AWARD NUMBER: W81XWH-17-C-0241

TITLE: Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

PRINCIPAL INVESTIGATOR: Adit Ginde, MD, MPH

CONTRACTING ORGANIZATION: Funded by the Department of Defense/SOCOM

REPORT DATE: February 28th, 2020

TYPE OF REPORT: Final Report

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

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Final Technical Report

Award Number: W81XWH-17-C-0241

Title: Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

Principal Investigator: Adit Ginde, MD, MPH

Date: February 28, 2020
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1. **INTRODUCTION**: Oxygen therapy has undisputed importance in the care of critically ill medical and trauma patients to treat and prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. The overall objective is to determine the feasibility, safety, and potential effectiveness of targeted normoxia as a strategy to conserve oxygen and improve clinical outcomes in critically ill trauma patients.

2. **KEYWORDS**: oxygenation, oxygen delivery, mechanical ventilation, normoxia, hyperoxia, hypoxia, critically ill, trauma, prolonged field care, limited resources, traumatic brain injury, hemorrhage

3. **ACCOMPLISHMENTS:**

   - **What were the major goals of the project?**
     
     **Aim 1. Define standard care for oxygen titration in critically ill trauma patients.**
     
     1) Obtain official ‘not-human subjects research’ determination from the Colorado Multiple Institutional Review Board—**Month 2**: 100% complete
     2) Perform literature review—**Month 2**: 100% complete
     3) Complete Delphi Stage 1—**Month 4**: 100% complete
     4) Complete Delphi Stage 2—**Month 6**: 100% complete
     5) Complete Delphi Stage 3—**Month 8**: 100% complete
     6) Complete Delphi Stage 4—**Month 11**: Not required
     7) Submit main manuscript for publication—**Month 14**: 100% complete

     **Aim 2. Compare the effectiveness of targeted normoxia and relative hyperoxia in critically ill trauma patients.**
     
     1) Obtain IRB approval—**Month 2**: 100% complete
     2) Obtain USAMRMC ORP approval—**Month 5**: 100% complete
     3) Complete data collection—**Month 8**: 100% complete
     4) Complete primary data analysis—**Month 12**: 100% complete
     5) Submit main manuscript for publication—**Month 15**: 95% complete

     **Aim 3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.**
     
     1) Finalize intervention and case report forms—**Month 9**: 100% complete
     2) Obtain IRB approval—**Month 11**: 100% complete
     3) Obtain USAMRMC ORP approval—**Month 14**: 100% complete
     4) Integrate clinical decision report in electronic medical record—**Month 14**: 100% complete
     5) Train clinical staff on intervention—**Month 15**: 100% complete
     6) Launch intervention period—**Month 16**: 100% complete
     7) Complete intervention period—**Month 21**: 100% complete
8) Complete primary data analysis—Month 22: 100% complete
9) Submit manuscript for publication—Month 24: 90% complete

- What was accomplished under these goals?

AIM 1:
- Published systematic review manuscript Journal of Trauma (2019) PMID: 31162333
- Delphi consensus presented at SOMSA 2019
- Delphi consensus presented at MHSRS 2019
- Delphi consensus manuscript drafted and under final review

AIM 2:
- Primary and Secondary Analysis complete
- Oral presentation at MHSRS 2019
- SOMSA 2020 (selected for poster presentation)
- Manuscript drafted and under final review

AIM 3:
- Local IRB approval
- HRPO approval
- Implementation completed
- Data collection completed
- Primary data analysis complete
- SOMSA 2020 (selected for oral presentation)
- Early draft of manuscript in process

Follow-on Work: Two multicenter trials

Strategy to Avoid Excessive Oxygenation (SAVE-O2) in Major Burn Patients
  - Grant # MTEC-19-08-MULTI-0043

Strategy to Avoid Excessive Oxygenation (SAVE-O2) in Critically Ill Trauma Patients
  - Selected for funding; funding # W81XWH-20-2-0001

- How were the results disseminated to communities of interest?
  - CoERCCC presentation (Nov 2018)
  - SOMSA Delphi presentation (April 2019)
  - Capability Development Integration Directorate (CDID) presentation (April 2019)
  - Oxygen Standardization Coordinating Group (OSCG) presentation (July 2019)
  - Presented Delphi consensus in poster form MHSRS (August 2019)
  - Presented AIM2 data analysis in oral form MHSRS (August 2019)
- Terry Adirim, MD, MPH, MBA (Acting Principal Deputy Assistant Secretary of Defense for Health Affairs) site visit (September 2019)
- Col Michael Davis, MD (Director of Combat Casualty Care Research Program) site visit (October 2019)
- CoERCCC presentation (Nov 2019)

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:
   - What was the impact on the development of the principal discipline(s) of the project?
     - Helped to define current standard care/best practices for oxygenation in critically ill trauma patients and collected important preliminary data leading to definitive multicenter trial funding
   - What was the impact on other disciplines?
     Nothing to Report
   - What was the impact on technology transfer?
     Nothing to report
   - What was the impact on society beyond science and technology?
     Nothing to Report

5. CHANGES/PROBLEMS:
   Nothing to Report
   - Changes in approach and reasons for change
     Nothing to report
   - Actual or anticipated problems or delays and actions or plans to resolve them
     Delay in manuscript(s) publications: There were delays in the final analysis phase of AIM3. Further delays have occurred in manuscript completion and submission due in part to the large number of co-authors that have participated in the project.

   ACTION PLAN:
   We will work diligently over the next few months to finalize manuscripts and prepare for submission to relevant medical civilian and/or military journals.
   - Changes that had a significant impact on expenditures
Nothing to report

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

- Significant changes in use or care of human subjects:
  Nothing to report

- Significant changes in use or care of vertebrate animals:
  N/A

- Significant changes in use of biohazards and/or select agents:
  N/A

6. PRODUCTS:

- Publications, conference papers, and presentations
  *CoERCCC presentation 2018
  *Delphi Consensus presented at SOMSA 2019
  *CDID presentation 2019
  * Systematic review published Journal of Trauma and Acute Care Surgery 2019
  * OSCG presentation 2019
  *Delphi Consensus poster presentation MHSRS 2019
  * AIM2 Data oral presentation at MHSRS 2019
  * Col Davis, MS USAF site visit to the University of Colorado
  * CoERCCC presentation 2019

- Other Products
  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- What individuals have worked on the project?
Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Change to PI other support:

See Below

PREVIOUS SUPPORT

Title: Vitamin D Supplementation and Immunosenescence in Older Long-Term Care Residents
Funding Agency: NIH/NIA Paul B. Beeson Career Development Award in Aging Research (K23)
Role: Principal Investigator
Description/Aims: The research goals of this K23 Award are to evaluate the role of vitamin D supplementation in 1) prevention of acute respiratory infection and 2) immune responses to influenza and varicella zoster virus (shingles) vaccine in older long-term care residents.
Funding Period: 9/2011-8/2015
Amount: $736,213
Time Commitment: 75%
Agency Contact: Judy Hannah, 301-496-676, hannahj@nia.nih.gov

Title: Proton Pump Inhibitors for Prevention of Septic Acute Kidney Injury
Funding Agency: NIH/Colorado Clinical and Translational Sciences Institute (CCTSI) Independent Investigator Award
Role: Principal Investigator
Description/Aims: The goals of this study are to better understand the dose and timing of proton pump inhibitor therapy to define the therapeutic window for kidney protection during experimental sepsis and to evaluate the association between early proton pump
inhibitor therapy and acute kidney injury severity in human patients hospitalized for septic shock.  
Funding Period: 4/2014-6/2015  
Amount: $60,000  
Time Commitment: 5%  
Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu

Title: *Reevaluation of Systemic Early neuromuscular blockade (ROSE)*  
Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network  
Role: Co-Site PI/Co-Investigator  
Description/Aims: The goal of this phase III trial is to determine the efficacy and safety of neuromuscular blockade in reducing mortality of emergency department and intensive care unit patients with moderate-severe acute respiratory distress syndrome.  
Funding Period: 11/2015-6/2018  
Amount: $291,050  
Time Commitment: 1%  
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)*  
Funding Agency: NHLBI/Massachusetts General Hospital Prevention and Early Treatment of Acute Lung Injury Network  
Role: Principal Investigator  
Description/Aims: The goal of this phase III trial is to determine if early administration of vitamin D reduces 90-day mortality in critically ill, vitamin D deficient patients at high-risk for developing acute respiratory distress syndrome (ARDS). I will lead the conduct of a 3,000 patient, 48-institution randomized controlled trial.  
Funding Period: 5/2016-1/2019  
Amount: $13,218,470  
Time Commitment: 10%  
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Targeting Steroid Resistance During Acute Exacerbations of COPD with Respiratory Failure – The AECOPD Resistance Study*  
Funding Agency: NIH/Colorado Clinical and Translational Sciences Institute (CCTSI) Team Science Award (PI: Vandivier)  
Role: Co-Investigator  
Description/Aims: The goals of this study is to determine the mechanisms and clinical implications of steroid resistance in emergency department patients during acute exacerbation of chronic obstructive pulmonary disease with respiratory failure who require mechanical ventilation and ICU admission.  
Funding Period: 7/2016-6/2018  
Amount: $100,000  
Time Commitment: 1%  
Agency Contact: Tim Lockie, 720-848-6660, tim.lockie@cuanschutz.edu
Title: Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat-Injured Special Operations Forces
Funding Agency: Department of Defense/U.S. Special Operations Command
Role: PD/PI
Description/Aims: The goal of this application is to determine the feasibility, safety, and potential effectiveness of targeted normoxia as a strategy to conserve oxygen and improve clinical outcomes in critically ill trauma patients.
Award Number: W81XWH-17-C-0241
Funding Period: 09/29/17-01/28/20
Amount: $274,272
Time Commitment: 10%
Agency Contact: Douglas Simpson, douglas.simpson@so.com.mil

Title: Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS)
Funding Agency: Johns Hopkins University - The Marcus Foundation, Inc
Role: SubAward PI
Description/Aims: The goal of this study is to test the efficacy of vitamin C, thiamine, and steroids in reducing in-hospital mortality in critically ill patients with sepsis.
Award Number: #2393 (Rothman)
Funding Period: 10/01/18-12/31/19
Amount: $219,394
Time Commitment: 2%
Agency Contact: Amanda Bistran-Hall, 410-361-7999, abistra1@jhmi.edu

CURRENT SUPPORT

Title: Colorado PETAL Clinical Center
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI) (Moss / Ginde)
Role: PD/PI
Description/Aims: The goal of this application is to participate in the selection and conduct of clinical trials for the prevention and early treatment of acute lung injury across a network of 12 clinical centers. Our clinical center includes two academic and four community hospitals in the greater Denver area and a robust infrastructure for recruitment of critically ill emergency department and intensive care unit patients into clinical trials.
Award Number: 1U01HL123010
Funding Period: 06/17/14-04/30/21
Amount: $373,520
Time Commitment: 12.5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: Prevention and Early Treatment of Acute Lung Injury (PETAL) Network: “Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator
Description/Aims: The goal of this phase III trial is to determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) or a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.
Award Number: U01HL123009 (Shapiro/Douglas)
Funding Period: 06/17/2014-04/30/21
Amount: $293,207
Time Commitment: 2.5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3)
Funding Agency: National Institute of Neurological Diseases and Stroke (NINDS)
Role: Co-Investigator
Description/Aims: The goal of this study to determine if there is evidence of clinical efficacy of a treatment protocol based on brain tissue oxygenation (PbtO2) monitoring compared to treatment based on intracranial pressure (ICP) monitoring alone.
Award Number: U01NS099046 (Barsan)
Funding Period: 07/01/18-06/30/23
Amount: $8,525,394
Time Commitment: 1%
Agency Contact: Maria Mendoza-Puccini, 301-496-9135, maria.mendoza.puccini@nih.gov

Title: EMS-TruShoC’ – A Prospective Trial of Low-Dose, High-Frequency, On-Site Training to Improve Trauma Field Care in Austere Settings
Funding Agency: Defense Health Agency (J9, Research and Development Directorate); US Department of the Air Force (59th Medical Wing)
Role: Co-Investigator
Description/Aims: The goal of this project is to implement EMS-TruShoC in an austere setting and assess the resultant educational and clinical outcomes. These prehospital trauma resuscitation concepts will inform future efforts to translate into USSOF and conventional military prehospital training and sustaining knowledge.
Award Number: FA8650-18-2-6934 (Mould-Millman/Schauer)
Funding Period: 07/30/18-07/29/20
Amount: $155,000
Time Commitment: 1.75%
Agency Contact: Clifford Johnson, 937-713-9922, Clifford.johnson.4@us.af.mil

Title: Vitamin D to Improve Outcomes by Leveraging Early Treatment: Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET BUD)
Funding Agency: Vanderbilt - National Heart, Lung, and Blood Institute (NHLBI)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this project is to determine the effect of vitamin D repletion on long-term cognitive outcomes in critically ill patients.
Award Number: R56HL141567 (Han)
Funding Period: 09/05/18-08/31/20
Amount: $92,352
Title: *Precision Medicine Approach to Vitamin D3 Administration in Critical Illness*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is using a precision medicine approach to investigate the clinical, genetic, and biochemical factors that determine response to vitamin D3 administration in critical illness.
Award Number: R01HL544166 (Leaf)
Funding Period: 07/01/19-06/30/23
Amount: $18,610
Time Commitment: 5%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Influenza Vaccine Effectiveness for Preventing Laboratory-Confirmed Severe Influenza-Associated Illness in US Adults*
Funding Agency: Centers for Disease Control and Prevention (CDC)
Role: SubAward PI/Co-Investigator
Description/Aims: The goal of this study is to understand the role of influenza infection in critical illness and the effectiveness of influenza vaccines for mitigating influenza-associated morbidity and mortality.
Award Number: 75D30119C05670 (Self)
Funding Period: 07/10/19-07/09/20
Amount: $82,371
Time Commitment: 1%
Agency Contact: Vallerie Redd, 770-488-2845

Title: *The Impact of Fluid Resuscitation on Glycocalyx Degradation in Septic Shock*
Funding Agency: National Heart, Lung, and Blood Institute (NHLBI)
Role: Co-Investigator (PI: Shapiro/Schmidt)
Description/Aims: The goal of this project is to determine the mechanism of intravenous fluid resuscitation in glycocalyx degradation and adverse clinical outcomes in septic shock.
Award Number: R01HL149422 (Shapiro/Schmidt)
Funding Period: 09/01/19-05/31/23
Amount: $11,000
Time Commitment: 1%
Agency Contact: Lora Reineck, 301-435-0222, lora.reineck@nih.gov

Title: *Establishing the Epidemiology and Outcomes of Combat-Relevant Prolonged Trauma Care: A Prospective Multicenter Prehospital Pilot Study in South Africa*
Funding Agency: Department of Defense (USAMCMR)
Role: Co-Investigator
Award Number: BA190054 (Mould Millman)
Description/Aims: The goal of this project is to assess the effect of prolonged durations of prehospital care, and key prehospital interventions, on morbidity and mortality of patients with combat-like injuries.
Funding Period: 09/30/19-09/29/21
Amount: $1,725,977
Time Commitment: 5%
Agency Contact: Jennifer Shankle, 301-619-2193, Jennifer.e.shankle.civ@mail.mil

Title: Multicenter Implementation Trial of Targeted Normoxia Strategy to Define Oxygen Requirements for Combat Casualty Care
Funding Agency: Department of Defense (Joint Warfighter Medical Research Program)
Role: Principal Investigator
Description/Aims: The goal of this study is to determine the feasibility, safety, and effectiveness of the targeted normoxia approach to conserve oxygen and improve clinical outcomes in critically injured patients.
Funding Period: 03/01/2020- 02/28/2023
Amount: $982,969
Time Commitment: 25%
Agency Contact: Sandy Snyder, 301-619-7047, sandy.j.snyder.civ@mail.mil

OVERLAP
None.

- What other organizations were involved as partners?
  - Nothing to report

8. SPECIAL REPORTING REQUIREMENTS
- COLLABORATIVE AWARDS:
Nothing to Report

- **QUAD CHARTS:**
  Attached

9. **APPENDICES:**
- CoERCCC presentation 2018
- SOMSA Delphi Consensus presentation 2019
- CDID presentation 2019
- Systematic review manuscript
- Delphi consensus abstract
- AIM 2 Observational abstract
- Oxygen standardization coordinating group
- Delphi consensus poster MHSRS 2019
- Observational AIM 2 data presentation MHSRS 2019
- Col Davis, MD site visit presentation
- AIM 3 pilot trial abstract
- CoERCCC presentation 2019
Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces

W81XWH–17–C–0241

PIs: Adit A. Ginde, MD, MPH; MAJ Steven Schauer, DO, MS
My Background

- Professor, University of Colorado
- Vice Chair for Research, Emergency Medicine & Anesthesiology
- Practicing emergency medicine physician
- Multicenter clinical trials in critical care
- NIH PETAL Network
Significance

- Supplemental oxygen key to avoid morbidity from hypoxia

- Excessive oxygen in EnRoute Care
  - Common practice
  - Unlikely to benefit; may cause harm
  - Expands mission size, weight, and logistics

- **Gap**: Limited data on optimal oxygen titration targets in critically injured patients
“Oxygenated inspired air is best provided via a tight fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”

“The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation… a pulse oximeter reading greater than 90%.”

