dubick, MA, Burmeister, DM. Palatability of Commercially Available Rehydration Solutions: Preferences of Active DutycService Members. Military Health System Research Symposium 2019 (Kissimmee, FL).

a. Poster
b. Presented
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- Matthew McIntyre, Charlotte J. Winkler, Belinda I. Gómez, Jean-Paul Lapierre, Joshua S. Little, Michael A. Dubick, Susannah Nicholson, David M. Burmeister. Intravenous Resuscitation Attenuates Gut Microbiome and Intestinal Changes after 40% TBSA Burn Injury in Swine. American Burn Association 2019 (Las Vegas, NV).

a. Oral
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Burmeister, OM, Gomez, BI, Chao, T, Gurney, JM, Kramer, G, Dubick, MA. The Operational Advantages of Utilizing Enteral Resuscitation for Severe Burn Injury in Prolonged Field Care Scenarios. Special Operations Medical Assembly, May 2018 (Charlotte, NC).

a. Oral
b. Presented
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- McIntyre MK, Winkler CJ, Gomez BI, Chao T, Little JS, Nicholson S, Dubick MA, Burmeister DM. (2018) Lactated Ringers Attenuates Gut Microbiome and Intestinal Changes after 40% TBSA Burn Injury in Swine. Oral Presentation at the 15th Annual Louis R.M. DelGuercio, MD Distinguished Visiting Professorship & Research Day. Valhalla, NY. December 19, 2018.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Tony Chao, Grace CY Chu, Belinda I. Gomez, Shanmugasundaram Natesan, Robert J. Christy, Michael A. Dubick, David M. Burmeister. Increased Mitochondrial Respiration and ROS Production from Adipose Derived Stem Cells is Passage Dependent. RegenMed San Antonio 2019.

a. Oral
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- DM Burmeister, BI Gómez, T Chao, LC Cancio, MA Dubick. 402 Enteral Resuscitation Shows Similar Efficacy to IV Resuscitation in a Porcine 40% TBSA Contact Model. Journal of Burn Care & Research 39 (suppl_1), S172-S172. *- Won best in class poster

a. Poster
b. Presented

c. Directly related to SOW, specific aims 1 and 2
d. DoD funding acknowledged

- BI Gómez, C He, T Chao, MA Dubick, DM Burmeister. 113 Effect of Intravenous Fluid Resuscitation Volumes on the Adrenal Response in Burn Injury in Swine. Journal of Burn Care & Research 39 (suppl_1), S62-S62.

a. Oral
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- T Chao, BI Gomez, TC Heard, MA Dubick, DM Burmeister. 413 Altered Renal and Cardiac Mitochondrial Activity After 40% TBSA in a Swine Model. Journal of Burn Care & Research 39 (suppl_1), S178-S178.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- BI Gómez, BK Harrington, T Chao, JS Little, TC Heard, MA Dubick, DM Burmeister. 229 Enteral Fluid Resuscitation Alters Splenic Function and Leukocyte Populations Post-Burn in Swine. Journal of Burn Care & Research 39 (suppl_1), S82-S82.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 1
d. DoD funding acknowledged

- DM Burmeister, BI Gomez, T Chao, L Cancio, M Dubick. 832: Enteral Resuscitation Of Moderate Burns Shows Similar Efficacy To IV Resuscitation In A Swine Model. Critical Care Medicine 46 (1), 400.

a. Poster
b. Presented
c. Directly related to SOW, specific aims 1 and 2
d. DoD funding acknowledged

- BI Gomez, T Chao, MA Dubick, DM Burmeister. 8 Limited Volume Lactated Ringer's and Plasma-lyte are Comparable for IV Resuscitation in a Pig Burn Model. Shock 49, 43.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- T Chao, BI Gomez, TC Heard, MA Dubick, DM Burmeister. 9 Fluid Resuscitation on Cardiac Mitochondrial Function in Severely Burned Swine. Shock 49, 43-44.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Tony Chao, Ph.D., Belinda Gómez, Ph.D., Tiffany Heard, SPC Joshua Little, Michael Dubick, Ph.D., David Burmeister, Ph.D. Fluid Resuscitation on Cardiac Mitochondrial Function in Severely Burned Swine. Military Health System Research Symposium, Kissimmee, FL, August 2018.

a. Oral
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Burmeister, DM, Bynum, J, Little, JS, Wu X, Gomez, BI, Chao, T, Gurney, JM, Darlington, D, Dubick, MA. The Effect of IV Resuscitation on Coagulation and Platelet Aggregation After 40% TBSA Burns in Swine. Military Health System Research Symposium, Kissimmee, FL, August 2018.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

