Ceftriaxone to PRevent pneumOnia and inflammaTion aftEr Cardiac arresT (PROTECT): a randomized-controlled trial and microbiome assessment

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Background

- In-hospital survival rates following out-of-hospital cardiac arrest (OHCA) have increased 5% in the past decade[1]
- Early-onset pneumonia occurs in ~65% of comatose patients and it reduces incidence of a good functional outcome[2]
- T-cell mediated inflammation may exacerbate secondary brain injury after OHCA
- Antibiotic prophylaxis with ceftriaxone may prevent early-onset pneumonia and reduce systematic inflammation[3]
- Antibacterial resistance is a global concern and judicious medication prescribing is recommended[4]
- No trial has examined antibiotic prophylaxis, inflammation, and the microbiome/resistome after OHCA

Specific Aims

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- **Specific Aim 1. Quantify the clinical and microbiologic effects of prophylactic ceftriaxone administration in comatose OHCA survivors**
  - **Aim 1a.** Conduct a single-center, randomized, placebo-controlled, quadruple-blinded trial in 120 comatose OHCA survivors to determine the effect of prophylactic ceftriaxone on EOP
  - **Aim 1b.** Determine the effect of prophylactic ceftriaxone on the bacterial resistome

- **Specific Aim 2. Determine if prophylactic ceftriaxone suppresses T cell-mediated inflammation via increased CD73/adenosine signaling.**
  - Quantify ceftriaxone-mediated adenosine generation and inhibition of pro-inflammatory T cell activation in cells isolated from OHCA survivors

Methods – Aim 1a (clinical trial)

- Subjects
  - OHCA, ≥18 years of age, comatose, (do not follow simple verbal commands), any initial heart rhythm
- Intervention
  - Ceftriaxone 2 gm IV q12h for 3 days starting within 6 hours of ICU admission
- Comparator
  - Matching placebo for 3 days starting within 6 hours of ICU admission
- Selected Efficacy Outcomes
  - Clinically-diagnosed EOP occurring <4 days after initiation of mechanical ventilation
  - Late-onset pneumonia ≥4 days after mechanical ventilation
  - Incidence of non-pulmonary infections
  - ICU-free days
  - Mechanical ventilator-free days

Ceftriaxone benefits:
- Bactericidal
- Susceptibility profile
- Low cost
- Administer over 30 min
- Safe
- Neuro-protective?

Methods – Aims 1b and 2

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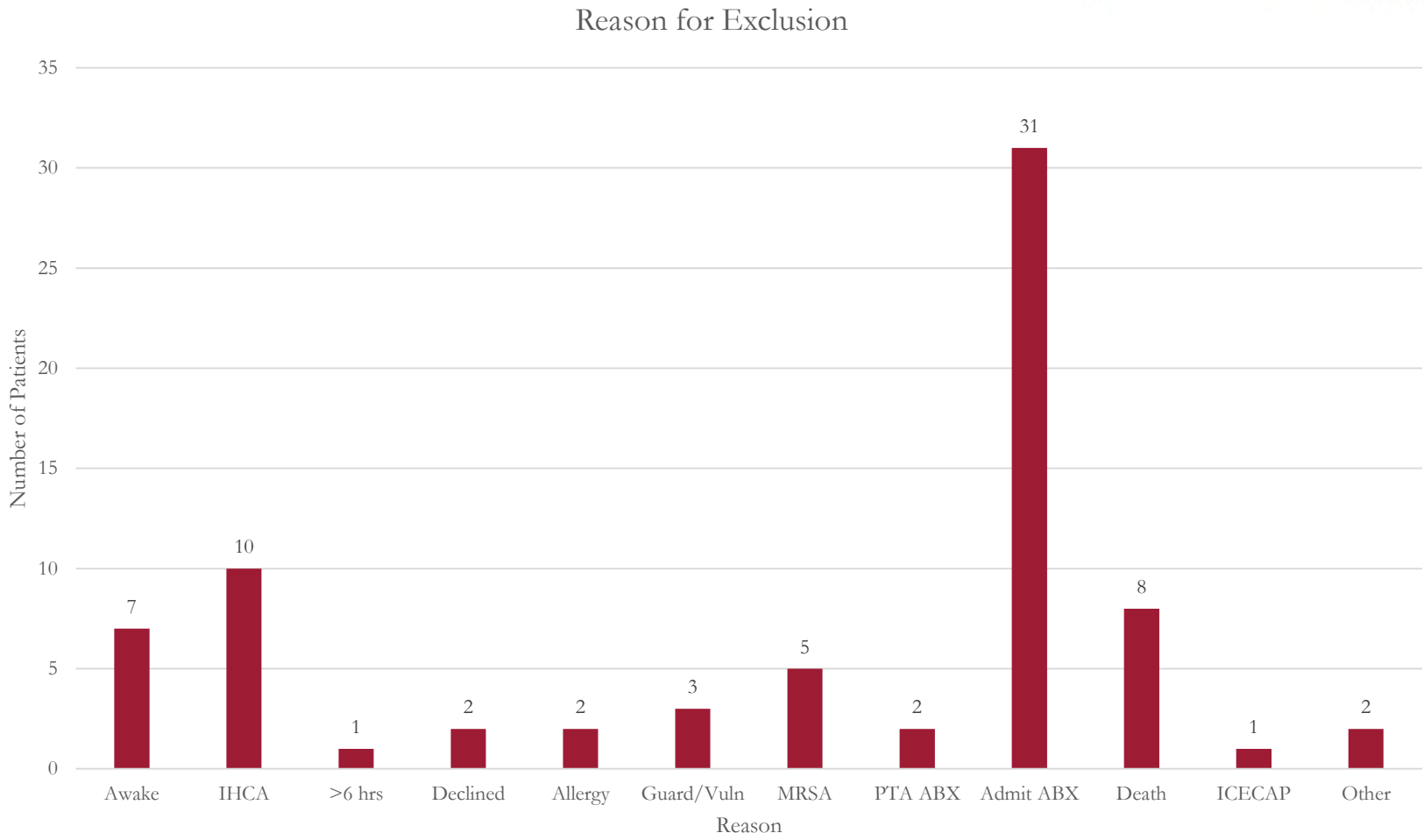
- Aim 1b (T-cell mediated inflammation)
  - Total nucleic acids extracted from sputum and rectal swabs with shotgun libraries prepared
  - Library preparation and sequencing reads will be performed at the UC Davis Genome Center
  - Remaining reads assembled into metagenomes using Velvet, and resistance genotypes will be identified and quantified using ResFams and ShortBRED