**Combat Casualty Care**
*Lessons Learned from OEF and OIF*

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Edited by
Eric Savitsky, MD
Colonel Brian Eastridge, MD
Hyperoxia Physiology

- μ-vascular PO₂ ↑ → peri-capillary O₂-diffusion ↑
  - Hb-SO₂ ↑ → DO₂ ↑
  - Inhibition of HPV / resorption atelectasis → right-to-left shunt ↑ → pulmonary gas exchange ↓
  - NO ↓ → SVR ↑ → MAP ↑
  - Inflammation ↓ ↔ HIF-1α ↓
  - ROS ↑ → host defense ↑
  - Mitochondrial O₂ consumption ↓ / carbohydrate oxidation ↑ → efficiency of mitochondrial respiration ↑
  - Mitochondrial O₂ consumption ↓ → ATP synthesis ↓
  - Inflammation ↑ ↔ NF-κB ↑
  - ROS ↑ → NO ↓ → oxidative / nitrosative stress ↑
  - ROS ↑ ↔ Uncoupling of mitochondrial respiration

- NO ↓ → μ-vascular perfusion ↓
## Rationale for Normoxia

<table>
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<tr>
<th>Hypoxia</th>
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<tr>
<td>- Anaerobic metabolism</td>
<td>• Vasoconstriction</td>
</tr>
<tr>
<td>- Cell death (necrosis)</td>
<td>• Oxidative stress</td>
</tr>
<tr>
<td>- Brain = 20% O2 consumption</td>
<td>• Pro-inflammatory</td>
</tr>
<tr>
<td></td>
<td>• Decreased mucociliary clearance in lung</td>
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Oxygen as a drug

![Diagram showing the relationship between oxygen dose and adverse response, with regions for Hypoxia, Normoxia, and Hyperoxia. The diagram highlights the threshold for adverse response and the region of homeostasis.]
Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Derek K Chu*, ‡, Lisa H-Y Kim*, ‡, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani
Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Interpretation: In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO2 range of 94-96%
Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Lancet 2018; 391: 1693-705

Derek K Chu*†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani

Interpretation In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94–96%. These results support the conservative administration of oxygen therapy.

But... no trauma
Critical Care Trials (non-trauma)

Panwar et al. AJRCCM 2016 (n=104)

Liberal Oxygen

Targeted Normoxia

p < 0.001

Girardis et al. JAMA 2016 (n=476)

Targeted Normoxia

Liberal Oxygen

Log-rank P = .02
Question

How do we advance definitive evidence for safe and effective oxygen targets in CCC/ERC?
Specific Aims—SOCOM

1. Define current standard care for oxygen titration in critically ill trauma patients
   ◦ Systematic review of existing relevant evidence
   ◦ SMEs to define consensus–based definitions

2. Compare effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
   ◦ Retrospective cohort study to define the association between oxygenation and clinical outcomes

3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients
   ◦ Demonstrate safe and feasible implementation
   ◦ Prepare for large, multicenter trial
Systematic Review

- Included (n=43)
  - 17 trauma studies
  - 26 non-trauma critical illness

- Conclusions
  - Overall association between lower oxygen/normoxia and improved clinical outcomes
  - Few trauma specific articles
    - 14 out of 17 related exclusively to TBI
    - No high quality/RCT data
  - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI
## Expert Panel (Military, n=13)

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<th>Speciality</th>
<th>Institution</th>
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<td>Becker</td>
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## Expert Panel (Civilian, n=18)

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Initial Rationale

1) Aim for “normoxia”
   - Aim for maintaining “normal” oxygen levels
   - The goal is to prevent hypoxia, not to achieve hyperoxia
   - Data do not support hyperoxia as the target, may be worse
   - Hypoxic episodes associated with worse outcomes, may need cushion to prevent hypoxia
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3) **Special considerations**
   - Consistency in recommendation valued over a subgroup-specific
   - Baseline lung function of combat injured is expected to be good
   - Oxygen levels can be lower in resource limited setting (PFC/ERC)
SpO2 low threshold

Low SpO2 Threshold

- 88%: 38.5% Strongly Agree, 26.9% Agree, 23.1% Disagree, 11.5% Strongly Disagree
- 90%: 25.9% Strongly Agree, 66.7% Agree, 7.4% Disagree
- 92%: 22.2% Strongly Agree, 40.7% Agree, 33.3% Disagree
- 94%: 21.4% Strongly Agree, 42.9% Agree, 35.7% Disagree
SpO2 high threshold

Percentage of Agreement/Disagreement

High SpO2 Threshold

- Strongly Agree
- Agree
- Disagree
- Strongly Disagree
PaO2 high threshold

Percentage of Agreement/Disagreement

High PaO2 Threshold

- **80**: 12.0% Strongly Agree, 64.0% Agree, 16.0% Disagree, 8.0% Strongly Disagree
- **90**: 3.8% Strongly Agree, 50.0% Agree, 30.8% Disagree, 15.4% Strongly Disagree
- **100**: 4.0% Strongly Agree, 52.0% Agree, 24.0% Disagree, 12.0% Strongly Disagree
- **120**: 20.0% Strongly Agree, 60.0% Agree, 12.0% Disagree, 28.0% Strongly Disagree
- **200**: 18.2% Strongly Agree, 27.3% Agree, 31.8% Disagree, 22.7% Strongly Disagree
- **300**: 23.1% Strongly Agree, 26.9% Agree, 19.2% Disagree, 30.8% Strongly Disagree
Lowest FiO2 to Maintain Oxygenation

FiO2 Values
- 21%: 65.5%
- 30%: 13.8%
- 40%: 10.3%
- 50%: 6.9%

Percentage of First/Second Choice
- First Choice
- Second Choice
Final Vote

The chart shows the percentage of agreement with oxygenation thresholds for different conditions. The thresholds and their corresponding percentages are as follows:

- Lower SpO2 Threshold: 90%, Upper SpO2 Threshold: 96%, Percentage: 89%
- Lower PaO2 Threshold: 60 mmHg, Upper PaO2 Threshold: 100 mmHg, Percentage: 89%
- Lowest FiO2: 21%, Percentage: 100%
Special considerations

- Severe TBI: 33%
- Hemorrhagic shock: 11%
- Lowest SpO₂ in resource limited settings:
  - 85–86%: 27% of respondents
  - 87–88%: 58% of respondents
  - 89–90%: 15% respondents
- No signal to change recommendation for:
  - major burn, mechanical ventilation, thoracic trauma
### Observational study

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<td>Hospital LOS (days); median (IQR)</td>
<td>6 (3–11)</td>
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<tr>
<td>In–Hospital Mortality</td>
<td>252 (8%)</td>
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Summary of Oxygen Exposure

Percentage of Time Spent by Oxygen Status as measured by SpO2

- Room Air
- ≤4L/min
- >4L/min

Oxygen Volume (L/min)

Non-MV

- Hypoxia (0-87)
- Mild Hypoxia (88-89)
- Normoxia (90-96)
- Hyperoxia (97-100)
Summary of Oxygen Exposure

Percentage of Time Spent by Oxygen Status as measured by SpO2

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<th>MV</th>
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<tr>
<td>≥21% - ≤30%</td>
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<td>&gt;30% - ≤40%</td>
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<td></td>
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<tr>
<td>&gt;40% - ≤50%</td>
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<td>&gt;50% - ≤60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60% - ≤100%</td>
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Oxygen Volume (L/min)

- Room Air
- ≤4L/min
- >4L/min

FiO2 (%)

- Hypoxia (0-87)
- Mild Hypoxia (88-89)
- Normoxia (90-96)
- Hyperoxia (97-100)
Initial Analysis

- Linear discriminant analysis with compositional data
- Models longitudinal oxygen exposure during first 7 days with outcome (mortality)

Proportion of time spent in oxygen category

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<th>Hyperoxia</th>
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<tr>
<td>Lived</td>
<td>4.0%</td>
<td>53.4%</td>
<td>42.6%</td>
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<td>Died</td>
<td>6.2%</td>
<td>24.5%</td>
<td>69.3%</td>
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Intervention—Pilot Testing

- Finalized standard care definitions for oxygen

- Submitted IRB applications
  - Colorado IRB review—approved (waiver of consent)
  - DoD/HRPO second level review—under review

- Optimize
  - Data collection strategy
  - Stakeholder engagement
  - Electronic clinical decision support

- Demonstrate feasibility and safety
Multicenter Normoxia Trial

- **Goal**: definitive, trauma/CCC–specific evidence to inform CPG and oxygen requirements
  - Particularly important for ERC/PFC

- **Design**: cluster randomized, stepped wedge implementation trial

- **Human subjects issues**: minimal risk, waiver of informed consent (efficient, cost savings)
Multicenter Normoxia Trial

- **Aim 1**: Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients

- **Aim 2**: Assess the safety of targeted normoxia implementation, as measured by number and duration of hypoxia and hyperoxia episodes

- **Aim 3**: Determine the clinical effectiveness of a targeted normoxia strategy compared to conventional oxygenation
Proposed Sites
Each site implements intervention in a staggered fashion with order randomized.
Other activities

- CDID—Oxygen working group
  - Oxygen requirements can drive the mission
  - Focus on ERC
  - Knowledge product is critical
  - Broad implementation requires definitive evidence

- COROLLA trial
  - NIH PETAL network
  - Testing SpO2 88–92%, 92–96%, >96%
  - Medical critical illness
Technology/Solutions

- Portable oxygen concentrators
  - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control
Contact

Adit A. Ginde, MD, MPH
adit.ginde@ucdenver.edu
Phone: 720–848–6777
Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces

Pls: Adit A. Ginde, MD, MPH; MAJ Steven Schauer, DO, MS

W81XWH-17-C-0241
My Background

- Professor, University of Colorado
- Vice Chair for Research, Emergency Medicine & Anesthesiology
- Practicing emergency medicine physician
- Multicenter clinical trials in critical care
- NIH PETAL Network
Significance

- Supplemental oxygen key to avoid morbidity from hypoxia

- Excessive oxygen in EnRoute Care
  - Common practice
  - Unlikely to benefit; may cause harm
  - Expands mission size, weight, and logistics

- **Gap:** Limited data on optimal oxygen titration targets in critically injured patients
“Oxygenated inspired air is best provided via a tight fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”

“The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation… a pulse oximeter reading greater than 90%.”
Hyperoxia Physiology

**Muscular PO_2**↑ → peri-capillary O_2-diffusion ↑

NO ↓ → SVR ↑ → MAP ↑

Inflammation ↓ ↔ HIF-1α ↓

ROS ↑ → host defense ↑

Mitochondrial O_2 consumption ↓ / carbohydrate oxidation ↑ → efficiency of mitochondrial respiration ↑

Hb-SO_2 ↑ → DO_2 ↑

Inhibition of HPV / resorption atelectasis → right-to-left shunt ↑ → pulmonary gas exchange ↓

NO ↓ → μ-vascular perfusion ↓

Inflammation ↑ ↔ NF-κB ↑

ROS ↑ → NO ↓ → oxidative / nitrosative stress ↑

ROS ↑ ↔ Uncoupling of mitochondrial respiration

Mitochondrial O_2 consumption ↓ → ATP synthesis ↓
# Rationale for Normoxia

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<th>Hyperoxia</th>
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<tbody>
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<td>Anaerobic metabolism</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Cell death (necrosis)</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Brain = 20% O2 consumption</td>
<td>Pro-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Decreased mucociliary clearance in lung</td>
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</table>
Oxygen as a drug

![Graph showing oxygen levels and adverse responses](image)

- **Death**
- **Hypoxia**
- **Normoxia**
- **Hyperoxia**

**Adverse Response** vs **Dose**

**Region of Homeostasis**

**Threshold for adverse response**
Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Lancet 2018; 391: 1693-705

Derek K Chu*,†, Lisa H-Y Kim*,†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani
Interpretation: In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO2 range of 94-96%
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**Interpretation** In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94–96%. These results support the conservative administration of oxygen therapy.

But...no trauma

- MI, 7
- Ischemic stroke, 6
- Surgical (non-trauma/non-critical), 3
- Critical illness (medical), 2
- Sepsis, 1
Critical Care Trials (non–trauma)

Panwar et al. AJRCCM 2016 (n=104)

Girardis et al. JAMA 2016 (n=476)
Question

How do we advance definitive evidence for safe and effective oxygen targets in CCC/ERC?
Specific Aims—SOCOM

1. Define current standard care for oxygen titration in critically ill trauma patients
   ◦ Systematic review of existing relevant evidence
   ◦ SMEs to define consensus–based definitions

2. Compare effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
   ◦ Retrospective cohort study to define the association between oxygenation and clinical outcomes

3. Develop and pilot test a targeted normoxia intervention in critically ill trauma patients
   ◦ Demonstrate safe and feasible implementation
   ◦ Prepare for large, multicenter trial
Systematic Review

- Included (n=43)
  - 17 trauma studies
  - 26 non-trauma critical illness

- Conclusions
  - Overall association between lower oxygen/normoxia and improved clinical outcomes
  - Few trauma specific articles
    - 14 out of 17 related exclusively to TBI
    - No high quality/RCT data
  - Supports need for further trauma-specific studies/RCTs, particularly beyond TBI
### Expert Panel (Military, n=13)

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Speciality</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Becker</td>
<td>Tyson</td>
<td>Trauma Surgery</td>
<td>SAMMC</td>
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<td>Chung</td>
<td>Kevin</td>
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<td>Keenan</td>
<td>Sean</td>
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<td>SOCOM/SOCEUR</td>
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<td>Mason</td>
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<td>Miles</td>
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<td>Benjamin</td>
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<tr>
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   - Baseline lung function of combat injured is expected to be good
   - Oxygen levels can be lower in resource limited setting (PFC/ERC)
SpO2 high threshold

Percentage of Agreement/Disagreement

- 94%
  - Strongly Agree: 7.8%
  - Agree: 29.6%
  - Disagree: 22.2%
  - Strongly Disagree: 48.2%

- 96%
  - Strongly Agree: 14.8%
  - Agree: 55.6%
  - Disagree: 22.2%
  - Strongly Disagree: 9.4%

- 98%
  - Strongly Agree: 11.5%
  - Agree: 46.2%
  - Disagree: 26.9%
  - Strongly Disagree: 15.4%

- 100%
  - Strongly Agree: 21.4%
  - Agree: 35.7%
  - Disagree: 17.9%
  - Strongly Disagree: 25.0%
PaO2 low threshold

- 60: 50.0% Strongly Agree, 38.5% Agree, 11.5% Disagree, 4.0% Strongly Disagree
- 70: 20.0% Strongly Agree, 64.0% Agree, 16.0% Disagree, 4.0% Strongly Disagree
- 80: 15.4% Strongly Agree, 53.8% Agree, 15.4% Disagree, 4.0% Strongly Disagree
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PaO2 high threshold

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- **Strongly Agree**
- **Agree**
- **Disagree**
- **Strongly Disagree**
Lowest FiO2 to Maintain Oxygenation

- 21% of first/second choice
- 69.0% of first/second choice
- 10.3% of first/second choice
- 6.9% of first/second choice

FiO2 Values:
- 21%
- 30%
- 40%
- 50%

First Choice vs. Second Choice
Final Vote

- Lower SpO2 Threshold: 90%
- Upper SpO2 Threshold: 96%
- Lower PaO2 Threshold: 60 mmHg
- Upper PaO2 Threshold: 100 mmHg
- Lowest FiO2: 21%

Percentage of Agreement with Oxygenation Thresholds:

- 89%
- 89%
- 96%
- 89%
- 100%
Special considerations

- Severe TBI: 33%
- Hemorrhagic shock: 11%
- Lowest SpO2 in resource limited settings
  - 85–86%: 27% of respondents
  - 87–88%: 58% of respondents
  - 89–90%: 15% respondents

- No signal to change recommendation for:
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<td>Hospital LOS (days); median (IQR)</td>
<td>6 (3–11)</td>
</tr>
<tr>
<td>In–Hospital Mortality</td>
<td>252 (8%)</td>
</tr>
</tbody>
</table>
Summary of Oxygen Exposure

Percentage of Time Spent by Oxygen Status as measured by SpO2

<table>
<thead>
<tr>
<th></th>
<th>Room Air</th>
<th>≤4L/min</th>
<th>&gt;4L/min</th>
</tr>
</thead>
</table>

Oxygen Volume (L/min)

Non-MV

- Hypoxia (0-87)
- Mild Hypoxia (88-89)
- Normoxia (90-96)
- Hyperoxia (97-100)
Summary of Oxygen Exposure

Percentage of Time Spent by Oxygen Status as measured by SpO2

<table>
<thead>
<tr>
<th>Room Air</th>
<th>≤4L/min</th>
<th>&gt;4L/min</th>
</tr>
</thead>
</table>

Oxygen Volume (L/min)

Non-MV

FiO2 (%)

<table>
<thead>
<tr>
<th>≥21% - ≤30%</th>
<th>&gt;30% - ≤40%</th>
<th>&gt;40% - ≤50%</th>
<th>&gt;50% - ≤60%</th>
<th>&gt;60% - ≤100%</th>
</tr>
</thead>
</table>

MV

Hypoxia (0-87)

Mild Hypoxia (88-89)

Normoxia (90-96)

Hyperoxia (97-100)
Initial Analysis

- Linear discriminant analysis with compositional data
- Models longitudinal oxygen exposure during first 7 days with outcome (mortality)

Proportion of time spent in oxygen category

<table>
<thead>
<tr>
<th></th>
<th>Hypoxia</th>
<th>Normoxia</th>
<th>Hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lived</td>
<td>4.0%</td>
<td>53.4%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Died</td>
<td>6.2%</td>
<td>24.5%</td>
<td>69.3%</td>
</tr>
</tbody>
</table>
Intervention—Pilot Testing

- Finalized standard care definitions for oxygen

- Submitted IRB applications
  - Colorado IRB review—approved (waiver of consent)
  - DoD/HRPO second level review—under review

- Optimize
  - Data collection strategy
  - Stakeholder engagement
  - Electronic clinical decision support

- Demonstrate feasibility and safety
**Multicenter Normoxia Trial**

- **Goal**: definitive, trauma/CCC–specific evidence to inform CPG and oxygen requirements
  - Particularly important for ERC/PFC

- **Design**: cluster randomized, stepped wedge implementation trial

- **Human subjects issues**: minimal risk, waiver of informed consent (efficient, cost savings)
Multicenter Normoxia Trial

- **Aim 1**: Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients

- **Aim 2**: Assess the safety of targeted normoxia implementation, as measured by number and duration of hypoxia and hyperoxia episodes

- **Aim 3**: Determine the clinical effectiveness of a targeted normoxia strategy compared to conventional oxygenation
Proposed Sites
Stepped wedge design

- Each site implements intervention in a staggered fashion with order randomized

<table>
<thead>
<tr>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-trial</td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Control Condition
Experimental Condition

Time
Other activities

- CDID—Oxygen working group
  - Oxygen requirements can drive the mission
  - Focus on ERC
  - Knowledge product is critical
  - Broad implementation requires definitive evidence

- COROLLA trial
  - NIH PETAL network
  - Testing SpO2 88–92%, 92–96%, >96%
  - Medical critical illness
Technology/Solutions

- Portable oxygen concentrators
  - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control
Contact

Adit A. Ginde, MD, MPH
adit.ginde@ucdenver.edu
Phone: 720–848–6777
A Consensus-Based Recommendation for Oxygenation Targets in Critically Injured Patients

Steven Schauer, DO, MS
MAJ USA MC
09 May 2019
None.