- Belinda I. Gómez, PhD, Tony Chao, PhD, SPC Joshua S. Little, Michael A. Dubick, PhD, David M. Burmeister, PhD. Limited Volume Lactated Ringer's and Plasma-Lyte are Comparable for IV Resuscitation in a Swine Burn Model. Military Health System Research Symposium, Kissimmee, FL, August 2018.

a. Poster
b. Presented
c. Directly related to SOW, specific aim 2
d. DoD funding acknowledged

d. Website(s) or other Internet site(s)

https://asprtracie.hhs.gov/technical-resources/28/burns/27
http://ameriburn.org/quality-care/mass-casualty/oral-fluid-resuscitation/

e. Technologies or techniques

Enteral Fluid delivery standard operating procedure.

f. Inventions, patent applications, and/or licenses

Nothing to Report

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g. Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name:	David Burmeister
Project Role:	PI
Nearest person month worked:	12
Contribution to Project:	Dr. Burmeister is providing technical oversight and leadership of the protocol. Specifically, he will oversee regulatory approval, supervise data collection and analysis, and coordinate team meetings to review planning and execution of the study.
Name:	Belinda Gomez
Project Role:	Postdoctoral Fellow
Nearest person month worked:	10
Contribution to Project:	Dr. Gomez assisted with animal procedures and processed blood/tissue samples.
Name:	Tony Chao
Project Role:	Postdoctoral Fellow
Nearest person month worked:	10

Contribution to Project:	Dr. Chao assisted with animal procedures and processed blood/tissue samples.

Name:	Tiffany Heard
Project Role:	Research Lab Technician III
Nearest person month worked:	7.0
Contribution to Project:	Tiffany is learning assays that examine mitochondria function.

Name:	Joshua Little
Project Role:	Private First Class
Nearest person month worked:	6
Contribution to Project:	Upon availability, PFC Little runs blood Vacutainer tubes to our biochemistry core lab, and aliquots plasma for later analysis.

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

Nothing to Report.

c. What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHART: Attached

9. APPENDICES

Appendix A: References.
Appendix B: 1-136 R00 Oral Rehydration Solution (ORS) CPG.pdf

References:

[1] Burmeister DM, McIntyre MK, Baker BA, Rizzo JA, Brown A, Natesan S, Chung KK and Christy RJ. Impact of Isolated Burns on Major Organs: A Large Animal Model Characterized. Shock 2016; 46: 137-147.

[2] Burmeister DM, Ponticorvo A, Yang B, Becerra SC, Choi B, Durkin AJ and Christy RJ. Utility of spatial frequency domain imaging (SFDI) and laser speckle imaging (LSI) to non-invasively diagnose burn depth in a porcine model. Burns 2015; 41: 1242-1252.

[3] Ponticorvo A, Burmeister DM, Yang B, Choi B, Christy RJ and Durkin AJ. Quantitative assessment of graded burn wounds in a porcine model using spatial frequency domain imaging (SFDI) and laser speckle imaging (LSI). Biomed Opt Express 2014; 5: 3467-3481.

[4] Burmeister DM, Gomez BI and Dubick MA. Molecular mechanisms of trauma-induced acute kidney injury: Inflammatory and metabolic insights from animal models. Biochim Biophys Acta Mol Basis Dis 2017; 1863: 2661-2671.

[5] Gomez BI, McIntyre MK, Gurney JM, Chung KK, Cancio LC, Dubick MA and Burmeister DM. Enteral resuscitation with oral rehydration solution to reduce acute kidney injury in burn victims: Evidence from a porcine model. PLoS One 2018; 13: e0195615.

[6] Gomez BI, Dubick MA, Schmidt EP, Shupp JW and Burmeister DM. Plasma and Urinary Glycosaminoglycans as Evidence for Endotheliopathy in a Swine Burn Model. J Surg Res 2020; 248: 28-37.

[7] Gomez BI, Harrington BK, Chao T, Chung KK, Dubick MA, Boggs NA and Burmeister DM. Impact of oral resuscitation on circulating and splenic leukocytes after burns. Burns 2020; 46: 567-578.

[8] Gomez BI, He C, Chao T, Dubick MA and Burmeister DM. Effect of Intravenous Fluid Volumes on the Adrenal Glucocorticoid Response After Burn Injury in Swine. J Burn Care Res 2018; 39: 652-660.

[9] Burmeister DM, Little JS, Gomez BI, Gurney J, Chao T, Cancio LC, Kramer GC and Dubick MA. Operational Advantages of Enteral Resuscitation Following Burn Injury in Resource-Poor Environments: Palatability of Commercially Available Solutions. J Spec Oper Med 2019; 19: 76-81.

[10] Burmeister D, Gómez B, Chao T, Cancio L and Dubick M. 402 Enteral Resuscitation Shows Similar Efficacy to IV Resuscitation in a Porcine 40% TBSA Contact Model. Journal of Burn Care & Research 2018; 39: S172-S172.