- Aim 2 (microbiome/resistome)
  - Multi-parametric flow cytometric analysis on whole blood cells before study drug and on study-day 1 and study-day 3
  - Percentage of CD3+ T cells, CD4+ and CD8+ subpopulations, and CD73 expression on T lymphocytes
  - Neutrophils and monocytes will be gated and cell surface expression of CD73 and production of TNF-α assayed

Results

- IRB approval June 29, 2021
- Open to enrollment August 10, 2021
- First enrollment August 20, 2021

- Screened n=83 subjects
- Enrolled n=14 (17%)



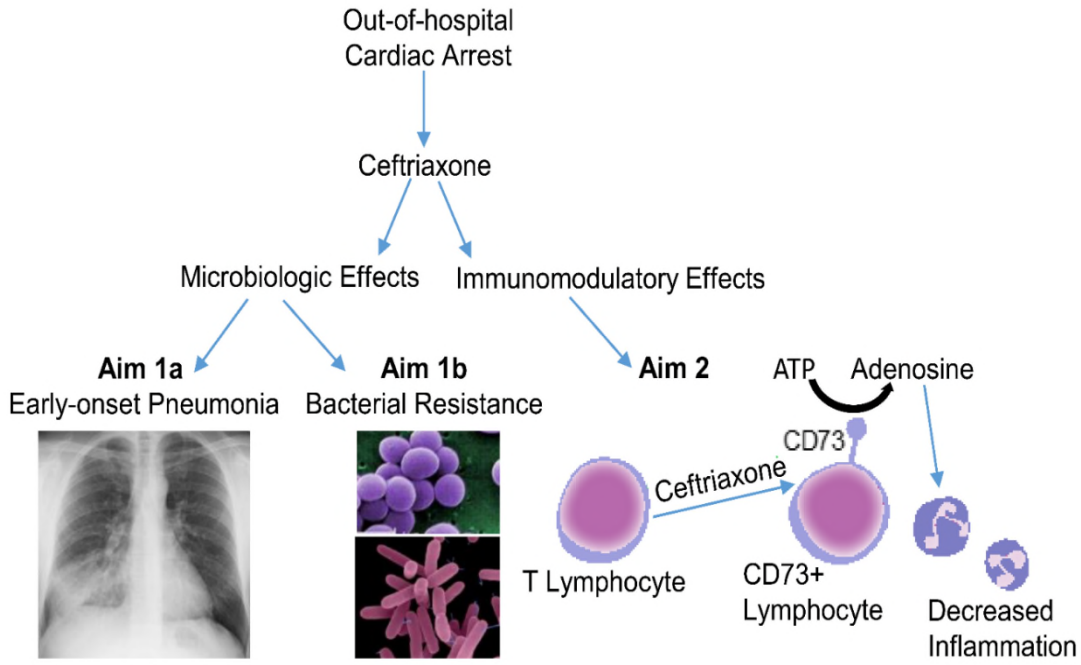
Discussion

- Anticipated trial completion middle of 2026

- Receipt of antibiotics biggest reason for exclusion
  - Reviewing our aspiration pneumonia approach

- What can we learn from survivors and families?
  - Remote consent experience?
  - Exception from Informed Consent experience?

- Likely need a second enrolling site
  - Discussions with Eastern Maine Medical Center



References

1. Circulation. 2021;143:e00
2. Am J Respir Crit Care Med. 2011;184:1048
3. The J Trauma Acute Care Surg. 2012;73:654
4. Lancet Infect Dis. 2018;18:132

- To review full protocol, please visit our open access publication in Trials journal of Clinicaltrials.gov:
  - Trials. 2022;23:197. PMID: 35246202
  - https://clinicaltrials.gov/ct2/show/NCT04999592

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