All grant funding comes from various Department of Defense Agencies.

I do not accept any commercial funding.
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 Air Force, the Department of the Army, or the Department of Defense.
Acknowledgements

Co-Investigators at the University of Colorado – Denver
  Adit Ginde, MD, MPH
  Vikhyat Bebarta, MD
  Erin Anderson, RN
  Jacqueline Jones, PhD

Funding – Special Operations Command (BAA - SO160106)

Thanks to all our expert participants! (some in audience now)
Methods

Ethics
» Submitted proposal to University of Colorado IRB → exempt survey determination

Survey
» Surveys on REDCap (Research Electronic Data Capture)
» Multi-stage Delphi consensus process
» Invited selected experts both military and civilian with experience in operational medicine, critical care, trauma, emergency medicine, and prehospital medicine to participate

Performed systematic review of available literature → provided to the expert participants
### Expert Participants

<table>
<thead>
<tr>
<th>LTC Tyson Becker</th>
<th>Jason Haukoos</th>
<th>LTC Ethan Miles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jason Brainard</td>
<td>David Huang</td>
<td>Ernest Moore</td>
</tr>
<tr>
<td>COL Kevin Chung</td>
<td>Juan-Pablo Idrovo</td>
<td>Craig Newgard</td>
</tr>
<tr>
<td>Mitchell Cohen</td>
<td>COL Sean Keenan</td>
<td>LTC Timothy Nunez</td>
</tr>
<tr>
<td>Brian Cotton</td>
<td>Akram Khan</td>
<td>COL (ret) John Oh</td>
</tr>
<tr>
<td>Pratik Doshi</td>
<td>LtCol Philip Mason</td>
<td>LTC Ted Redmon</td>
</tr>
<tr>
<td>Franklin Guyette</td>
<td>Robert McIntyre</td>
<td>LTC Jamie Reisburg</td>
</tr>
<tr>
<td>Todd Rice</td>
<td>LtCol Stephen Rush</td>
<td>Martin Schreiber</td>
</tr>
<tr>
<td>Wesley Self</td>
<td>Jason Sperry</td>
<td>CDR Joshua Tobin</td>
</tr>
<tr>
<td>CDR Benjamin Walrath</td>
<td>Henry Wang</td>
<td>LTC Ramey Wilson</td>
</tr>
<tr>
<td>Franklin Wright</td>
<td></td>
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</tr>
</tbody>
</table>
Results

Of the 31 invited experts, 26 completed the first round, 28 completed the second round, 27 completed the final round; all participated in at least one round.

» Round 1 → narrowed the potential SpO2 range to 88-100% and PaO2 to 60-300mmHg
  » Only 20% noted changes based on presence of TBI or hemorrhagic shock

» Round 2 → narrowed to 90-96% and 60-100mmHg targets
  » Lowest acceptable FiO2 21% (ambient air)

» Round 3 → 89% accepted the limits at 90-96% and upper limit of 100mmHg, 96% accepted lower at 60mmHg
  » All accepted lowest FiO2 at 21%
  » 33% recommended higher oxygenation for TBI and 11% for hemorrhagic shock
  » Resource limited setting most recommended lower target of 88%
A. Agreement with Lower SpO2 Thresholds in Delphi Stage 2

Percentage of Agreement/Disagreement

Low SpO2 Ranges

- 88%: 11% Strongly Agree, 22% Agree, 26% Disagree, 41% Strongly Disagree
- 90%: 7% Strongly Agree, 67% Agree, 26% Disagree, 41% Strongly Disagree
- 92%: 4% Strongly Agree, 41% Agree, 22% Disagree, 21% Strongly Disagree
- 94%: 36% Strongly Agree, 43% Agree, 21% Disagree, 21% Strongly Disagree
B. Agreement with Higher SpO2 Thresholds in Delphi Stage 2

% Agreement/Disagreement

<table>
<thead>
<tr>
<th>SpO2 Range</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>94%</td>
<td>30%</td>
<td>22%</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>96%</td>
<td>56%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td>44%</td>
<td>26%</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td>100%</td>
<td>18%</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High SpO2 Range

Legend:
- **Strongly Agree**
- **Agree**
- **Disagree**
- **Strongly Disagree**
Agreement with Lowest Acceptable FiO2 in Delphi Stage 2

- **FiO2 Values**
  - 21: 66%
  - 30: 69%
  - 40: 10%
  - 50: 7%

- **Percentage of First Choice/Second Choice**
  - 21: 3%
  - 30: 14%
  - 40: 10%
  - 50: 7%
Figure 6: Delphi Percentage of Agreement with Oxygenation Thresholds

- Lower SpO2 Threshold: 90%
- Upper SpO2 Threshold: 96%
- Lower PaO2 Threshold: 60 mmHg
- Upper PaO2 Threshold: 100 mmHg
- Lowest FiO2: 21%

Percentage of Agreement with Oxygenation Thresholds:
- 89%
- 89%
- 96%
- 89%
- 100%
Conclusions

Consensus-based standard for oxygenation targets in critically injured patients

SpO2 90-96% (88-96% with resource-limitations)
PaO2 60-100 mmHg
Lowest acceptable FiO2 21%
Adjustments for TBI, burns, major hemorrhage, etc. likely not needed

Expert consensus → prospective, clinical validation needed
Questions?
Comments?
Feedback?

Steven Schauer
US Army Institute of Surgical Research
59th Medical Wing
Steven.g.Schauer.mil@mail.mil
210-771-0706
Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN, Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH, Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, Aurora, Colorado

BACKGROUND: Oxygen therapy is frequently administered to critically ill trauma patients to avoid hypoxia, but optimal oxygenation strategies are not clear. We conducted a systematic review of oxygen targets and clinical outcomes in trauma and critically ill patients. We searched Ovid MEDLINE, Cochrane Library, Embase, and Web of Science Core Collection from 1946 through 2017. Our initial search yielded 14,774 articles with 209 remaining after abstract review. We reviewed full text articles of human subjects with conditions of interest, an oxygen exposure or measurement, and clinical outcomes, narrowing the review to 43 articles. We assessed article quality using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria.

RESULTS: Of the 43 final studies meeting inclusions criteria, 17 focused on trauma and 26 studies focused on medical and/or surgical critical illness without trauma specifically. Four trauma studies supported lower oxygenation/normoxia, two supported higher oxygenation, and 11 supported neither normoxia nor higher oxygenation (five neutral and six supported avoidance of hypoxia). Fifteen critical illness studies supported lower oxygenation/normoxia, one supported higher oxygenation, and 10 supported neither normoxia nor higher oxygenation (nine neutral and one supported avoidance of hypoxia). We identified seven randomized controlled trials (four high quality, three moderate quality). Of the high-quality randomized controlled trials (none trauma-related), one supported lower oxygenation/normoxia and three were neutral. Of the moderate-quality randomized controlled trials (one trauma-related), one supported higher oxygenation, one was neutral, and one supported avoidance of hypoxia.

CONCLUSION: We identified few trauma-specific studies beyond traumatic brain injury; none were high quality. Extrapolating primarily from nontrauma critical illness, reduced oxygen administration targeting normoxia in critically ill trauma patients may result in better or equivalent clinical outcomes. Additional trauma-specific trials are needed to determine the optimal oxygen strategy in critically injured patients. (J Trauma Acute Care Surg. 2019;00: 00-00. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review, Level IV.

KEY WORDS: Oxygenation, hyperoxia, trauma, critical care.

Oxygen is frequently administered to critically injured patients to prevent hypoxia and enhance oxygen delivery. Excessive oxygen supplementation often occurs in clinical practice leading to hyperoxia. While the detrimental effects of hyperoxia in trauma patients are well described, hyperoxia may also have adverse effects. Limited evidence in critically ill patients indicates that even modest amounts of hyperoxia may be harmful. Several studies demonstrate an increase in morbidity and mortality among patients receiving supraphysiologic levels of oxygen. However, most studies focus exclusively on medical patients, as reflected by prior systematic reviews on this topic. Data are sparse in critically ill trauma patients, and no systematic reviews focused on this population have been published. There is also significant heterogeneity in the definition of hyperoxia with arterial partial pressures of oxygen ranging from 100 mm Hg to 300 mm Hg. Recent studies have identified safe upper limits of oxygen saturation (SpO2) at 96% and partial pressure of oxygen (PaO2) at 150 mm Hg in critically ill patients without trauma. It remains unclear how to apply these findings to critically ill trauma patients.

Beyond patient morbidity, the avoidance of hyperoxia may also improve resource utilization. Both forward combat areas and en route care rely on a limited supply of oxygen and other supplies. The extent to which hyperoxia is not beneficial or even harmful would decrease the logistic burden of oxygen procurement in forward military operations and other austere settings.

Defining optimal oxygenation targets are highly relevant to reduce morbidity associated with both hyperoxia and hypoxia. In resource-limited settings this carries further benefit. While some evidence exists to support the avoidance of hyperoxia in other patient populations, understanding of the evidence relevant to critically ill trauma patients is lacking. Therefore, we conducted a systematic review of clinical trials and epidemiological studies of oxygen targets and clinical outcomes in trauma and critically ill patients.
METHODS

We conducted a systematic review using the Cochrane Collaboration approach. We prepared the protocol and review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines.14

Study Eligibility Criteria

Population
We conducted a systematic review of the optimal oxygen target ranges relevant to critically ill trauma patients. We included studies evaluating adult human patients from both civilian and military populations.

Search Strategy and Data Sources
A medical librarian (K.S.) conducted a comprehensive literature search from 1946 to 2017. Our search focused on trauma (i.e., acute bodily injury) and critical illness (i.e., requiring intensive care unit [ICU] level of care). We identified relevant publications by searching Ovid MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Versions, 1946 to present), Cochrane Library (via Wiley, including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, and NHS Economic Evaluation Database, 1992 to present), Embase (via Elsevier, Embase.com, 1947 to present), and Web of Science Core Collection (via Thomson Reuters, including Science Citation Index Expanded 1974 to present, and Social Sciences Citation Index 1974 to present). We excluded animal studies, conference abstracts, conference papers, and conference reviews. We included randomized controlled trials, prospective interventional, and observational (prospective and retrospective) studies. Other systematic reviews, meta-analyses, or narrative reviews were not included. See Supplemental Digital Content, Appendix, http://links.lww.com/TA/B430 for database search strategies.

The comprehensive literature search yielded 14,777 non-duplicate articles for title/abstract review (DJD, ELA; Fig. 1). We excluded articles not using human subjects and subjects younger than 18 years. We included patients who had trauma but no critical illness, trauma with critical illness or critical illness without trauma. Two authors (D.J.D., E.L.A.) independently reviewed full text for all articles to identify human research studies with trauma or critical illness and analysis of oxygen exposure/measurement and clinical outcomes (i.e., mortality, length of stay [LOS], or...
acute organ injury). A third author (A.A.G.) reviewed articles when there was not consensus among the primary reviewers. Final determination was made by complete consensus of all three reviewers. The final search yielded 43 articles for inclusion in this systematic review.

**Quality Assessment**

Two authors (D.J.D. and E.L.A.) independently completed risk of bias assessments for each included article using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria to determine the quality of the evidence. Disagreements were settled by a third author (A.A.G.).

**Outcomes**

Our primary outcome was mortality, typically in-hospital, as reported in the primary study. Secondly, we evaluated hospital LOS, ICU LOS, and acute organ injury (including duration of mechanical ventilation and ventilator free days). Acute organ injury varied by study but included Glasgow Coma Scale (GCS) or modified Rankin Scale at discharge as well as new liver, cardiovascular, or renal failure defined as a Sequential Organ Failure Assessment (SOFA) score of 3 or greater for the corresponding organ occurring 48 hours or more after ICU admission.

**Data Synthesis**

Patient and study characteristics were reviewed independently by two authors (D.J.D. and E.L.A.). Disagreements were settled by a third author (A.A.G.). When we identified multiple outcomes of interest, all were included, noting when one of the outcomes was clearly indicated as the primary outcome of that study. Due to the paucity of randomized controlled trials directly comparing levels of oxygen delivery, we did not perform meta-analysis nor other quantitative synthesis of the results.

**RESULTS**

**Study Characteristics**

Of the 43 final studies included in our systematic review, 17 focused on trauma, of which 14 of 17 were exclusively TBI and 11 of 17 studies were critically ill trauma patients (most predominately TBI). The remaining 26 studies focused on medical and surgical critical illness without trauma specifically. All studies were from the civilian setting.

Trauma studies are summarized in Table 1. None were high-quality evidence, eight were moderate-quality evidence, and nine were low-quality evidence studies. The specific definitions of lower oxygenation/normoxia, and higher oxygenation/hyperoxia varied substantially between studies. Four trauma studies supported lower oxygenation/normoxia, two supported higher oxygenation, and 11 supported neither normoxia nor higher oxygenation (five neutral relative to clinical outcomes and six supported avoidance of hypoxia).

The critical illness (nontrauma) studies were comprised of four high-quality evidence, four moderate-quality evidence, and 18 low-quality evidence studies (Table 2). Fifteen critical illness studies supported lower oxygenation/normoxia, one supported higher oxygenation, and 10 supported neither normoxia nor higher oxygenation (nine neutral relative to clinical outcomes and one supported avoidance of hypoxia).

Overall there were seven randomized controlled trials (four high-quality, three moderate-quality). Of the high-quality randomized controlled trials (none trauma-focused), one study supported lower oxygenation/normoxia and three were neutral. Of the moderate-quality randomized controlled trials (one trauma-related), one study supported higher oxygenation, one was neutral, and one supported avoidance of hypoxia. These results are summarized in Figure 2.

**Primary Outcome**

Our primary outcome was mortality which was reported in 13 of the 17 trauma studies and 21 of the 26 critical illness studies, including two of the four critical illness studies, which were high-quality evidence. The majority of these studies reported in-hospital mortality; however, two studies reported 30-day mortality, while two studies reported 6-month mortality (Tables 1 and 2). A statistically significant difference in mortality was noted for the avoidance of hypoxia in TBI patients in three studies while the study by DesPrez et al. was the only trauma study with predominately non-TBI trauma patients, which reported a statistically significant mortality difference in favor of normoxia (Fig. 2).

**Secondary Outcomes**

Hospital LOS was reported in one trauma study and six critical illness studies. Three studies reported longer hospital LOS (at least 1 day) with higher oxygenation and four studies were neutral. Intensive care unit LOS was reported in two trauma studies and seven critical illness studies. Three studies reported higher ventilator free days with normoxia vs. higher oxygenation, and four studies were neutral. Other acute organ injury was reported in nine critical illness studies and three trauma studies. These secondary outcomes include neurologic outcomes such as GCS score or modified Rankin Scale at discharge as well as new liver, cardiovascular or renal failure defined as a SOFA score of 3 or greater for the corresponding organ occurring 48 hours or more after ICU admission. These findings are summarized in Tables 1 and 2.