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1.0 PURPOSE

To establish a process for the administration of enteral resuscitation fluids in adult burn patients.

2.0 OVERVIEW

Patients with burns >20% TBSA require fluid resuscitation to address hypovolemia that develops secondary to capillary leak and increased insensible losses. Intravenous fluids (IVF) have been the mainstay of volume resuscitation in these patients. Enteral resuscitation has been found to be safe[1] and to reduce IVF requirements.[2] Reduction in IVF requirements may help prevent the co-morbidities associated with volume overload.

3.0 REFERENCES

All references are the most current version/revision unless otherwise specified.

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4.0 ADDITIONAL READING

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5.0 RECORDS

All references are the most current revision unless otherwise specified.

Identifier	Title
N/A	Burn Navigator entries

6.0 ABBREVIATIONS, ACRONYMS AND TERMS

Identifier	Description
GI	Gastrointestinal
IVF	Intravenous Fluid
NGT	Nasogastric Tube
ORG	Orogastric Tube
ORS	Oral Rehydration Solution
TBSA	Total Body Surface Area
WHO	World Health Organization

7.0 MATERIALS/EQUIPMENT

- ORS
- Burn Navigator

8.0 SAFETY INFORMATION

See Exclusions.

9.0 RESPONSIBILITIES

As defined throughout this procedure.

10.0 PROCEDURE

ORS Administration

10.1 Per physician discretion, oral rehydration solution (ORS) can be administered via a nasogastric tube (NGT) or orogastric tube (OGT) as part of the initial fluid resuscitation (within the first 24 hours).

10.2 The World Health Organization recommends pre-packaged ORS that contains 2.6 g sodium chloride, 1.5 g potassium chloride, 2.9 g trisodium citrate, and 13.5 g glucose per liter. ORS via the NGT or OGT is initiated with the head of bed elevated by 30-45 degrees, after the initial shower is completed and after the placement of the NGT or OGT is confirmed by x-ray. The gastric motility agent naloxone (2-4 mg Narcan q4h) is given enterally upon initiation of ORS to aid in GI motility. Gastric residuals are checked to ensure they are less than 300 cc prior to initiation of ORS. If residuals are over 300 cc on initial check, dispose of the gastric contents and check residuals again in 1-2 hours to see if initiation of ORS is warranted.

10.3 The Burn Center nursing staff mixes one ORS packet in 1 L of sterile water according to the package directions. When reconstituted, the date and time shall be labeled accordingly. The solution can be used up to 24 hours after reconstitution but then must be discarded.

10.4 Reconstituted ORS is placed in the enteral bag (rather than the flush bag) for the eKangaroo pump. When enteral nutrition is initiated during ORS use, the enteral nutrition formula is placed in the flush bag and started at 20 cc flushes each hour, increasing per usual practice, but as boluses rather than as a continuous drip until ORS fluid resuscitation is completed.

10.5 ORS is initiated through the NGT or OGT at 200 cc/hour and is increased by 100 cc/hour up to 400 cc/hour.

10.6 Gastric residuals are initially checked hourly, and then extended to every other hour by physician order based on tolerance (i.e., residuals <300 cc). ORS administration, if stopped, can be reinitiated in 2 hours at 200 cc/hour. If low-volume vomiting occurs, ORS can be re-initiated (assuming low residuals) in as early as one hour; restart at 200 cc and advance as tolerated to goal.

10.7 The usual computerized decision support (i.e., Burn Navigator) for fluid resuscitation is used and the IVF rate is adjusted in the usual fashion, as the fluid absorption via the GI tract can be variable. Additionally, this decision support system will be used to document enteral fluids.

10.8 ORS administration will stop when the decision support system is discontinued.

11.0 EXCLUSIONS

DO NOT USE ORS in any of the following situations:

- GI tract not appropriate for enteral fluid resuscitation (i.e., recent gastric bypass surgery, which could cause dumping, or GI tract not in continuity).
- Significant vasopressor use, defined as norepinephrine > 5 mcg/min (with or without vasopressin).
- Burn size ≥50% TBSA
- Admission ≥24 hours after injury
- Age ≥65 years old
- Baux score ≥100

12.0 EXPECTED OUTCOMES

- Safe administration of ORS: gastric residuals <400 cc, no aspiration
- Correction of burn shock with improvements in base deficit, lactate, vasopressor use
- ORS may result in lower IVF requirements during the initial fluid resuscitation
- ORS may decrease total resuscitation volumes and related complications of edema

13.0 APPENDICES

Identifier	Title
N/A	N/A

14.0 REVISION HISTORY

Rev	Effective Date	Description of Change	Changed By:
00	28Dec2018	New	N/A