**DISCUSSION**

Our systematic review demonstrates that no high-quality evidence and only one (moderate quality) randomized controlled trial has been published analyzing optimal oxygen administration in trauma patients and clinical outcomes. Even with a low-quality assessment, few trauma-specific studies were identified beyond traumatic brain injury. We extrapolated some evidence from medical and surgical (nontrauma) critical illness, where there is a growing literature base and some randomized controlled trials. Normoxia for critically ill patients was most commonly defined as SpO2 of 88% to 96% or a PaO2 of 60 mm Hg to 150 mm Hg; however, significant heterogeneity in this definition exists. Notably if a patient was not receiving

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<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design/Participants/Inclusion Criteria</th>
<th>Oxygen Exposure</th>
<th>Outcome Measures</th>
<th>Results*</th>
<th>Conclusions</th>
<th>GRADE Level of Evidence</th>
<th>Support of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>da Costa (2017)</td>
<td>Prospective observational/single center/Brazil n = 200 Mean age: 37 y Population of interest: Trauma: 100% · TBI: 65% (GCS score &lt;9, ISS &gt;16)</td>
<td>Data Collection: 4 time points from scene of trauma to 24 h postadmission -Arterial hemoglobin O2 saturation prior to supplemental oxygen</td>
<td>Primary: 30-d Mortality</td>
<td>No Oxygen vs. Oxygen 30-d Mortality: OR, 0.988 (0.981–0.995)</td>
<td>A 1% increase in arterial hemoglobin O2 saturation was associated with a 1.2% decrease in the odds of mortality in trauma patients</td>
<td>II</td>
<td>Supports Avoidance of Hypoxia</td>
</tr>
<tr>
<td>Taher (2016)</td>
<td>RCT/single center/Iran n = 68 Mean age: 43 y Population of Interest: Trauma: 100% · TBI: 100% · Mechanically ventilated: 100%</td>
<td>Data Collection: During the first 6 h of admission Intervention: -80% FIO2 Control: -50% FIO2</td>
<td>Primary: Glasgow Outcome Scale (GOS)</td>
<td>FIO2 80% vs. FIO2 50% GOS at Discharge: p value 0.723 GOS at 6 mo: p value 0.024</td>
<td>FIO2 of 80% was associated with improved neurological outcome when compared to an FIO2 of 50% in severe TBI patients</td>
<td>II</td>
<td>Supports Higher Oxygenation</td>
</tr>
<tr>
<td>Mascia (2007)</td>
<td>Prospective observational/multicenter/Italy n = 86 Mean age: 45 y Population of Interest: Trauma: 100% · TBI: 100% (GCS score &lt;9) · Mechanically ventilated: 100%</td>
<td>Data Collection: 1st 24 h of admission - Mean PaO2</td>
<td>Primary: Acute Lung Injury</td>
<td>High PaO2/FIO2 vs. Low PaO2/FIO2 Acute Lung Injury: OR, 0.98 (0.98–0.99), p = 0.04</td>
<td>Low PaO2/FIO2 ratios were associated with the development of acute lung injury when compared to higher PaO2/FIO2 ratios in TBI patients</td>
<td>II</td>
<td>Supports Avoidance of Hypoxia</td>
</tr>
<tr>
<td>Chi (2006)</td>
<td>Prospective observational/multicenter/USA N = 150 Mean age: 34 y Population of Interest: Trauma: 100% · TBI: 100% (GCS score ≤ 12, AIS score ≥ 3)</td>
<td>Data Collection: Prehospital Oxygen -SpO2 &lt; 92% (Hypoxic) *occurred at least once -SpO2 ≥ 92% (Not Hypoxic)</td>
<td>Primary: In-Hospital Mortality</td>
<td>Hypoxic vs. Not Hypoxic Mortality: OR, 2.66 (p = 0.04)</td>
<td>Hypoxia in the prehospital setting significantly increases the odds of mortality in severe TBI patients</td>
<td>II</td>
<td>Supports Avoidance of Hypoxia</td>
</tr>
<tr>
<td>Davis (2004)</td>
<td>Prospective observational/multicenter/USA (San Diego) n = 426 Mean age: 35 y Population of Interest: Major trauma = 100% · TBI: 100% (GCS score 2-8) · Mechanically ventilated: 100%</td>
<td>Data Collection: Prehospital -Lowest Preintubation SpO2 -Lowest Postintubation SpO2 *received oxygen for 60 seconds prior to rapid sequence intubation medications</td>
<td>Primary: In-Hospital Mortality</td>
<td>Hyoxia in preintubation and postintubation In-Hospital Mortality: Preintubation: OR, 0.31 (0.06–1.56) Postintubation: OR, 1.39 (0.35–5.55)</td>
<td>Lowest SpO2 before or after paramedic intubation is not associated with an increase in mortality for major trauma patients</td>
<td>II</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author/Year</th>
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<th>GRADE Level of Evidence</th>
<th>Support of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolias (2004)⁹</td>
<td>Prospective observational/multicenter/USA n = 52 Mean age: 34 y Population of Interest: Trauma: 100% · TBI: 100% · Mechanically ventilated: 100%</td>
<td>Data Collection: Starting within 6 h of admission to ICU Intervention: - FIO₂ = 100% for 24 h Control: Historical cohort, matching intervention group - FIO₂ per usual care</td>
<td>Primary: Neurological Outcomes by GOS</td>
<td>FIO₂ 100% vs. Historical FIO₂ Mean GOS 3 mo: p = NS Mean GOS 6 mo: p = NS</td>
<td>Hyperoxia did not change clinical outcomes in severe TBI patients when compared to the historical control group</td>
<td>II Neutral</td>
<td></td>
</tr>
<tr>
<td>Manley (2001)¹⁰</td>
<td>Prospective observational/single center/USA (San Francisco) n = 107 Mean age: 46 y Population of Interest: Trauma: 100% · TBI: 100% (GCS score ≤ 12) · ICU: 60%</td>
<td>Data Collection: In the emergency department - Any Hypoxia Episode (SpO₂ &lt; 92%)</td>
<td>Primary: In-hospital mortality</td>
<td>Hypoxia on in-hospital mortality in TBI patients Mortality: OR, 1.26 (0.56–2.83); p = 0.57</td>
<td>Hypoxia showed no increase in in-hospital mortality in TBI patients</td>
<td>II Neutral</td>
<td></td>
</tr>
<tr>
<td>Gentleman (1992)¹¹</td>
<td>Prospective observational/single center/United Kingdom n = 600 Mean age: 33 y Population of Interest: Trauma: 100% · TBI: 100% (used CT scan to determine)</td>
<td>Data Collection: Prior to ICU admission - PaO₂ &lt; 70 mm Hg (hypoxia)</td>
<td>Primary: 6 mo Mortality</td>
<td>PaO₂ of &lt;70 mm Hg (hypoxia) and Hypotension No Systemic Insult: 43% (199) Hypoxia or Hypotension: 74% (75) Hypoxia and hypotension: 100% (8)</td>
<td>Hypoxia with or without hypotension increased the risk of mortality in TBI patients</td>
<td>II Supports Avoidance of Hypoxia</td>
<td></td>
</tr>
<tr>
<td>Fujita (2017)¹²</td>
<td>Retrospective/multicenter/Japan n = 129 Mean age: not reported Population of Interest: Trauma: 100% · TBI: 100% (GCS score 4–8)</td>
<td>Data Collection: First day of admission - PaO₂ just prior to hypothermia</td>
<td>Survival to hospital discharge (secondary) Discharge GCS score (primary)</td>
<td>PaO₂ (continuous) and Clinical Outcomes Survival: OR, 1.004 (0.983–1.000) p = 0.037 GCS score: OR, 1.452 (1.027–20.53) p = 0.035</td>
<td>Hyperoxemia was associated with improved neurological outcomes and a decrease in mortality in TBI patients</td>
<td>III Supports Higher Oxygenation</td>
<td></td>
</tr>
</tbody>
</table>

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<td>DesPrez (2017)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Retrospective/Multicenter/USA (Vanderbilt) N = 329 Mean age: 51 y Population of Interest: Critically Ill: 100% · Trauma = 52% · Medical = 31% · Mechanically ventilated: 100%</td>
<td>Data Collection: Recorded for each ICU day - Lowest PaO2/FIO2 - Lowest SpO2/FIO2 - Highest MAP - Oxygen saturation index calculated: SpO2 × MAP / 100 FIO2</td>
<td>Primary: In-Hospital Mortality Secondary: Ventilator-free days</td>
<td>Oxygen Saturation Index and Clinical Outcomes Mortality: OR, 1.128 (1.056–1.424); p &lt; 0.008 Ventilator-free days: OR, −0.167 (−0.284 to −0.050); p = 0.005</td>
<td>Increased OSI was associated with higher in hospital mortality and fewer ventilator-free days in critically ill patients</td>
<td>III</td>
<td>Supports Normoxia</td>
</tr>
<tr>
<td>Russell (2017)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Retrospective/single center/USA N = 471 Mean age: 42 y Population of Interest: Trauma: 100% · Mechanically ventilated: 100% · TBI: 56%</td>
<td>Data Collection: - Highest PaO2 in the first 24 h of ICU admission with corresponding FIO2</td>
<td>Primary: in-hospital mortality</td>
<td>Hyperoxia vs. Normoxia Maximum PaO2: OR, 1.27 (0.72–2.25); 0.41 FIO2: OR, 0.94 (0.77–1.15); 0.54</td>
<td>Hyperoxia was not associated with higher in-hospital mortality or worse neurological outcomes in TBI patients when compared to normoxia</td>
<td>III</td>
<td>Neutral</td>
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<tr>
<td>Raj (2013)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Retrospective/multicenter/Finland n = 1,116 Mean age: 54 y Population of Interest: Trauma: 100% · TBI: 100% (GCS score &lt;12)</td>
<td>Data Collection: Based on Highest measured alveolar-arterial O2 gradient or Lowest measured PaO2 value during first 24 h of ICU admission - PaO2: &lt;75 mm Hg (hypoxemia) - PaO2: 75–100 mm Hg (normoxemia) - PaO2: &gt;100 mm Hg (hyperoxemia)</td>
<td>Primary: 6-mo Mortality Secondary: In-Hospital Mortality</td>
<td>Hyperoxemia/Hypoxemia vs. Normoxemia in TBI 6 mo mortality hypoxemia vs. Normoxemia: OR, 0.90 (0.57–1.41); p = 0.65 Hyperoxemia vs. normoxemia: OR, 0.88 (0.63–1.22); p = 0.43 Hyperoxemia vs. hypoxemia: OR, 0.97 (0.63–1.50); p = 0.90 In-hospital mortality hypoxemia vs. normoxemia: 1.01 (0.63–1.62); p = 0.97 Hyperoxemia vs. Normoxemia: 0.94 (0.65–1.36); p = 0.75 Hyperoxemia vs. hypoxemia: 0.93 (0.59–1.47); p = 0.77</td>
<td>Hypoxemia, Normoxemia, and Hyperoxemia had similar 6 mo and in-hospital mortality in critically ill TBI patients</td>
<td>III</td>
<td>Neutral</td>
</tr>
<tr>
<td>Brenner (2012)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Retrospective/Single center/USA (Baltimore) n = 1,547 Mean age: 41 y Population of Interest: Trauma: 100% · TBI: 100% (AIS score ≥11)</td>
<td>Data Collection: 1st 24 h of hospitalization - PaO2: &lt;100 mm Hg - PaO2: 100–200 mm Hg - PaO2: &gt;200 mm Hg *ABGs were taken at four different time points and averaged to be placed within the three categories stated above</td>
<td>Primary: In-Hospital Mortality</td>
<td>PaO2 Comparisons in TBI PaO2 &lt; 100 vs. 100–200 mm Hg: OR, 2.20 (1.33–3.63) PaO2 &gt; 200 vs. 100–200 mm Hg: OR, 1.50 (1.15–1.97) PaO2 &gt; 0.59 &gt; 200 vs. 100 mm Hg: OR, 0.59 (0.35–1.00)</td>
<td>Higher and lower PaO2 levels within 24 h of admission were associated with an increase in mortality and worse functional outcomes in severe TBI patients</td>
<td>III</td>
<td>Supports Normoxia</td>
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<td>Davis (2009)</td>
<td>Retrospective/multicenter/USA (San Diego) n = 3,420 Mean age: 39 y Population of Interest: Trauma patients: 100% TBI: 100% (moderate-severe TBI by GCS score, ISS ≥ 3)</td>
<td>Data collection: PaO2 on hospital arrival - PaO2: &lt;100 mm Hg (hypoxemia) - PaO2: 110–487 mm Hg (normoxia) - PaO2: &gt;487 mm Hg (hyperoxemia)</td>
<td>Primary: Survival to hospital discharge</td>
<td>Hypoxia/normoxia/hyperoxia and survival of TBI patients Hypoxemia: OR, 0.54 (0.42–0.69) Normoxia: OR, 1.90 (1.52–2.38) Severe hyperoxemia: OR, 0.50 (0.36–0.71)</td>
<td>Compared to normoxemia, hypoxemia and severe hyperoxemia were both associated with lower survival in TBI patients</td>
<td>III</td>
<td>Supports Normoxia</td>
</tr>
<tr>
<td>Stockinger (2004)</td>
<td>Retrospective/single center/USA n = 5,090 Mean age: 30 y Population of Interest: Trauma: 100% Requiring transport to Level I trauma center</td>
<td>Data collection: Prehospital - Supplemental oxygen (O2) - No supplemental oxygen (no O2)</td>
<td>Primary: In-Hospital Mortality</td>
<td>Supplemental vs. no supplemental oxygen in the prehospital setting and mortality Supplemental Oxygen: 2.3% No Supplemental Oxygen: 1.1% p = 0.0011</td>
<td>Supplemental oxygen increased the odds of mortality when compared to patients that received no supplemental oxygen in level 1 trauma patients</td>
<td>III</td>
<td>Supports Normoxia</td>
</tr>
<tr>
<td>Jones (1994)</td>
<td>Prospective observational/single center/Scotland n = 124 Mean age: 38 y Population of Interest: Trauma: 100% TBI: 100% (GCS score ≤ 12, ISS ≥ 16) ICU: 100%</td>
<td>Data collection: Hypoxemia vs. normoxia/hyperoxia *oxygenation thresholds not defined</td>
<td>Primary: In-Hospital Mortality</td>
<td>Hypoxemia on Mortality Mortality: p = 0.02 *data not shown</td>
<td>Hypoxemia associated with an increase in mortality in patients with TBI</td>
<td>III</td>
<td>Supports avoidance of hypoxia</td>
</tr>
<tr>
<td>Stocchetti (1996)</td>
<td>Retrospective single center/Italy n = 49 Mean age: 37 y Population of Interest: Trauma: 100% TBI: 100%</td>
<td>Data Collection: - Arterial oxygen saturation * Information was collected at scene of trauma</td>
<td>In-Hospital Mortality</td>
<td>Arterial oxygen saturation and mortality (%) &lt;60%: 50% 60–80%: 44% 81–90%: 15% &gt;90%: 14%</td>
<td>Hypoxemia was associated with poor outcomes when compared to normoxia and hyperoxia in TBI patients</td>
<td>IV</td>
<td>Supports avoidance of hypoxia</td>
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ABG, arterial blood gas; AIS, Abbreviated Injury Scale; AKI, acute kidney injury; CPC, cerebral performance categories; GRADE, Grading of Recommendations Assessment Development and Education; GOS, Glasgow Outcome Scale; HLOS, hospital length of stay; IMV, invasive mechanical ventilation; ISS, Injury Severity Score; OI, Oxygen Index; OSI, Oxygen Saturation Index; OR, odds ratio; n, arterial blood; SSI, surgical site infection; VFD, ventilator-free days.

*Bold emphasis represents, p < 0.05.
### Table 2. Nontrauma Critical Care Articles Included in Systematic Review (n = 26)

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| Girardis (2016)² | RCT/Single center/Italy N = 434 Mean Age: 64 y Population of Interest: Critically Ill: 100% · Medical: 38% · Surgical: 62% | Conservative: During entire ICU stay: PaO₂ 70–100 mm Hg - SpO₂ 94–98% Conventional: PaO₂ ≥ 150 mm Hg - SpO₂ 97-100% | Primary: ICU Mortality | Conservative vs. Conventional 
Oxygenation 
ICU Mortality: 0.086 (0.017–0.150); p = 0.01 | Conservative oxygen therapy was associated with a decrease in mortality, organ failure and infections when compared with the conventional oxygen group |
| Panwar (2016)⁵ | RCT/Multicenter/Australia/NZ/France N = 104 Mean Age: 62 y Population of Interest: Critically Ill: 100% · Trauma: 4% · Surgical: 35% · Mechanically ventilated: 100% | Intervention: Every 4 h, d 0–7 Conservative: Target SpO₂: 88–92% - Actual Mean SpO₂: 93% Liberal: - Actual Target SpO₂: ≥96% - Mean SpO₂: 97% | 90 d Mortality (secondary) Mean AUC for oxygenation values (primary) | SpO₂ 88–92% vs. SpO₂ ≥ 96% 90 d Mortality: Conservative: 21 Liberal: 19; p = 0.74 Mean AUC for oxygen values: Conservative: 93%; Liberal: 97%; p < 0.001 | Conservative oxygen therapy is feasible and appears safe to implement in mechanically ventilated patients in the ICU, compared to liberal oxygenation therapy |
| Parke (2016)¹¹ | RCT/Multicenter/Australia/NZ N = 298 Mean Age: 65 y Population of Interest: Cardiac Surgery: 100% · Cardiopulmonary bypass: 100% | Data Collection: During cardiopulmonary bypass Intervention: PaO₂: 75–90 mm Hg Control: SpO₂ ≥99% | Primary: Acute Kidney Injury (AKI) (primary) Hospital LOS (secondary) | PaO₂ 75–90 mm Hg vs. SpO₂ ≥ 99% Acute Kidney Injury: OR, 5.8 (16.1–4.7); p = 0.28 Hospital LOS: Control: 8.9 Intervention: 9.6; p = 0.65 | Normoxia and hyperoxia had a similar incidence of acute kidney injury, IMV duration, ICU LOS, and hospital LOS in cardiac bypass surgery patients |
| Smit (2016)¹² | RCT/Single center/Netherlands N = 50 Mean Age: 67 y Population of Interest: Critically Ill: 100% · Coronary artery bypass graft (CABG) surgery | Intervention: PaO₂: 130–150 mm Hg during CBP - PaO₂: 80–100 mm Hg in ICU Control: PaO₂: 200–220 mm Hg during CBP - PaO₂: 130–150 mm Hg in ICU * Timing of PaO₂ was not defined * FiO₂ was adjusted to keep PaO₂ values within target range for protocol | Primary: Myocardial Injury (CK-MB) | Conservative vs. Conventional 
Oxygenation 
PaO₂ CBP: p = <0.0001 PaO₂ ICU: p = 0.034 | Hyperoxia and normoxia groups had similar clinical outcomes in critically ill CABG patients |

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<td>Stolmeijer (2014)³³</td>
<td>Prospective/Single center/Netherlands N = 83</td>
<td>Population of Interest: Critically Ill: 100% - Two or more SIRS criteria - Suspicion of infection - Mechanically Ventilated: 100%</td>
<td>Data Collection: On arrival to ED placed on: FIO2 0.4 (Venti Mask) 5 min after supplemental oxygen: PaO₂ &gt; 71 mm Hg, FIO2 down-titrated to a normal SpO₂: PaO₂ &lt; 71 mm Hg, flow rate increased to 15 L/min with FIO2 0.6-0.8 Hyperoxia: PaO₂ &gt; 101 mm Hg Normoxia: PaO₂ 70-100 mm Hg</td>
<td>Primary: In-Hospital Mortality Hyperoxia vs. Normoxia on in-hospital mortality Normoxia: p = 0.199 Hyperoxia: p = 0.199</td>
<td>Hyperoxia and normoxia had similar in-hospital mortality in mechanically ventilated sepsis patients</td>
<td>II</td>
<td>Neutral</td>
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<tr>
<td>Suzuki (2014)⁶</td>
<td>Prospective Interventions/Single center/Australia n = 105</td>
<td>Mean age: 58 y Population of Interest: Critically Ill: 100% - Mechanically Ventilated: 100%</td>
<td>Data Collection: - SpO₂ 90-92% (Conservative) - Target at clinicians discretion (Conventional)</td>
<td>Hospital Survival at 28 d (secondary) Oxygenation in the first 10 d (primary) Conservative vs. Conventional Oxygenation Hospital Survival at 28 d: OR, 0.35 (0.12-1.06); p = 0.062 Change in Oxygenation in the first 10 d: Conventional: SpO₂ 98.4% Conservative: SpO₂ 95.3% p = &lt;0.001</td>
<td>Conservative oxygen therapy was feasible, safe and associated with some improvement in clinical outcomes in mechanically ventilated patients</td>
<td>II</td>
<td>Supports normoxia</td>
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<tr>
<td>Young (2014)³⁴</td>
<td>RCT/Multicenter/ New Zealand N = 18</td>
<td>Mean Age: 67 y Population of Interest: Critically Ill: 100% - Cardiac Arrest: 100%</td>
<td>Data Collection: Prehospital oxygenation targets (median) Intervention (conservative): SpO₂ 90-94% Control (standard): SpO₂ 89%</td>
<td>Primary: Prehospital oxygen saturations ICU LOS Hospital LOS Standard vs. Conservative Oxygen Prehospital Median: Standard: SpO₂ 95.8% (92.3-96.5) Conservative: SpO₂ 79.5 (73.8-90.3) p = 0.046 ICU LOS: Standard: 43 d (39.3-93) Conservative: 64.2 d (51.5-188.6) Hospital LOS: Standard: 129.4 d (51.5-188.6) Conservative: 95.3 d (27.7-653.9)</td>
<td>In a small pilot trial, conservative oxygen titration in prehospital setting after cardiac arrest was not feasible due to hypoxic episodes</td>
<td>II</td>
<td>Supports avoidance of hypoxia</td>
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<td>Lee (2010)</td>
<td>RCT/Single center/ South Korea N = 56 Mean Age: 55 y Population of Interest: Isolated valvular heart surgery</td>
<td>Data Collection: During reperfusion Intervention: - FI02: 0.7 (hyperoxia) Control: - FI02: 0.5 (normoxia)</td>
<td>Postoperative: Hospital LOS ICU LOS Ventilator Time</td>
<td>Hypoxemia vs. Normoxia Ventilator Time: Hyperoxia: 13 h Normoxia: 16 h p = 0.15 ICU LOS: Hyperoxia: 3.1 d Normoxia: 2.9 d; p = 0.409 Hospital LOS: Hyperoxia: 11.5 d Normoxia: 11.2 d; p = 0.789</td>
<td>Oxygenation strategy was not associated with clinical outcomes</td>
<td>II Neutral</td>
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<tr>
<td>Helmerhorst (2017)</td>
<td>Retrospective/Multicenter/ Netherlands N = 14,441 Mean age: 65 y Population of Interest: Critically Ill: 100%· ICU: 100%· Mechanically Ventilated: 83%· Surgical: 44%</td>
<td>Data Collection: 1st PaO2, highest PaO2 worst PaO2 and average PaO2 within the first 24 h of hospital stay - PaO2: &gt;200 mm Hg (Severe Hyperoxia) - PaO2: 120–200 mm Hg (Mild Hyperoxia) - PaO2: 60–120 mm Hg (Normoxia)</td>
<td>Primary: In-Hospital Mortality</td>
<td>Mild Hyperoxia/Severe Hyperoxia vs. Normoxia In Hospital Mortality Mild Hyperoxia: OR, 0.91 (0.79–1.05) In Hospital Mortality Severe Hyperoxia: OR, 1.11 (0.92–1.34)</td>
<td>Hyperoxemia was not associated with a statistically significant change in mortality or ventilator-free days when compared to normoxia in critically ill mechanically ventilated patients</td>
<td>III Neutral</td>
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<tr>
<td>Johnson (2017)</td>
<td>Retrospective/Multicenter/ United States N = 544 Mean Age: 61 y Population of Interest: Critically Ill: 100%· Cardiac Arrest: 100%</td>
<td>Data Collection: Median PaO2 values 1 h to 48 h in timed increments - PaO2: &gt;300 mm Hg (Hyperoxemia) - PaO2: 60–300 mm Hg (Normoxia) - PaO2: &lt;60 mm Hg (Hypoxemia)</td>
<td>Survival at hospital discharge (secondary) Neurological outcomes at hospital discharge (primary)</td>
<td>Hypoxemia/Hypoxemia vs. Normoxia Survival at hospital discharge: 1 h Hypoxemia vs. Normoxia: OR, 0.79 (0.41–1.52) 1 h Hypoxemia vs. Normoxia: OR, 1.50 (0.93–2.44) 12 h Hypoxemia vs. Normoxia: OR, 0.71 (0.26–1.94) 12 h Hypoxemia vs. Normoxia: OR, 0.17 (0.03–0.89) 48 h Hypoxemia vs. Normoxia: OR, 2.97 (0.23–38.84) 48 h Hypoxemia vs. Normoxia: OR, 0.22 (0.02–2.04) * Similar results for neurological outcomes*</td>
<td>There was no association between PaO2 and neurological outcome within the first 48 h after cardiac arrest among survivors. Hyperoxemia was associated with some evidence of lower survival.</td>
<td>III Supports normoxia</td>
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<td>Schernthaner (2017)</td>
<td>Retrospective/Single center/Germany N = 475 Mean Age: 69 y Population of Interest: Critically Ill: 100% Noninvasive ventilation: 100%</td>
<td>Observational Groups: PaO2 ≥ 97.5 mm Hg (Hyperoxemia) PaO2 ≥ 97.5 mm Hg (Normoxemia) (peak PaO2 level used for grouping)</td>
<td>Primary: In-Hospital Mortality Long Term Mortality</td>
<td>Hyperoxemia vs. Normoxemia In-Hospital Mortality: 28% vs. 13%; p = 0.05 Long Term Mortality &gt; 97.5 mm Hg: OR, 1.69 (1.19-2.42); p = 0.004</td>
<td>Hyperoxemia was associated with higher in-hospital mortality and long term mortality when compared to normoxemia in patients receiving noninvasive mechanical ventilation</td>
<td>III</td>
<td>Supports normoxia</td>
</tr>
<tr>
<td>Staehr-Rye (2017)</td>
<td>Retrospective/ Multicenter/USA N = 73922 Mean Age: 56 y Population of Interest: Surgery (nonthoracic): 100% Mechanically Ventilated: 100%</td>
<td>Data Collection: Median FIO2 intraoperatively - Group 1: 0.31 (reference) - Group 2: 0.41 - Group 3: 0.52 - Group 4: 0.58 - Group 5: 0.79</td>
<td>7-d mortality 30-d mortality (secondary) Major respiratory complications (primary)</td>
<td>High FIO2 vs. Low FIO2 7-d mortality: OR, 2.09 (0.81-5.43) 30-d mortality: OR, 1.97 (1.30-2.99) Respiratory complications: OR, 1.99 (1.72-2.31)</td>
<td>There is a dose-dependent association between high intraoperative FIO2 with higher major respiratory complications and 30 d mortality, when compared to low intraoperative FIO2</td>
<td>III</td>
<td>Supports normoxia</td>
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<tr>
<td>Wang (2017)</td>
<td>Retrospective/ Multicenter/USA N = 9186 Mean Age: 65 y Population of Interest: Critically Ill: 100% Cardiac Arrest: 100%</td>
<td>Data Collection: Based on first, last or any measurement within the first 24 h - PaO2 ≥ 300 mm Hg (Hyperoxemia) - PaO2 60-299 mm Hg (Normoxemia) - PaO2 &lt; 60 mm Hg (Hypoxemia) * ROC protocol did not dictate the timing or frequency of ABG measurements</td>
<td>Primary: In-Hospital Mortality</td>
<td>Hyperoxemia/Hypoxemia vs. Normoxemia Initial PaO2 hyperoxemia vs. normoxemia: OR, 1.10 (0.97-1.26) Initial PaO2 Hypoxemia vs. Normoxemia: OR, 1.30 (1.30-1.92) Final PaO2 Hyperoxemia vs. Normoxemia: OR, 1.60 (1.26-2.04) Final PaO2 Hypoxemia vs. Normoxemia: OR, 3.06 (2.42-3.86) Any PaO2 Hyperoxemia vs. Normoxemia: OR, 1.25 (1.11-1.41) Any PaO2 Hypoxemia vs. Normoxemia: OR, 1.76 (1.54-2.02)</td>
<td>Hyperoxemia and hypoxemia were both associated with higher mortality when compared to the normoxia group in cardiac arrest patients with ROSC</td>
<td>III</td>
<td>Supports normoxia</td>
</tr>
<tr>
<td>Christ (2016)</td>
<td>Retrospective/Single center/Germany N = 124 Mean Age: 69 y Population of Interest: Critically Ill: 100% Cardiac Arrest: 100%</td>
<td>Data Collection: ABGs within 60 min after hospital admission -Hyperoxia -Normoxia * PaO2 thresholds not defined</td>
<td>Primary: Survival to hospital discharge</td>
<td>Hypoxemia vs. Normoxia Survival to discharge: Hypoxemia: 54.3% Normoxia: 34.9%; p = 0.04</td>
<td>Hyperoxia in the short period postarrest is associated with higher survival in cardiac arrest patients</td>
<td>III</td>
<td>Supports higher oxygenation</td>
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<td>Six (2016)</td>
<td>Retrospective/Single center/France N = 503</td>
<td>Data Collection: Daily PaO₂ - PaO₂ &gt; 120 mm Hg (Hyperoxemia) * One PaO₂ &gt; 120 mm Hg was considered a day with hyperoxemia * hypoxemia and normoxemia were not defined</td>
<td>Primary: Hyperoxemia related to the development of VAP VAP: OR, 1.68 (1.16–2.42); ( p = 0.006 )</td>
<td>Hyperoxemia is an independent risk factor in the development of ventilator acquired pneumonia in mechanically ventilated patients</td>
<td>III</td>
<td>Supports normoxia</td>
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<tr>
<td>Elmer (2015)</td>
<td>Retrospective/Single center/USA (Pittsburgh) N = 184</td>
<td>Data Collection: PaO₂ first 24 h, in hourly intervals - PaO₂ &gt; 300 mm Hg (severe hyperoxia) - PaO₂: 101–299 mm Hg (moderate hyperoxia) - PaO₂: 60–100 mm Hg (normoxia) - PaO₂ &lt; 60 mm Hg (hypoxia)</td>
<td>Primary: Survival to hospital discharge</td>
<td>Relationship of PaO₂ levels in first 24 h and Survival to Discharge Severe Hyperoxia: OR, 0.84 (0.72–0.98); ( p = 0.02 ) Moderate Hyperoxia: OR, 1.01 (0.96–1.05); ( p = 0.79 ) Normoxia: OR, 0.74 (0.47–1.16); ( p = 0.20 ) Hypoxia: OR, 1.01 (0.99–1.033; ( p = 0.25 )</td>
<td>Severe hyperoxia PaO₂ &gt; 300 mm Hg was associated with lower survival in cardiac arrest patients with ROSC</td>
<td>III</td>
<td>Supports normoxia</td>
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<tr>
<td>Rincon (2015)</td>
<td>Retrospective/Multicenter/USA (Philadelphia) N = 1388</td>
<td>Observational Groups: Any of the ABGs or follow up ABGs - PaO₂ &gt; 60 mm Hg (hypoxia) - PaO₂ &gt; 300 mm Hg (hyperoxia) * Normoxia defined as no episodes of hypoxia or hyperoxia</td>
<td>Primary: In-Hospital Mortality</td>
<td>Hypoxia and Hypoxia vs. Normoxia Hyperoxia: OR, 2.5 (1.1–6.1); ( p = 0.04 ) Hypoxia: OR, 1.9 (1.2–3.3); ( p &lt; 0.0001 )</td>
<td>Both hyperoxia and hypoxia was associated with higher in-hospital mortality when compared to normoxia in mechanically ventilated intracranial hemorrhage patients</td>
<td>III</td>
<td>Supports normoxia</td>
</tr>
<tr>
<td>Wang (2015)</td>
<td>Retrospective/Single center/Taiwan N = 550</td>
<td>Data Collection: First value after first sustained ROSC - PaO₂ - PaCO₂</td>
<td>Survival to hospital discharge (secondary) Favorable neurological status at discharge (primary)</td>
<td>Oxygenation and Favorable Neurological Outcome Survival: PaO₂ 70–240 mm Hg: OR, 1.85 (1.21–2.85); ( p = 0.00 ) Favorable Neurological Outcome: PaO₂ 70–240 mm Hg: OR, 1.96 (1.08–3.64); ( p = 0.03 )</td>
<td>PaO₂ of 70–240 mm Hg was associated with favorable neurological outcomes and a higher survival to discharge in cardiac arrest patients with ROSC</td>
<td>III</td>
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<tr>
<td>Rincon (2014)</td>
<td>Retrospective/Multicenter/USA (Philadelphia) N = 2894 Mean Age: 61 y Population of Interest: Critically Ill: 100% · Mechanically Ventilated: 100% · Stroke, Subarachnoid Hemorrhage (SAH) · Intracranial hemorrhage</td>
<td>Observational Groups: First ABG within the first 24 h of admission to the ICU · PaO2: &lt; 60 mm Hg (Hypoxia) · PaO2: 60-300 mm Hg (Normoxia) · PaO2: &gt;300 mm Hg (Hyperoxia)</td>
<td>Primary: In-Hospital Mortality</td>
<td>Normoxia vs. Hypoxia/ Hyperoxia In-Hospital Mortality Hypoxia: OR, 1.22 (1.04–1.48); p = 0.04 Hypoxia: OR, 0.88 (0.71–1.10)</td>
<td>Hyperoxia, but not hypoxia, was associated with higher in-hospital mortality in critically ill stroke patients, when compared to normoxia</td>
<td>III</td>
<td>Supports normoxia</td>
</tr>
<tr>
<td>Ihle (2013)</td>
<td>Retrospective/ Multicenter/Canada N = 584 Mean Age: 64 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%</td>
<td>Data Collection: PaO2 within first 24 h in ICU · PaO2: &lt; 60 mm Hg (hypoxia) · PaO2: 60–299 mm Hg (normoxia) · PaO2: ≥300 mm Hg (hyperoxia)</td>
<td>Primary: In-Hospital mortality</td>
<td>Hypoxia/hyperoxia vs. Normoxia Hypoxia vs. normoxia: OR, 0.93 (0.47–1.87) Hyperoxia vs. Normoxia: OR, 1.20 (0.51–2.82)</td>
<td>Hyperoxia and hypoxia, when compared with normoxia, had no association with in-hospital mortality in postcardiac arrest patients</td>
<td>III</td>
<td>Neutral</td>
</tr>
<tr>
<td>Janz (2012)</td>
<td>Retrospective/Single center/USA (Nashville) N = 170 Mean Age: 61 y Population of Interest: Critically Ill: 100% · Cardiac Arrest: 100%</td>
<td>Data Collection: Highest PaO2 within 1st 24 h postcardiac arrest</td>
<td>Primary: In-Hospital Mortality Secondary: Poor neurological outcome at discharge</td>
<td>High PaO2 values in relation to in-hospital mortality and poor neurological outcomes In-Hospital mortality: OR, 1.439 (1.028–2.015); p = 0.03 Poor neurological outcomes: OR, 1.485 (1.032–2.136); p = 0.03</td>
<td>High PaO2 levels in the postarrest setting were associated with increased risk of in-hospital mortality and poor neurological outcomes at discharge</td>
<td>III</td>
<td>Supports normoxia</td>
</tr>
<tr>
<td>Young (2012)</td>
<td>Retrospective/Multicenter/ Australia/NZ N = 2643 Mean Age: 66 y Population of Interest: Critically Ill: 100% · Mechanically ventilated: 100% · Ischemic Stroke: 100%</td>
<td>Observational Groups: Most abnormal PaO2 during the first 24 h of admission in the ICU, defined as the PaO2 associated with the highest alveolar-arterial (A-a) gradient</td>
<td>Primary: In-Hospital Mortality</td>
<td>Most abnormal PaO2 and Mortality PaO2 0–69: OR, 1.14 (0.76–1.72) PaO2 &gt; 69–83: OR, 1.15 (0.76–1.74) PaO2 &gt; 83–93: OR, 0.99 (0.65–1.51) PaO2 &gt; 93–105: OR, 1.48 (0.97–2.26) PaO2 &gt; 105–117: OR, 0.94 (0.62–1.53) PaO2 &gt; 117–140: OR, 1.01 (0.67–1.53) PaO2 &gt; 140–174: OR, 1.20 (0.80–1.81) PaO2 &gt; 174–226: OR, 0.82 (0.55–1.22) PaO2 &gt; 226–341: OR, 1.01 (0.69–1.47) PaO2 &gt; 341–611: OR, 1.00 (reference)</td>
<td>The most abnormal PaO2 within 24 h was not associated with in-hospital mortality in mechanically ventilated stroke patients</td>
<td>III</td>
<td>Neutral</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Study Design/Participants/Inclusion Criteria</td>
<td>Oxygen Exposure</td>
<td>Outcome Measures</td>
<td>Results*</td>
<td>Conclusions</td>
<td>GRADE Level of Evidence</td>
<td>Support of Evidence</td>
</tr>
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<tr>
<td>Kilgannon (2011)7</td>
<td>Retrospective/Multicenter/USA</td>
<td>Data collection: First PaO2 in ICU - PaO2 &gt; 300 mm Hg (Hyperoxia) - PaO2 60-300 mm Hg (Normoxia) - PaO2 &lt; 60 mm Hg (Hypoxia)</td>
<td>Primary: In-Hospital Mortality</td>
<td>PaO2 (continuous) and Mortality In-hospital mortality: OR, 1.06 (1.05-1.07) for rise of 25 mm Hg; p = 0.001</td>
<td>A 25 mm Hg increase of PaO2 showed a 6% increase in the odds of death in cardiac arrest patients</td>
<td>III Supports normoxia</td>
<td></td>
</tr>
<tr>
<td>Kilgannon (2010)</td>
<td>Retrospective/Multicenter/USA</td>
<td>Data Collection: First ABG in ICU - PaO2 &gt; 300 mm Hg (Hyperoxia) - PaO2 30-300 mm Hg (Normoxia) - PaO2 &lt; 60 mm Hg (Hypoxia)</td>
<td>Primary: In-Hospital Mortality</td>
<td>Oxygenation and mortality Hypoxia vs. normoxia: OR, 1.3 (1.1-1.5); p = 0.009 Hyperoxia vs. normoxia: OR, 1.8 (1.5-2.2); p &lt; 0.01</td>
<td>Arterial hyperoxia associated with higher in-hospital mortality compared to normoxia and hypoxia</td>
<td>III Supports normoxia</td>
<td></td>
</tr>
<tr>
<td>de Jonge (2008)58</td>
<td>Retrospective/Multicenter/Netherlands</td>
<td>Data Collection: Mean PaO2 during the entire ICU stay - PaO2</td>
<td>Primary: In-Hospital Mortality</td>
<td>Mean PaO2 on mortality for the entire ICU stay PaO2 60 mm Hg: OR, 1.63 (1.16-2.3) PaO2 60-80 mm Hg: OR, 1.51 (1.18-1.96) PaO2 80-95 mm Hg: OR, 1.25 (0.99-1.57) PaO2 95-123 mm Hg: N/A PaO2 &gt; 123 mm Hg: OR, 1.04 (0.64-1.68)</td>
<td>High PaO2 values within the first 24 h of hospital stay and lower PaO2 values during the entire ICU stay had higher odds of mortality in critically ill patients</td>
<td>III Supports normoxia</td>
<td></td>
</tr>
<tr>
<td>Brown (2006)99</td>
<td>Retrospective/Single center/USA (Spokane)</td>
<td>Data Collection: During Cardiopulmonary bypass - PaO2 300-350 mm Hg (Hyperoxia) - PaO2 200-250 mm Hg (normoxia)</td>
<td>ICU LOS Ventilator Time</td>
<td>Hypoxia vs. Normoxia ICU LOS: Hyperoxic: 38.6 d Normoxic: 29.2 d; p = 0.42 Ventilator Time: Hyperoxic: 9.4 h Normoxic: 7.2 h; p = 0.10</td>
<td>Hyperoxia and normoxia had similar clinical outcomes in patients receiving cardiopulmonary bypass</td>
<td>III Neutral</td>
<td></td>
</tr>
</tbody>
</table>

*Bold emphasis represents, p < 0.05.
supplemental oxygen (i.e., room air), this would not qualify as
modifiable hyperoxia regardless of the their SpO2 or PaO2.
Based on these studies, we found an association between re-
duced oxygen administration targeting normoxia and better or
equivalent clinical outcomes. Several studies showed an associ-
ation between avoidance of hypoxia and improved outcomes—
this indicates a balanced assessment is indicated.

Only four high-quality randomized control trials (RCTs)
were identified in our systematic review, all focusing on
nontrauma critically ill patients.4,5,13,52 Two focused primarily
on cardiac surgical patients, while the other two enrolled mixed
medical and surgical populations (most were medical). None of
these trials enrolled trauma patients. The two trials focusing on
cardiac surgery patients demonstrated no difference between
normoxia and higher oxygenation in a variety of ICU outcomes.
However, the trials by Girardis et al.4 and Panwar et al.5 dem-
onstrated safety and possibly efficacy for normoxia in critically ill
patients (mostly medical). Both trials compared “conservative”
therapy (SpO2 94–98% and 88–92%, respectively) with “liberal”
oxxygen therapy (SpO2 ≥ 97% and ≥96%, respectively).
Conservative oxygen therapy, a surrogate for normoxia, was fea-
sible and safe in one pilot trial and was associated with lower
mortality in the other.4 Collectively, these trials represent the
highest level of evidence included in this systematic review and
highlight the need for additional and larger clinical trials
with a specific focus on trauma patients.

Overall limited and low-quality evidence exists for trauma
patients. The balance of evidence suggests that avoidance of
hypoxia is of paramount importance in critically ill trauma patients,
which likely reflects current clinical practice. However, emerging
evidence supporting avoidance of hyperoxia may be similarly im-
portant. Several low-quality studies suggest that trauma patients,
like other critically ill patients, may experience harm from aggres-
sive oxygen administration.27,29,30,50 The optimal level of oxygen-
ation in trauma patients remains unknown. Future studies are
needed to clarify oxygen targets for noninvasive pulse oximetry
and arterial oxygen measurements, which we believe will have
importance to the civilian and military settings.

Oxygenation may be represented as a continuum. The com-
peting interests of avoiding both hyperoxia and hypoxia must be
addressed in each clinical situation. For example, patients with
TBI are at high risk for cerebral ischemia due to insufficient cere-
bral blood flow and oxygen delivery. Eight of the included trauma
studies, predominately TBI patients, support either the avoidance
of hypoxia or higher supplemental oxygen delivery.18,20,23,26,33–36
The remainder of the included trauma studies, again mostly com-
prised of TBI patients, were neutral or supported normoxia. One
possible conclusion from these data is to avoid hypoxia at all costs
by allowing permissive hyperoxia in TBI patients. Another would
be to titrate supplemental oxygen to normoxia in TBI patients.
Further investigation is needed to better elucidate ideal oxygena-
tion targets in this patient population.

It is possible that hyperoxia, similar to other exposures,
may display dose-dependent adverse effects. Unfortunately, many
of the studies in this systematic review analyzed the initial
PaO2/SpO2 on admission or the highest/lowest value during the
ICU or hospital course. Therefore, the dose-dependent nature of
oxygen toxicity is nearly impossible to elicit from the currently
available data. One important area of future research includes ex-
amining the association between total time spent with hyperoxia
with outcomes in critically ill trauma patients. Second, targeted re-
search is needed to drive optimal clinical parameters for the lower
and upper limits for oxygen saturations (readily measurable in
almost all settings).

Of note, the World Health Organization released a guide-
line in 2016 recommending the usage of 80% fraction of in-
spired oxygen (FIO2) intraoperatively to prevent surgical site
infection.53 This recommendation was based on conflicting data
from some small clinical trials. Indeed, a recent Cochrane Review
of 28 RCTs demonstrated no difference in the rate of surgical site
infection if a high FIO2 (>60%) was used intraoperatively. The au-
thors could not support the routine use of high intraoperative FIO2
due to the significant risk of adverse events, including mortality
and lack of benefit for surgical site infections.

A recently published systematic review and meta-analysis12
examined 25 RCTs related to oxygenation in acute illness and
found increased mortality with liberal/excessive oxygen admin-
istration. However, most trials were in nontrauma and noncritically
ill patients, limiting relevance to critically ill trauma patients. Only
three studies overlapped with the current systematic review (two
critical illness trials and one trauma, specifically TBI). There-
fore, this meta-analysis is complimentary but minimally overlap-
ping to our systematic review, which focuses specifically on
evidence relevant to critically ill trauma patients.

We identified four relevant ongoing trials addressing
hyperoxia or optimal oxygen titration: ACTRN1261500957594,
NCT03174002, NCT02713451, and NCT02321072. All of these
trials include a broad population of critically ill patients (mostly
medical) without a specific focus on trauma. Accordingly, ran-
donized controlled trials to determine the optimal oxygen titra-
tion in critically ill trauma patients are urgently needed.

Limitations of this systematic review include a paucity of
high-quality evidence that met inclusion criteria. As noted previ-
ously, only four high-quality RCTs were identified for this sys-
tematic review, and none of these were trauma-specific. A
second limitation of this review is the broad range of definitions for both hyperoxia and normoxia. Within the 43 included publications, hyperoxia or conventional treatment was defined as anything from a PaO$_2$ of 120 mm Hg or greater to a PaO$_2$ of 300 mm Hg or greater. Occasionally SpO$_2$ was used to make this distinction, and these values ranged from SpO$_2$ of 95% or greater to SpO$_2$ of 99% or greater. We defined the most common ranges used to define normoxia. However, without a standardized definition for hyperoxia, it is more challenging to evaluate specific oxygenation thresholds. The role of nitrogen remains unclear and is beyond the scope of this study. Another limitation is the differences between TBI patients and those with other forms of traumatic injuries such as the titration of oxygen to maintain cerebral perfusion. Most of the included trauma studies enrolled TBI as their primary patient population. In routine clinical care, there may be a correlation between severity of TBI and amount of supplemental oxygen administered, particularly early in the hospital course to avoid hypoxia and cerebral ischemia. The avoidance of hypoxia, rather than targeting hyperoxia, has become an emerging theme in TBI populations which requires specific prospective interventional study. Another limitation is the challenge of creating conclusions from predominantly observational research.

CONCLUSION

In this systematic review of oxygenation in critically ill trauma patients, there were few trauma-specific studies identified beyond TBI; none were high quality. Extrapolating primarily from lower-quality studies and from nontrauma critical illness, the preponderance of evidence supports an association between reduced oxygen administration with targeted normoxia and better or equivalent clinical outcomes. Whether this translates to trauma-specific populations remains unclear. Avoidance of hypoxia was also associated with better outcomes in several studies, including TBI/trauma. This systematic review supports the need for prospective, trauma-specific investigation to determine the optimal oxygenation strategy that is most applicable to trauma care.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORSHP


DISCLOSURE

This trial was supported by the Department of Defense/US Special Operations Command (USSOCOM) (W81XWH-17-C-0241). This manuscript expresses the authors’ opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government. There are no other funding disclosures or conflicts of interest to declare.

REFERENCES


Consensus-Based Recommendation for Oxygenation Targets in Critically Injured Patients

MAJ Steven G. Schauer, DO¹, Erin Anderson, RN², LTC Cord Cunningham, MD, MPH¹, Jacqueline Jones, PhD, RN³, Col Vikhyat S. Bebarta, MD², Adit A. Ginde, MD, MPH²

¹ US Army Institute of Surgical Research, Fort Sam Houston, TX
² University of Colorado School of Medicine, Aurora, CO
³ University of Colorado College of Nursing, Aurora, CO

Background: Prehospital oxygen supplementation frequently occurs, even in the combat setting. Consensus on optimal oxygenation targets remains unclear.

Methods: We conducted a three-round modified Delphi process to reach consensus among military and civilian experts in trauma surgery, emergency medicine, and critical care. The focus of the electronic survey process was defining oxygen titration goals, including oxygen saturation (SpO2), arterial oxygenation (PaO2), and fraction of inspired oxygen (FiO2) in critically injured patients. We also evaluated differences in specific trauma subgroups.

Results: Of the 31 invited experts (13 military, 18 civilian), 26 completed the first round, 28 completed the second round, and 27 completed the final round. All experts participated in at least one round. In the first (open-ended) round, we narrowed the potential SpO2 range to 88-100% and PaO2 range 60-300 mmHg. TBI, hemorrhagic shock, and resource-limited settings had at least 20% of respondents who would alter targets. In the second round, the highest agreement was for a lower SpO2 threshold 90%, upper SpO2 threshold 96%, lower PaO2 threshold 60 mmHg, upper PaO2 threshold 100 mmHg, and for lowest acceptable FiO2 of 21%. In the final round, 89% of experts accepted the lower and upper SpO2 thresholds (90% and 96%) and upper PaO2 threshold (100 mmHg); 96% of experts accepted the lower PaO2 threshold (60 mmHg); and all accepted the lowest acceptable FiO2 (21%). For subgroups, 33% of experts recommended a higher oxygenation target for TBI and 11% for hemorrhagic shock. Most (84%) recommended a lower oxygenation target for resource-limited settings (majority recommending SpO2 88%).

Conclusion: We defined a consensus-based standard for oxygenation targets in critically injured patients as SpO2 90-96% (88-96% with resource-limitations), PaO2 60-100 mmHg, and lowest acceptable FiO2 21%. These standards represent expert consensus, but higher quality prospective data is needed to validate these findings.

Disclosures: Funded by the Department of Defense/ SOCOM (W81XWH-17-C-0241). This abstract expresses the authors’ opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.
Association between Hyperoxia, Supplemental Oxygen, and Mortality in Critically Injured Patients

David J. Douin, MD¹, Caroline Ledbetter, MPH², Erin L. Anderson, RN¹, MAJ Steven G. Schauer, DO, MS³,⁴, Yang Wang, PhD², Franklin L. Wright, MD¹, COL Vikhyat S. Bebarta, MD¹,⁴, Adit A. Ginde, MD, MPH¹

¹ University of Colorado School of Medicine, Aurora, CO
² Colorado School of Public Health, Aurora, CO
³ US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX
⁴ US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX

Background: Oxygen therapy has undisputed importance in combat casualty care to treat and prevent morbidity associated with hypoxia. However, generous supplemental oxygen is routine, and often results in hyperoxia. Emerging evidence indicates that even modest hyperoxia may increase morbidity and mortality, but limited evidence exists specifically for trauma patients. In addition, oxygen is a limited resource that is challenging to obtain in austere settings—e.g., prolonged field care and en route care, requiring substantial resources, space, weight and logistics to procure. In this study, we evaluated the association between hyperoxia and supplemental oxygen delivery with in-hospital mortality in critically injured patients.

Methods: We conducted a multicenter, retrospective observational cohort study at the two Level I and one Level II trauma centers in Colorado. We defined our cohort of critically injured patients as having an ICD-10 code for injury/trauma and requiring admission to the intensive care unit within 24 hours of emergency department arrival from October 2015 to June 2018. The primary predictor was oxygenation, defined by all recorded oxygen saturation (SpO₂) values measured during the first 7 days of hospitalization. We defined the oxygen exposure as the following categories based on our prior consensus work: hyperoxia (97-100%), normoxia (90-96%), borderline hypoxia (88-89%), or hypoxia (<88%), with each individual patient’s oxygen exposure defined as the proportion and cumulative duration of time spent in each category during the first 7 days of hospitalization. The primary clinical outcome was in-hospital mortality, which we analyzed using time dependent covariates with a Cox regression model. We calculated hazard ratios for the interaction of the SpO₂ and FiO₂ values. The results were adjusted for demographics (age, sex, race/ethnicity), mechanism of injury, APACHE II Score, Elixhauser comorbidities (stratified by cardiopulmonary and non-cardiopulmonary), and cigarette smoking status.

Results: We included 3,288 visits that met our case definition for critically injured patients. The median age was 54 years (IQR 34-69), and patients were 66% male, 67% non-Hispanic white, 8% non-Hispanic black, and 16% Hispanic. Blunt trauma mechanism was present in 66% of cases, 72% arrived by EMS, and the mean APACHE II score was 9.6 (SD 6.8). The primary outcome of in-hospital mortality occurred in 252 (7.7%) of patients, with 41% of cases requiring mechanical ventilation and the mean hospital length of stay among survivors was 10 days (SD 15.9). Mean ventilator free days to day 28 was 24 (SD 8.4) and mean hospital free days to day 90
was 74 days (SD 24). Of the 226,057 patient-hours recorded, 108,296 (46%) had hyperoxia, 108,296 (52%) had normoxia, 3,858 (2%) had borderline hypoxia, and 3,177 (1%) had hypoxia. During hyperoxia, the adjusted risk of mortality was higher for higher fraction of inspired oxygen (FiO2): at SpO2 of 100%, the adjusted hazard ratios for FiO2 at 100%, 80%, and 60% were 11.7 (95%CI 5.2-6.2), 5.5 (95%CI 2.6-11.6), and 2.0 (95%CI 1.0-4.2), respectively and for FiO2 at 21% and 30% were 0.14 (95%CI 0.08-0.26) and 0.29(95%CI, 0.18-0.46), respectively. Similarly, at SpO2 of 96%, the adjusted hazard ratios for FiO2 at 100%, 80%, and 60% were 14.5 (95%CI 6.7-31.4), 7.5 (95%CI 3.7-15.1), and 3.2 (95%CI 1.6-6.1), respectively and for FiO2 at 21% and 30% were 0.32 (95%CI 0.19-0.53) and 0.58 (95%CI, 0.37-0.90), respectively.

**Conclusion:** In this large multicenter cohort of critically injured civilian patients, hyperoxia was present during nearly half of the time during the first 7 days of hospitalization. During hyperoxia, higher oxygen administration was associated with a greater risk of mortality, while lower oxygen administration was associated with a lower risk of mortality. Prospective interventional studies are required to determine the causal association between hyperoxia and clinical outcomes and optimal target oxygen concentrations in critically injured patients.

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**Character count:** 4,061 (with spaces)
Association between Hyperoxia, Supplemental Oxygen, and Mortality in Critically Injured Patients

Presenter: Adit A. Ginde, MD, MPH
Co–Authors: Erin L. Anderson, RN, MAJ Steven G. Schauer, DO, MS, David J. Douin, MD, Caroline Ledbetter, MPH, Yang Wang, PhD, MAJ Franklin L. Wright, MD, Col Vikhyat S. Bebarta, MD

University of Colorado Anschutz Medical Campus
School of Medicine
Disclosures

- Authors have no conflicts of interest to report.

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  - USSOCOM W81XWH–17–C–0241

- This presentation expresses authors’ own opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.
Current State

“Oxygenated inspired air is best provided via a tight-fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”

“The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”
Paradigm Shift

- Supplemental oxygen key to avoid morbidity from hypoxia

- Excessive oxygen in En Route Care
  - Common practice
  - Unlikely to benefit; may cause harm
  - Expands mission weight, cube, and logistics/power; safety issues

- **Gap**: Limited data on optimal oxygen titration targets in critically injured patients
Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN, Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH, Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, Aurora, Colorado
Conclusions

- Overall association between lower oxygen/normoxia and improved clinical outcomes
- Few trauma specific articles
  - 14 out of 17 trauma related exclusively to TBI
  - No high quality/clinical trial data
- Supports need for further trauma-specific studies/clinical trials, particularly beyond TBI
Objective

To evaluate the association between hyperoxia and supplemental oxygen delivery with in-hospital mortality in critically injured patients
Methods

- **Design**: Multicenter retrospective observational cohort
  - Two Level 1 and one Level 2 civilian trauma centers in Colorado

- **Cohort**: ICD–10 code for trauma + ICU admission (2015–18)

- **Exposure**: SpO2 and FiO2 during the first 7d of hospitalization
  - Hyperoxia: SpO2 97–100%
  - Normoxia: SpO2 90–96%
  - Hypoxia: SpO2 <88% (borderline: 88–89%)
  - FiO2 categories: 21%, 22–30%, 31–40%, >40%
Analysis

- **Primary Outcome: In–Hospital Mortality**
  - Cox proportion hazard model with time–varying covariates
  - All available SpO2 and FiO2 data used (constant between measurements)
  - Non–linear association and interaction incorporated

- **Ventilator Free Days** to Day 28
  - Negative binominal distribution in general linear model

- **Hospital Free Days** to Day 90
  - Poisson distribution in a general linear model

- Adjusted for demographics, injury mech, APACHE II Score, comorbidities (cardiopulmonary and non–cardiopulmonary), and smoking
Results—Characteristics

- **Cohort Size:** n=3,464 patients
- **Demographics:** mean age 53y, male 65%, white 68%
- **Mechanism:** fall 35%, MVC 31%, burn 8%, penetrating 7%
- **Clinical:** EMS arrival 73%, mech vent 41%, mean APACHE 8
- **Outcomes**
  - In–Hospital Mortality 7.6%
  - VFD 23.7 days (of 28)
  - HFD 73.7 days (of 90)
Adjusted Mortality Risk by SpO2 & FiO2
## Adjusted Incident Rate Ratios for VFD and HFD

<table>
<thead>
<tr>
<th>SpO2 category (FiO2)</th>
<th>VFD</th>
<th>HFD</th>
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<tr>
<td>Normoxia (21%)</td>
<td>1.09 (1.07–1.10)</td>
<td>1.07 (1.06–1.07)</td>
</tr>
<tr>
<td>Normoxia (22–30%)</td>
<td>1.04 (1.03–1.06)</td>
<td>1.03 (1.03–1.04)</td>
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<tr>
<td>Normoxia (31–40%)</td>
<td>1.01 (1.00–1.03)</td>
<td>1.01 (1.01–1.02)</td>
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<tr>
<td>Normoxia (&gt;40%)</td>
<td>0.98 (0.97–1.00)</td>
<td>0.98 (0.98–0.99)</td>
</tr>
<tr>
<td>Hyperoxia (21%)</td>
<td>1.02 (1.01–1.04)</td>
<td>1.02 (1.01–1.02)</td>
</tr>
<tr>
<td>Hyperoxia (22–30%)</td>
<td>1.00 (0.98–1.01)</td>
<td>0.99 (0.99–1.00)</td>
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<tr>
<td>Hyperoxia (31–40%)</td>
<td>0.99 (0.97–1.00)</td>
<td>0.98 (0.98–0.99)</td>
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<tr>
<td>Hyperoxia (&gt;40%)</td>
<td>Reference</td>
<td>Reference</td>
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</table>
Limitations

- Retrospective data
- Observational—confounding by indication
- Geographically limited, higher elevation
- Primary endpoint (mortality) is uncommon
Conclusions

- Hyperoxia common in critically ill trauma patients
- During hyperoxia, higher oxygen administration associated with higher mortality and morbidity (lower VFD, HFD)
- Lower oxygen administration and targeting normoxia may result in better clinical outcomes
  - Additional logistical/operational benefit
- Future directions: multicenter interventional trial
Questions?

Adit A. Ginde, MD, MPH
adit.ginde@ucdenver.edu
Phone: 720–848–6777
Introduction

- Oxygen supplementation is frequently used in critically injured trauma casualties in the combat setting.
- Oxygen supplies in the deployed setting are limited.
- We currently lack oxygen supplementation specific guidelines for the combat setting.

Objectives

We sought to develop and expert consensus panel on oxygen targets for critically injured trauma patients maximizing outcomes while minimizing oxygen use.

Methods

- We conducted a prospective study using the multi-stage, modified Delphi consensus process of subject matter experts across many disciplines of medicine and surgery including both military and non-military physicians.
- Provided them with a systematic review of available literature in advance to help inform their opinions.

Results

- 31 invited experts → 26 completed first round, 28 completed second round, 27 completed the final round, all participated in at least one round.
- When caveating limited resources, the expert panel felt a target SPO2 of 88-96% was ideal.

Conclusions

- Target SPO2 range is 90-96% in general.
- Target SPO2 range in resource limited setting is 88-96%.
- PAO2 target is 60-100mmHg.
- Lowest acceptable FiO2 is 21%.

Funding

Our study was supported by the Special Operations Command grant W81XWH-17-C-0241.

Statements

The Colorado Multiple Institutional Review Board and Human Research Protections Office reviewed and determined this study was exempt from IRB oversight.
Targeted Normoxia to Conserve Oxygen and Improve Outcomes in Combat Injured Special Forces

PIs: Adit A. Ginde, MD, MPH, University of Colorado
MAJ Steven Schauer, DO, MS, USAISR/59 MDW
Significance

• Supplemental oxygen key to avoid morbidity from hypoxia

• Excessive oxygen
  – Common practice
  – Unlikely to benefit; may cause harm
  – Expands mission weight, cube, and logistics; safety issues

• **Gap**: Limited data on optimal oxygen titration targets in critically injured patients
Normoxia: Avoids hypoxia **AND** hyperoxia

- **Hypoxia**: < 88%
- **Normoxia**: 88 - 89%
- **Hyperoxia**: > 96%

Graph showing the relationship between oxygen saturation and mortality.
Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

PI: Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS  Org: University of Colorado Denver/USAISR  Award Amount: $519,119

Study Aims

- **Aim 1:** Define standard care for oxygen titration in critically ill trauma patients
- **Aim 2:** Compare the effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
- **Aim 3:** Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

Approach

**Aim 1** is a Delphi process with subject matter experts to define normoxia targets (minimizing supplemental oxygen) after major trauma and develop consensus clinical practice guidelines. **Aim 2** is a retrospective cohort study to measure severity-adjusted clinical outcomes of normoxia, compared with relative hyperoxia (conventional oxygen) in critically ill trauma patients. **Aim 3** is a pilot implementation study of the targeted normoxia study to test the feasibility of implementation in critically ill trauma patients.

Timeline and Cost

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Updated: April 15, 2019

Goals/Milestones

**CY17 Goals** (3 months) – Preparatory Work
- Design survey and identify experts/respondents (Aim 1)
- Develop electronic chart abstraction tool (Aim 2)
- Obtain IRB approvals (Aims 1 and 2)

**CY18 Goals** (12 months) – Define Normoxia Targets
- Begin Delphi process (Aim 1)
- Begin data collection (Aim 2)
- Analyze responses and develop clinical practice guideline (Aim 1)
- Complete data collection and analysis (Aim 2)
- Disseminate results (Aims 1 and 2)
- Develop intervention and case report forms (Aim 3)
- Obtain IRB approval (Aim 3)

**CY19 Goals** (9 months) – Implementation Results and Next Steps
- Implement intervention and begin data collection (Aim 3)
- Complete data collection and analysis (Aim 3)
- Disseminate results (Aim 3)
- Prepare for large scale implementation

Targeted normoxia improves survival and conserves oxygen in medical patients. We will study in trauma.
Aim 1a: Systematic Review

• Included (n=43)
  – 17 trauma studies
  – 26 non-trauma critical illness

• Conclusions
  – Overall association between lower oxygen/normoxia and improved clinical outcomes
  – Few trauma specific articles
    ➢ 14 out of 17 related exclusively to TBI
    ➢ No high quality/RCT data
  – Supports need for further trauma-specific studies/RCTs, particularly beyond TBI
### Aim 1b: Expert Panel (Military)

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Also 18 civilian experts part of the panel
Aim 1b: SpO2 low threshold

Percentage of Agreement/Disagreement

- 88%: 38.5% Strongly Agree, 25.9% Agree, 11.5% Disagree, 35.7% Strongly Disagree
- 90%: 66.7% Strongly Agree, 23.1% Agree, 7.4% Disagree, 3.7% Strongly Disagree
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- 94%: 42.9% Strongly Agree, 21.4% Agree, 3.7% Disagree, 35.7% Strongly Disagree

Low SpO2 Threshold

Return to Quad Chart
Aim 1b: SpO2 high threshold
Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2
Aim 2: Most patients on supplemental oxygen are **hyperoxic**

Percent of obs in each SpO₂ Category

<table>
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<th>SpO₂ Category</th>
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<tbody>
<tr>
<td>Hypoxia</td>
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<tr>
<td>Mild Hypoxia</td>
<td>0.0%</td>
</tr>
<tr>
<td>Normoxia</td>
<td>10.0%</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>90.0%</td>
</tr>
</tbody>
</table>

FiO₂ Category:
- 21
- <21 - 30
- >30 - 40
- >40 - 50
- >50 - 60
- >60
- NA
Higher oxygen supplementation associated with **increased mortality** at all SpO2 levels.
Aim 3: Pilot Intervention Launched

- Finalized standard care definitions for oxygen
- Approved IRB applications
  - Colorado IRB review—approved (waiver of consent)
  - DoD/HRPO second level review—approved
- Implementation
  - Data collection strategy
  - Stakeholder engagement
  - Electronic clinical decision support
- Demonstrate feasibility and safety
Areas in need of improvement:

Please continue to titrate below 1L NC if SpO2 > 96%
Multicenter Implementation Trial of Targeted Normoxia Strategy to Inform Oxygen Requirements for Combat Casualty Care

Military PI: MAJ Steven Schauer, DO, MS
Civilian PI: Adit Ginde, MD, MPH
Org: USAISR/59 MDW
Org: University of Colorado Denver

Problem, Hypothesis and Military Relevance
- Oxygen is a limited resource that is challenging to obtain in combat settings
- Critical to determine oxygen requirements for combat injured to optimize care and conserve oxygen
- Hypothesis: Targeted normoxia will reduce harm from hypoxia/hyperoxia and reduce need for oxygen
- Findings will provide immediate actionable data to define oxygen requirements for critically injured warfighters and inform changes to CPGs

Proposed Solution
Aim 1. Measure the impact of targeted normoxia implementation on oxygen consumption/requirements
Aim 2. Determine the safety of targeted normoxia
Aim 3. Determine the effectiveness of targeted normoxia on patient-centered outcomes

Approach: Multicenter cluster randomized, stepped wedge implementation trial targeted normoxia (goal SpO2 90-96%). Waiver of consent greatly enhances efficiency (EFIC not required). Enrollment of critically ill trauma patients at 8 centers (anticipated n=6240).

Timeline and Total Cost
<table>
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Stepped Wedge Cluster Randomized Trial

Sites

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Time

Post-Implementation (Intervention)
Pre-Implementation (Control)
Multicenter Normoxia Trial

- **Goal**: definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
  - Particularly important for ERC/PFC

- **Design**: cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients)

- **Human subjects issues**: minimal risk, waiver of informed consent (efficient, cost savings)
Technology/Materiel Solutions

- Portable oxygen concentrators
  - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control

Diagram:

- Target \( \text{SpO}_2 \)
- \( \text{FIO}_2 \) Needed
- Vent
- \( \text{FIO}_2 \) delivered
- \( V_T \), etc. delivered
- \( \text{O}_2 \) to patient
- Pulse-ox
- \( \text{SpO}_2 \)
Strategy to Avoid Excessive Oxygen (SAVE-O2) for Combat Casualty Care

PIs: Adit A. Ginde, MD, MPH, University of Colorado
MAJ Steven Schauer, DO, MS, USAISR/59 MDW
Current State

- “Oxygenated inspired air is best provided via a tight-fitting oxygen reservoir face mask with a flow rate of at least 10 L/min.”
- “The goal of airway/ventilatory support in the tactical setting is to maintain adequate tissue oxygenation... a pulse oximeter reading greater than 90%.”
Significance

• Supplemental oxygen key to avoid morbidity from hypoxia

• Excessive oxygen
  – Common practice
  – Unlikely to benefit; may cause harm
  – Expands mission weight, cube, and logistics; safety issues

• Gap: Limited data on optimal oxygen titration targets in critically injured patients
Normoxia: Avoid hypoxia **AND** hyperoxia

Oxygen Saturation

<table>
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<tr>
<td>&lt; 88%</td>
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Mortality
• **Conclusions:** ...more than 1 in 5 casualties overall had documented hyperoxia..., 1 in 3 intubated, and almost 1 in 2 TBI casualties. With limited oxygen supplies in theater and logistical challenges with oxygen resupply, efforts to avoid unnecessary oxygen supplementation may have material impact on preserving this scarce resource and avoid potential detrimental clinical effects from supraphysiologic oxygen concentrations.
Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

**PI:** Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS  
**Org:** University of Colorado Denver/USAISR  
**Award Amount:** $519,119

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- Prepare for large scale implementation

*Updated: April 15, 2019*
Aim 1a: Systematic Review

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN, Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH, Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, Aurora, Colorado
Aim 1a: Systematic Review

• **Included (n=43)**
  – 17 trauma studies
  – 26 non-trauma critical illness

• **Conclusions**
  – Overall association between lower oxygen/normoxia and improved clinical outcomes
  – Few trauma specific articles
    - 14 out of 17 related exclusively to TBI
    - No high quality/RCT data
  – Supports need for further trauma-specific studies/RCTs, particularly beyond TBI
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Also 18 civilian experts part of the panel
Aim 1b: SpO2 low threshold

Percentage of Agreement/Disagreement

Low SpO2 Threshold

- 88%
  - Strongly Agree: 38.5%
  - Agree: 26.9%
  - Disagree: 23.1%
  - Strongly Disagree: 11.5%

- 90%
  - Strongly Agree: 25.9%
  - Agree: 66.7%
  - Disagree: 7.4%
  - Strongly Disagree: 0%

- 92%
  - Strongly Agree: 22.2%
  - Agree: 40.7%
  - Disagree: 33.3%
  - Strongly Disagree: 0%

- 94%
  - Strongly Agree: 21.4%
  - Agree: 42.9%
  - Disagree: 35.7%
  - Strongly Disagree: 0%
Aim 1b: SpO2 high threshold
Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2

- Lower SpO2 Threshold: 90%
- Upper SpO2 Threshold: 96%
- Lower PaO2 Threshold: 60 mmHg
- Upper PaO2 Threshold: 100 mmHg
- Lowest FiO2: 21%

Percentage of Agreement with Oxygenation Thresholds:
- 89%
- 89%
- 96%
- 89%
- 100%
Special considerations

- Severe TBI: 33% would increase SpO2 range
- Hemorrhagic shock: 11% would increase SpO2 range
- Lowest SpO2 in resource limited settings
  - 85-86%: 27% respondents
  - 87-88%: 58% respondents
  - 89-90%: 15% respondents
- No signal to change recommendation for: major burn, mechanical ventilation, thoracic trauma
Aim 2: Observational Study

- **Cohort Size**: n=3,464 patients

- **Demographics**: mean age 53y, male 65%, white 68%

- **Mechanism**: fall 35%, MVC 31%, burn 8%, penetrating 7%

- **Clinical**: EMS arrival 73%, mech vent 41%, mean APACHE 8

- **Outcomes**
  - In-Hospital Mortality 7.6%
  - VFD 23.7 days (of 28)
  - HFD 73.7 days (of 90)
Aim 2: Observational Study
Most pts on supplemental O2 are hyperoxic
Higher oxygen supplementation associated with increased mortality at all SpO2 levels.
### Adjusted Incident Rate Ratios for VFD and HFD

<table>
<thead>
<tr>
<th>SpO2 category (FiO2)</th>
<th>VFD</th>
<th>HFD</th>
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<tbody>
<tr>
<td>Normoxia (21%)</td>
<td><strong>1.09</strong> (1.07-1.10)</td>
<td><strong>1.07</strong> (1.06-1.07)</td>
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<tr>
<td>Normoxia (22-30%)</td>
<td><strong>1.04</strong> (1.03-1.06)</td>
<td><strong>1.03</strong> (1.03-1.04)</td>
</tr>
<tr>
<td>Normoxia (31-40%)</td>
<td>1.01 (1.00-1.03)</td>
<td><strong>1.01</strong> (1.01-1.02)</td>
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<td>Normoxia (&gt;40%)</td>
<td>0.98 (0.97-1.00)</td>
<td><strong>0.98</strong> (0.98-0.99)</td>
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<tr>
<td>Hyperoxia (21%)</td>
<td><strong>1.02</strong> (1.01-1.04)</td>
<td><strong>1.02</strong> (1.01-1.02)</td>
</tr>
<tr>
<td>Hyperoxia (22-30%)</td>
<td>1.00 (0.98-1.01)</td>
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<tr>
<td>Hyperoxia (&gt;40%)</td>
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Aim 3: Pilot Intervention

- Finalized standard care definitions for oxygen
- Approved IRB applications
  - Colorado IRB review—approved (waiver of consent)
  - DoD/HRPO second level review—approved
- Implementation
  - Data collection strategy
  - Stakeholder engagement
  - Electronic clinical decision support
- Demonstrated feasibility and safety
  - n=201 post-intervention (Jan-July 2019)
Pilot Implementation

Room Air

1-3 L/min

4-6 L/min

>6 L/min

Percent of Time

Day 0 - 3

Day 4-7

Normoxia

Hyperoxia

FiO₂ Category

(Missing)

>60%

>50% - 60%

>40% - 50%

>30% - 40%

>21% - 30%

21%

Return to Quad Chart
Aim 3: Pilot Intervention

- Significantly increased normoxia and reduced FiO2/supplementation oxygen administration
- No increase in hypoxia
- Mortality, VFD, HFD were similar in pre- and post-implementation groups
Objective

Our **overall objective** is to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply.

**Aim 1.** Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients.

**Aim 2.** Determine the safety of targeted normoxia.

**Aim 3.** Determine the clinical effectiveness of targeted normoxia.

Approach

Multicenter cluster randomized, stepped wedge implementation trial of the targeted normoxia approach (SpO2 90-96%). Efficiency will be greatly enhanced by a waiver of informed consent since protocol implementation is minimal risk (EFIC not required).

Impact

Our findings will provide immediately actionable data to define oxygenation practices in critically injured warfighters and civilians and aid in the development of clinical practice guidelines.

### Timeline and Cost

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**Estimated Budget ($K)**

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Updated: October 19, 2019

### Goals/Milestones

**Year 1 Goals** (12 months) – Preparatory Work
- Obtain IRB/HRPO approval
- Develop Standard Operating Procedure Documents (SOPs)
- Create Site Materials
- Site Initiation Visits/Training
- Develop Data Collection Infrastructure
- Begin Site Implementation

**Year 2 Goals** (12 months) – Implementation
- Randomized Implementation
- Site Monitoring
- Data Collection

**Year 3 Goals** (12 Months) – Data Collection/Data Analysis
- Randomized Implementation/Site Monitoring
- Data Collection
- Data Analysis
- Dissemination
Proposed Sites

- Oregon Health & Science University
- Denver Health
- University of Pittsburgh
- University of Cincinnati
- University of Texas - Houston
- Vanderbilt University
- San Antonio Military Medical Center
- University of Alabama - Birmingham
Stepped Wedge Cluster Randomized Trial

Sites

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Time

Post-Implementation (Intervention)

Pre-Implementation (Control)
Multicenter Normoxia Trial (JWMPR)

• **Goal**: definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
  – Particularly important for ERC/PFC
  – Focus on polytrauma

• **Design**: cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients)

• **Human subjects issues**: minimal risk, waiver of informed consent (efficient, cost savings)
Multicenter Normoxia Trial (MTEC)

- **Goal:** major burn-specific evidence to inform CPG and oxygen requirements
  - Particularly important to focus on burn wound healing

- **Design:** cluster randomized, stepped wedge implementation trial (6 sites, n~2340 patients)

- **Sites:** U.S. Army Institute of Surgical Research, University of Alabama-Birmingham, University of Cincinnati, University of Colorado, University of Pittsburgh, Vanderbilt University
Technology/Materiel Solutions

- Portable oxygen concentrators
  - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control
Transition Plan

• Inform a change to CPGs (e.g., JTS, CCATT) and TCCC guidelines related to oxygen
• Submit findings to DTIC; present at MHSRS and SOMSA
• Continue work with CDID/AMMED Joint Oxygen Working Group
• Disseminate to military leadership/training agencies including:
  1. Joint Trauma System (CPG)
  2. USAF Air Mobility Command (CPG)
  3. Special Operations Command (CPG and training)
  4. Tri-service Health Readiness Center of Excellence
  5. CCATT Pilot Unit (QI/QC process)
  6. CSTARS/CCATT/TCCET course directors (training)
  7. CoTCCC and CoERCCC (guidelines)
  8. Navy Corpsmen training program (training)
Discussion/Questions

Adit A. Ginde, MD, MPH
adit.ginde@cuanschutz.edu
Phone: 720-848-6777

University of Colorado
Anschutz Medical Campus
School of Medicine
Pilot Implementation Trial of Targeted Normoxia to Reduce Oxygen Requirements for Critically Injured Patients

David J. Douin, MD1, Erin L. Anderson, RN1, Caroline Ledbetter, MPH2, MAJ Steven G. Schauer, DO, MS3,4, Franklin L. Wright, MD1, Robert T. Neumann, MD,1 Col Vikhyat S. Bebarta, MD1,4, Adit A. Ginde, MD, MPH1

1 University of Colorado School of Medicine, Aurora, CO
2 Colorado School of Public Health, Aurora, CO
3 US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX
4 US Air Force 59th Medical Wing, Office of the Chief Scientist, JBSA Lackland, TX

Background: Generous oxygen supplementation and hyperoxia are common in civilian and combat trauma patients but unlikely improves outcomes. We evaluated an intervention to reduce oxygen administration by targeting normoxia in critically injured patients.

Methods: We conducted a quasi-experimental before-after study in the ED and ICUs at a Colorado Level 1 trauma center in 2018-19. Our cohort had an ICD-10 code for injury/trauma and required ICU admission within 24 hours of arrival. The clinical team implemented a multimodal intervention to target normoxia, defined as SpO2 90-96% during the ED and ICU course. The focus was to decrease FiO2/supplemental oxygen for SpO2 >96%. The intervention group was eligible patients for 6 months after the normoxia implementation and the control group was 12 months prior to the implementation. The primary outcome was SpO2 and FiO2 during the first 7 days of hospitalization.

Results: The 572 patients were mean age 54 years, 69% male, 54% non-Hispanic white, 79% blunt trauma mechanism, and mean APACHE II score 10.5. Hospital mortality occurred in 6.5% of patients. The use of no supplemental oxygen (FiO2 21% or room air) increased 30.8% of patient-hours (control) to 37.5% (intervention) and use of high volume oxygen (FiO2 >30%) decreased from 36.5% to 21.0%, respectively. Normoxia or use of no supplemental oxygen increased from 58.3% (control) to 65.1% (intervention). The incidence of hypoxia (SpO2 <88%) was similar in the control (1.1%) and intervention (1.0%) periods. Clinical outcomes were similar: hospital mortality (difference 2.3%; 95%CI, -2.5 to 7.1%), ventilator-free days (difference 0.0 days; 95%CI, -1.5 to 1.6), and hospital-free days (difference 2.1 days; 95%CI, -2.2 to 6.3).

Conclusion: The normoxia intervention decreased supplemental oxygen use and increased normoxia without increasing hypoxia. This pilot study was underpowered for clinical outcomes; a larger multicenter trial will determine the impact on clinical outcomes.

Disclosures: Funded by the Department of Defense/SOCOM (W81XWH-17-C-0241). This abstract expresses the authors’ opinions and does not reflect the policy or opinions of the Department of the Army, Department of the Air Force, Department of Defense, or US Government.
Strategy to Avoid Excessive Oxygen (SAVE-O2) for Combat Casualty Care

PIs: Adit A. Ginde, MD, MPH, University of Colorado
MAJ Steven Schauer, DO, MS, USAISR/59 MDW
Vik Bebarta, MD, Col, USAF IMA, 59th MDW/ST, Univ of Colorado, Director, CU Center for COMBAT Research
Today

Knowledge Gap/Needs on hyperoxia
Current literature
USSOCOM Normoxia Project Summary
USAMRDC Normoxia multicenter trial (SAVE-O2)
Significance

• Supplemental oxygen – avoids morbidity from hypoxia

• Excessive oxygen
  – Common practice and in written into training documents
  – Unlikely to benefit; may cause harm
  – Expands mission weight, cube, and logistics; safety issues, cost
  – Excess O2 bad for critical medical pts, no clear data in trauma

• **Gap:** Limited data on optimal oxygen titration targets in critically injured patients
Normoxia: Avoid hypoxia **AND** hyperoxia

<table>
<thead>
<tr>
<th>Oxygen Saturation</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>&lt; 88%</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>88-89%</td>
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</tr>
<tr>
<td>90-96%</td>
<td>Normoxia</td>
</tr>
<tr>
<td>&gt;96%</td>
<td>Hyperoxia</td>
</tr>
</tbody>
</table>
Conclusions:

...1 in 5 casualties overall, 1 in 3 intubated, and almost 1 in 2 TBI casualties had documented hyperoxia.

Avoiding **unnecessary O2 supplementation** may

1. Have material impact on preserving this scarce resource (logistics and cost)
2. Avoid potential detrimental clinical effects from supraphysiologic oxygen concentrations.
Targeted Normoxia to Conserve Oxygen and Improve Clinical Outcomes in Combat Injured Special Operations Forces

PI: Adit Ginde, MD, MPH; MAJ Steven Schauer, DO, MS  Org: University of Colorado Denver/USAISR  Award: W81XWH-17-0241

Study Aims

- **Aim 1**: Define standard care for oxygen titration in critically ill trauma patients
- **Aim 2**: Compare the effectiveness of normoxia and relative hyperoxia in critically ill trauma patients
- **Aim 3**: Develop and pilot test a targeted normoxia intervention in critically ill trauma patients.

Approach

Aim 1 is a Delphi process with subject matter experts to define normoxia targets (minimizing supplemental oxygen) after major trauma and develop consensus clinical practice guidelines. Aim 2 is a retrospective cohort study to measure severity-adjusted clinical outcomes of normoxia, compared with relative hyperoxia (conventional oxygen) in critically ill trauma patients. Aim 3 is a pilot implementation study of the targeted normoxia study to test the feasibility of implementation in critically ill trauma patients.

Timeline and Cost

<table>
<thead>
<tr>
<th>Activities</th>
<th>CY 17</th>
<th>CY 18</th>
<th>CY 18</th>
<th>CY 19</th>
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<tbody>
<tr>
<td>Define standard care</td>
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<tr>
<td>Develop large scale intervention</td>
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</table>

Goals/Milestones

**CY17 Goals** (3 months) – Preparatory Work
- Design survey and identify experts/respondents (Aim 1)
- Develop electronic chart abstraction tool (Aim 2)
- Obtain IRB approvals (Aims 1 and 2)

**CY18 Goals** (12 months) – Define Normoxia Targets
- Begin Delphi process (Aim 1)
- Begin data collection (Aim 2)
- Analyze responses and develop clinical practice guideline (Aim 1)
- Complete data collection and analysis (Aim 2)
- Disseminate results (Aims 1 and 2)
- Develop intervention and case report forms (Aim 3)
- Obtain IRB approval (Aim 3)

**CY19 Goals** (9 months) – Implementation Results and Next Steps
- Implement intervention and begin data collection (Aim 3)
- Complete data collection and analysis (Aim 3)
- Disseminate results (Aim 3)
- Prepare for large scale implementation

Updated: April 15, 2019
Aim 1a: Systematic Review

Systematic review of oxygenation and clinical outcomes to inform oxygen targets in critically ill trauma patients

David J. Douin, MD, Steven G. Schauer, DO, MS, Erin L. Anderson, RN, Jacqueline Jones, PhD, RN, Kristen DeSanto, MS, Cord W. Cunningham, MD, MPH, Vikhyat S. Bebarta, MD, and Adit A. Ginde, MD, MPH, Aurora, Colorado

Conclusions
Lower oxygen/ normoxia → improved outcomes
Few trauma specific articles; No high quality/RCT data
Supports need for trauma-specific studies/RCTs, particularly beyond TBI
## Aim 1b: Expert Panel (Military)

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Speciality</th>
<th>Institution</th>
</tr>
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<tr>
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<td>Kevin</td>
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<tr>
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<td>Sean</td>
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<td>Philip</td>
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<tr>
<td>Miles</td>
<td>Ethan</td>
<td>Other</td>
<td>Ft. Benning</td>
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<tr>
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<td>Jamie</td>
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<td>Naval Medical Center</td>
</tr>
<tr>
<td>Wilson</td>
<td>Ramey</td>
<td>Other</td>
<td>SOCAFRICOM</td>
</tr>
</tbody>
</table>

Also 18 civilian experts part of the panel.
Aim 1b: Final Vote for SpO2, PaO2, and lowest FiO2

- Lower SpO2 Threshold: 90%
- Upper SpO2 Threshold: 96%
- Lower PaO2 Threshold: 60 mmHg
- Upper PaO2 Threshold: 100 mmHg
- Lowest FiO2: 21%

Percentage of Agreement with Oxygenation Thresholds:
- 89%
- 89%
- 96%
- 89%
- 100%
Aim 2: Observational Study

Most pts on supplemental O2 are hyperoxic.
Higher oxygen supplementation associated with increased mortality at all SpO2 levels.
Aim 3: Pilot Intervention

- Finalized standard care definitions for oxygen

- Approved IRB applications
  - Colorado IRB review—approved (waiver of consent)
  - DoD/HRPO second level review—approved

- Implementation
  - Data collection strategy
  - Stakeholder engagement
  - Electronic clinical decision support

- Demonstrated feasibility and safety
  - n=201 post-intervention (Jan-July 2019)
Aim 3: Pilot Intervention

- We significantly increased normoxia and reduced FiO2/oxygen administration
- No increase in hypoxia
- Mortality, Vent FD, Hospital FD were similar in pre- and post-implementation groups
- Clinical outcomes to be evaluated in multicenter trial
Objective

Our **overall objective** is to determine oxygen titration goals for combat injured to optimize care by reducing harm associated with hypoxia and hyperoxia and to conserve limited oxygen supply.

**Aim 1.** Measure the impact of targeted normoxia implementation on oxygen requirements in critically injured patients.

**Aim 2.** Determine the safety of targeted normoxia.

**Aim 3.** Determine the clinical effectiveness of targeted normoxia.

Approach

Multicenter cluster randomized, stepped wedge implementation trial of the targeted normoxia approach (SpO2 90-96%). Efficiency will be greatly enhanced by a waiver of informed consent since protocol implementation is minimal risk (EFIC not required).

Impact

Our findings will provide immediately actionable data to define oxygenation practices in critically injured warfighters and civilians and aid in the development of clinical practice guidelines.

### Timeline and Cost

<table>
<thead>
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<th>Activities</th>
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<th>Year 2</th>
<th>Year 3</th>
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<td>Preparatory Work</td>
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<tr>
<td>Data Collection</td>
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<tr>
<td>Analysis/Dissemination</td>
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</table>

### Goals/Milestones

**Year 1 Goals** (12 months) – Preparatory Work
- Obtain IRB/HRPO approval
- Develop Standard Operating Procedure Documents (SOPs)
- Create Site Materials
- Site Initiation Visits/Training
- Develop Data Collection Infrastructure
- Begin Site Implementation

**Year 2 Goals** (12 months) – Implementation
- Randomized Implementation
- Site Monitoring
- Data Collection

**Year 3 Goals** (12 Months) – Data Collection/Data Analysis
- Randomized Implementation/Site Monitoring
- Data Collection
- Data Analysis
- Dissemination

Updated: October 19, 2019
Proposed Sites

- University of Pittsburgh
- University of Cincinnati
- Oregon Health & Science University
- University of Texas - Houston
- University of Colorado (CCQ Denver Health (site))
- Vanderbilt University (IDCC and site)
- San Antonio Military Medical Center
- University of Alabama - Birmingham
Stepped Wedge Cluster Randomized Trial

Sites

1
2
3
4
5
6
7
8

Time

Pre-Implementation (Control)
Post-Implementation (Intervention)
Multicenter Normoxia Trial (JWMPR)

- **Goal**: definitive, trauma/CCC-specific evidence to inform CPG and oxygen requirements
  - Particularly important for ERC/PFC
  - Focus on polytrauma

- **Design**: cluster randomized, stepped wedge implementation trial (8 sites, n~6240 patients); Trauma surgeons at Site Co-PIs

- **Human subjects issues**: minimal risk, waiver of informed consent (efficient, cost savings)
Multicenter Normoxia Trial (MTEC)

- **Goal**: major burn-specific evidence to inform CPG and oxygen requirements
  - Particularly important to focus on burn wound healing

- **Design**: cluster randomized, stepped wedge implementation trial (6 sites, n~2340 patients); Burn surgeons Site CO-Pis.

- **Sites**: U.S. Army Institute of Surgical Research, University of Alabama-Birmingham, University of Cincinnati, University of Colorado, University of Pittsburgh, Vanderbilt University
Technology/Materiel Solutions

- Portable oxygen concentrators
  - Benefit greatly by decreased oxygen requirement
- Pulse oxygen delivery
- Rebreathing system
- Autonomous closed loop control
CU Anschutz Center for COmbat Medicine and BATtlefield (COMBAT) Research

Mission: To improve the care of combat related injury and illness through innovation, research, and advanced development with military and civilian collaboration.
Emergency Medicine

Surgery

CU Center for COMBAT Research – Anschutz Medical Campus

Anesthesiology

Dean of the School of Medicine
CU Anschutz Center for COMBAT Research
Focused on high priority, high impact, pragmatic, forward combat casualty care solutions
Three Level 1 trauma centers, prehospital, bioengineering, etc
Getting “products” out the door
Discussion/Questions

Adit A. Ginde, MD, MPH
adit.ginde@cuanschutz.edu
Phone: 720-848-6777

Vik Bebarta, MD; Col, USAF IMA, MC
Vikhyat.bebarta@cuanschuz.edu 720-848-6789

University of Colorado
Anschutz Medical Campus
School of Medicine
Clinical Coordinating Center
University of Colorado
Principal Investigator: Adit Ginde MD, MPH
Project Manager: Erin Anderson, RN
Data Analysis Core: Krithika Suresh, PhD
Caroline Ledbetter, MPH
Informatics Core

Organizational Chart

University of Alabama-Birmingham
Site PI: Jan Jansen, MBBS, PhD
Study Coordinator
IT Department

University of Pittsburgh
Site PI: Scott Gunn, MD
Study Coordinator
IT Department

University of Texas-Houston
Site PI: Pratik Doshi, MD
Study Coordinator
IT Department

Vanderbilt
Site PI: Wesley Self, MD, MPH
Study Coordinator
IT Department

Denver Health
Site PI: Jason Haukoos, MD
Study Coordinator
IT Department

Oregon Health & Sciences University
Site PI: Martin Schreiber, MD
Study Coordinator
IT Department

University of Cincinnati
Site PI: Richard Branson, MS, RRT
Study Coordinator
IT Department

SAMMC
Site PI: MAJ Steven Schauer, DO, MS
Study Coordinator
IT Department

Intramural Investigators
MAJ Steven Schauer, DO, MS
Dario Rodriquez Jr., MSc, RRT

Department of Defense
Scientific Officer
Sandy Snyder, MSN, RN

COMBAT Research Center
Col Vikhyat Bebarta, MD
Col Kathleen Flarity, DNP, PhD
MAJ Jerome McKay, PhD

Colorado Multiple Institutional Review Board (COMIRB)

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